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Vitamin D deficiency and frailty in older Americans

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Abstract

Objective—To explore the relation between 25-hydroxy-vitamin D deficiency and frailty. Frailty is a multidimensional phenotype that describes declining physical function and a vulnerability to adverse outcomes in the setting of physical stress such as illness or hospitalization. Low serum concentrations of 25-hydroxyvitamin D are known to be associated with multiple chronic diseases such as cardiovascular disease and diabetes, in addition to all cause mortality.

Design—Using data from the Third National Health and Nutrition Survey (NHANES III), we evaluated the association between low serum 25-hydroxyvitamin D concentration and frailty, defined according to a set of criteria derived from a definition previously described and validated.

Subjects—Nationally representative survey of noninstitutionalized US residents collected between 1988 and 1994.

Results—25-Hydroxyvitamin D deficiency, defined as a serum concentration <15 ng mL^{-1}, was associated with a 3.7-fold increase in the odds of frailty amongst whites and a fourfold increase in the odds of frailty amongst non-whites. This association persisted after sensitivity analyses adjusting for season of the year and latitude of residence, intended to reduce misclassification of persons as 25-hydroxyvitamin D deficient or insufficient.

Conclusion—Low serum 25-hydroxyvitamin D concentrations are associated with frailty amongst older adults.

Keywords

ageing; muscle metabolism; nutrition; risk factors; vitamins

Introduction

Frailty is a multidimensional phenotype that describes declining physical function and a vulnerability to adverse health outcomes in the setting of physical stress such as illness or hospitalization [1–5]. Multiple instruments to operationalize a definition of frailty have been developed and validated [1]. One such index, proposed by Fried and colleagues, defines frailty as the presence of three or more of five criteria: unintentional weight loss, exhaustion, weakness, slow walking speed and low physical activity [4]. Using the Fried criteria, estimates of the prevalence of frailty amongst independently living adults vary from 7% of persons older than 65 years to 40% of persons older than 80 years; prevalence estimates are

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higher amongst persons with diabetes and other chronic debilitating diseases [2–4,6]. Frailty, using this definition, is associated with increased risk of falls, hospitalization, disability and death [4]. However, diagnosing frailty in the clinical setting can be cumbersome because most indices of frailty require a combination of anthropometry and physical function testing.

Serum concentrations of 25-hydroxyvitamin D are known to decline with age. Moreover, rates of 25-hydoxyvitamin D deficiency are higher amongst groups that are at high risk for poor physical functioning: older individuals, women and non-whites [7–9]. Our prior work has described higher rates of frailty amongst non-whites and women [10]. 25-hydroxyvitamin D deficiency is also associated with debilitating chronic diseases, such as hypertension, chronic kidney disease, insulin resistance and diabetes, obesity, and cardiovascular disease, as well as other age-related conditions that may influence physical functioning, such as macular degeneration and osteopenia [9,11–19].

A small number of studies have previously evaluated the relation between low serum 25-hydroxyvitamin D and frailty, but these studies have been in disease-limited patient populations or have employed nonstandard definitions of frailty [20–22]. We hypothesized that 25-hydroxyvitamin D deficiency would be associated with frailty in older adults, independent of the associations seen amongst frailty, advanced age and chronic medical conditions, and that the association between frailty and 25-hydroxyvitamin D would differ by race.

Methods

Data source

We obtained individual level data from the Third National Health and Nutrition Evaluation Survey (NHANES III), a nationally representative survey of the health status of persons residing in the United States (US) collected between 1988 and 1994. NHANES III is a cross-sectional, multistage, stratified, clustered probability sample of the US civilian noninstitutionalized population conducted by the National Center for Health Statistics, a branch of the Centers for Disease Control and Prevention (CDC) [23]. The purpose of NHANES is to determine the prevalence of major diseases and potential risk factors for diseases in the general US population. NHANES conducts both interviews and physical examinations. The interview includes demographic, socioeconomic, dietary and health-related questions. The examination is conducted at a mobile evaluation center (MEC) or the participant's home and consists of medical, dental, and physiological measurements, as well as laboratory tests administered by highly trained medical personnel. The Institutional Review Board for the CDC approved NHANES III and all participants provided written consent. The present study was granted exempt status by the Institutional Review Board of Stanford University School of Medicine.

Study sample

We identified all participants who completed an NHANES interview between 1988 and 1994 (n = 33 198). We limited the study population to persons aged 60 years or older at the time of their NHANES examination who had 25-hydroxyvitamin D data available (n = 5335). We excluded persons for whom sufficient data to assess frailty (described below) were unavailable (n = 7). Persons who chose to be examined in their homes rather than in an MEC were eligible for phlebotomy including an assay for serum 25-hydroxyvitamin D. A large fraction of home examined persons (66%) were missing 25-hydroxyvitamin D data; thus, we excluded home examined persons from our primary analysis. Home examined participants (n = 422) were more likely to be older (mean age 77.8 years) and non-Hispanic

white and more likely to have multiple comorbidities than those examined in an MEC. The analytic dataset included the remaining 5048 persons (Fig. 1).

Frailty

We defined frailty based on a modification of the Fried criteria [4]. Our definition adheres to the five frailty domains previously established, but customizes the criteria for application to NHANES III data [10].

1. Low body weight for height, defined as Quetelet's (bodymass) index ≤ 18.5 kg m^{-2}.
2. Slow walking, defined as the slowest quintile adjusted for sex, in a timed 8-foot walk.
3. Weakness, defined as present if participants answered 'some difficulty,' 'much difficulty,' or 'unable to do' when asked how much difficulty they have 'lifting or carrying something as heavy as ten pounds (like a sack of potatoes or rice).'
4. Exhaustion, defined as present if participants answered 'some difficulty,' 'much difficulty,' or 'unable to do' when asked how much difficulty they have 'walking from one room to the other on the same level.'
5. Low physical activity, defined as present if participants answered 'less active' when asked 'Compared with most (men/women) your age, would you say that you are more active, less active or about the same?'

We included persons with available data for three or more frailty domains in our analysis. If three or more domains were present according to the above criteria, the person was considered frail for the purposes of our analysis.

25-Hydroxyvitamin D

All NHANES participants over the age of 12 years were eligible for measurement of serum 25-hydroxyvitamin D concentration. Blood samples collected in the MEC were centrifuged and serum was divided into aliquots and stored at −70 °C until they were shipped on dry ice to a central laboratory, where they were stored at −70 °C until analysis. Analysis was performed using the DiaSorin radioimmune assay kit (Stillwater, MN, USA) to measure 25-hydroxyvitamin D with a lower limit of detection of 3.5 ng mL^{-1}.

For reasons related to the convenience and safety of MEC staff, survey participants living in northeastern and upper midwestern states were primarily sampled between April and September. Survey participants living in southern states were sampled throughout the year with the majority of sampling occurring between October and April [23].

We used conventional definitions of 25-hydroxyvitamin D deficiency (serum 25-hydroxyvitamin D concentration <15 ng mL^{-1}) and 25-hydroxyvitamin D insufficiency (serum 25-hydroxyvitamin D concentration of 15 to <30 ng mL^{-1}).

Other explanatory variables

We ascertained participant race based on self-report and classified participants as 'white' or 'non-white' (includes participants of black and all other races). We estimated socioeconomic status (SES) using the poverty income ratio (PIR) which is based on income thresholds from the US Census Bureau that vary by family size and composition. We considered participants with PIR values <2.00 to be of low SES; we considered participants with PIR values ≥2.00 to be of high SES.

We considered participants to have diabetes if a physician had informed them that they had diabetes or if they recorded a haemoglobin A1c ≥6%. We considered participants to have evidence of liver disease if they recorded an aspartate aminotransferase (AST) >37 U L^{-1} or alanine aminotransferase (ALT) >40 U L^{-1} for men and either AST or ALT >31 U L^{-1} for women. We defined chronic kidney disease as either prevalent micro- or macro-albuminuria (defined as a single urinary albumin-to-creatinine ratio ≥30 mg g^{-1}) in the presence of a normal estimated glomerular filtration rate (eGFR, calculated using the Mayo quadratic equation) or an eGFR <60 mL min^{-1} per 1.73 m^2 [24,25]. We considered participants to have peripheral arterial disease if they reported activity-related calf pain that was relieved with rest. Similarly, we considered participants to have coronary artery disease if they reported activity-related chest pain that was relieved with rest, or if they reported a prior myocardial infarction. We identified participants with arthritis, cancer, chronic lung disease, congestive heart failure or history of stroke based on self-reported physician diagnosis. We considered the presence of one or more of peripheral arterial disease, coronary artery disease, heart failure or stroke as 'overt cardiovascular disease.' Blood pressure was measured according to a protocol described elsewhere; hypertension was defined according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines [26,27].

Statistical analysis

We conducted data analysis with sas, version 9.1.3 (SAS Institute, Inc., Cary, NC, USA), accounting for oversampling, stratification and clustering [28]. Because serum 25-hydroxyvitamin D concentrations differ widely by race, we conducted race stratified analyses (white and non-white) for frailty. We controlled for demographic factors (age, sex, and poverty, as described above) as well as seven comorbidities (diabetes, history of nondermatologic cancer, chronic lung disease, chronic liver disease, chronic kidney disease, overt cardiovascular disease and arthritis); only chronic lung disease was not significantly associated with frailty and was removed from our model. For the discrete frailty outcome, we performed multi-variable logistic regression adjusting for sociodemographic factors and comorbid conditions that were associated with frailty at $P < 0.20$ in bivariate analyses. In logistic regression models, we assessed discrimination using the area under the receiver operating characteristic (ROC) curve and we assessed calibration using the Hosmer–Lemeshow goodness-of-fit test. The Hosmer–Lemeshow test compares model performance (observed versus expected) across deciles of risk, to test whether the model is biased (i.e., performs differentially at the extremes of risk). A nonsignificant value for the Hosmer–Lemeshow χ^2 suggests an absence of such bias.

Because serum 25-hydroxyvitamin D concentrations vary by season of the year and by latitude, persons may be misclassified with vitamin D deficiency or insufficiency depending on the time of year that measurements were made. Further complicating matters, the NHANES strategy of sampling persons living in colder climates primarily in the summer months and persons living in warmer climates primarily in the winter months also raised concern for misclassification bias. We addressed these complexities in the following manner: for the primary analysis, we excluded season and latitude. This naïve and analytically conservative approach assumes that the measured concentration of 25-hydroxyvitamin D reflects the participants' time-averaged 25-hydroxyvitamin D exposure. However, participants measured during July in Minnesota, for example, might be misclassified as having higher 25-hydroxyvitamin D concentrations than their time-averaged exposure. Therefore, we conducted the following sensitivity analyses:

1. Seasonally adjusted 25-hydroxyvitamin D: using data from persons residing in states grouped into the census region of the South (Fig. 2), we created a regression model that allowed us to adjust for month of 25-hydroxyvitamin D measurement.

The South was chosen because it was the only census region in which data were collected year-round. We then applied that model to persons residing in other regions and created race-stratified logistic regression models, as in the primary analysis, using seasonally adjusted 25-hydroxyvitamin D.

2. Latitude adjusted 25-hydroxyvitamin D: For survey participants residing in counties with over 500 000 inhabitants, the county name is available in the NHANES III dataset. Using data from the US Census Bureau, we created a dichotomous latitude variable to sort these participants into those living at latitudes >40° and those living at latitudes ≤40° (Fig. 2). We created a separate logistic regression model to estimate the odds of frailty associated with living in northern states.

Results

Of the 33 994 NHANES III participants, 5048 participants met inclusion criteria (Fig. 1). Study sample is described in Table 1. The distribution of serum 25-hydroxyvitamin D concentrations amongst whites and non-whites is shown in Fig. 3. Mean values were significantly lower amongst non-whites [22.0 (0.6) vs. 28.2 (0.3) ng mL^{-1}, $P < 0.0001$].

25-Hydroxyvitamin D and frailty

Serum 25-hydroxyvitamin D was associated with frailty in both whites and non-whites. Amongst whites, 25-hydroxyvitamin D *deficiency* was associated with a significant increase in the odds of frailty, even after adjustment for age (stratified by decade), sex and comorbidities (Table 2). 25-hydroxyvitamin D *insufficiency* was not associated with the odds of frailty amongst whites. Amongst non-whites, both 25-hydroxyvitamin D deficiency and insufficiency were associated with a significant increase in the odds of frailty (Table 3).

Seasonally adjusted 25-hydroxyvitamin D

Figure 4 shows the distribution of 25-hydroxyvitamin D concentrations by calendar month amongst participants residing in Southern states. From the regression model we developed, we derived a ‘correction factor’ for each month of the year which was then applied to survey participants residing in the other regions of the country (Fig. 4). Our corrected values resulted in 794 persons being reclassified in the following manner: 180 moved from deficient to insufficient; 191 from insufficient to deficient; 202 from insufficient to normal; and 176 from normal to insufficient. Corresponding odds of frailty for seasonally adjusted 25-hydroxyvitamin D deficiency and insufficiency for whites were 2.7 (95% CI 1.6–4.6) and 0.9 (0.5–1.7) and for non-whites were 2.4 (0.9–6.3) and 2.2 (1.1–4.4).

25-Hydroxyvitamin D adjusted for latitude

In the subset of survey participants for whom latitude data were available (1599 whites and 593 non-whites), rates of frailty were increased for both whites and non-whites residing north of the 40° latitude line. Amongst whites living north of 40°, 6.2% were frail, compared to 4.1% residing south of 40°. Amongst non-whites living north of 40°, 10.4% were frail, as opposed to 6.9% amongst non-whites living south of 40°. Amongst whites, living north of the 40° latitude line conferred an odds ratio of 2.2 (95% CI 1.4–3.7) for frailty even when controlling for measured 25-hydroxyvitamin D concentration, age, sex, SES and comorbidities, indicating probable misclassification of 25-hydroxyvitamin D status by a single 25-hydroxyvitamin D determination. Amongst non-whites, the odds of frailty associated with living in the northern latitudes were nominally increased but not statistically significant ($P = 0.5$). These results are summarized in Table 4.

Discussion

Using data from a nationally representative sample of older adults, we found serum 25-hydroxyvitamin D concentration to be associated with frailty. Amongst whites, 25-hydroxyvitamin D deficiency was associated with a threefold increase in the odds of frailty; the odds of frailty were even higher amongst non-whites with 25-hydroxyvitamin D deficiency. 25-hydroxyvitamin D insufficiency was also associated with frailty amongst non-whites.

Two recent studies described a high prevalence of 25-hydroxyvitamin D deficiency (and insufficiency) in the general population, with higher rates in older persons and racial and ethnic minorities [7,8]. Other studies have noted strong associations amongst 25-hydroxyvitamin D deficiency, mortality and a variety of morbidities. For example, using data from NHANES III, Melamed and colleagues showed that adults with vitamin D deficiency experienced a 26% increased risk in all-cause mortality over a 10-year follow-up period [14]. Similarly, researchers in the Netherlands demonstrated an increased rate of nursing home admission in older adults with vitamin D deficiency [29]. These results may be unsurprising given the well-known association between 25-hydroxyvitamin D deficiency and numerous chronic diseases. For example, 25-hydroxyvitamin D deficiency is associated increased risks of diabetes [11,14,30] and hypertension [12,14].

In addition to the association between 25-hydroxyvitamin D deficiency and chronic disease, there are other potential connections between 25-hydroxyvitamin D status and frailty. 25-hydroxyvitamin D deficiency may result in proximal muscle weakness, which could limit a person's capacity to maintain levels of physical activity and/or performance [31,32]. A physiological explanation for proximal muscle weakness may relate to the binding of 1,25-dihydroxyvitamin D, the activated form of 25-hydroxyvitamin D, on nuclear receptors in skeletal muscle cells, resulting in increased protein synthesis and muscle cell growth [33,34]. Consistent with this observation, numerous studies demonstrate a reduction in the risk of falls following vitamin D supplementation. A recent meta-analysis, which combined results from five randomized controlled trials, concluded that vitamin D supplementation may reduce the risk of falls amongst older persons by 20% [35]. Even more striking, recent results from Moreira-Pfrimer and colleagues, demonstrate that vitamin D supplementation in older adults may increased lower extremity strength [36].

The association between 25-hydroxyvitamin D and frailty could reflect factors relating 25-hydroxyvitamin D to health status, or could reflect ‘reverse causality.’ In other words, frail older adults may spend fewer hours outdoors than more physically able older adults, not gaining the benefits of conversion of 7-dehydrocholesterol (in skin) to cholecalciferol by ultraviolet B radiation. Because home-examined NHANES participants were excluded from our analysis, confounding by differences in sun exposure may have been mitigated, albeit not eliminated or adequately controlled for. The fact that latitude was associated with frailty after accounting for a single 25-hydroxyvitamin D determination suggests residual confounding by sun exposure. However, even if the association we describe between frailty and 25-hydroxyvitamin D concentration is mediated by differences in sun exposure amongst frail and robust older adults, this observation does not negate the possibility that vitamin D supplementation may protect or restore physical functioning in frail people.

Recent reports suggest that the prevalence of 25-hydroxyvitamin D deficiency is increasing in the US. In fact, an analysis comparing rates of 25-hydroxyvitamin D deficiency between NHANES samples from 1988 to 1994 and those from 2001 to 2004 showed a clear trend towards lower serum 25-hydroxyvitamin D concentrations across all demographic groups, with an especially worrisome increase in the rate of 25-hydroxyvitamin D deficiency

amongst blacks [7]. Given our findings of a strong association between 25-hydroxyvitamin D deficiency and frailty, the increased prevalence of 25-hydroxyvitamin D insufficiency and deficiency are particularly problematic as our population ages.

Potential differences in the association of 25-hydroxyvitamin D with frailty by race, i.e., somewhat stronger associations at lower threshold 25-hydroxyvitamin D concentrations for non-white participants, highlight the need to consider race when assessing optimal vitamin D status.

At least three recent studies have evaluated the possible association between 25-hydroxyvitamin D deficiency and frailty. Boxer *et al.* reported that amongst persons with systolic heart failure, low serum 25-hydroxyvitamin D predicted a higher frailty score [21]. Puts *et al.* report a significant association between lower serum 25-hydroxyvitamin D and frailty amongst persons older than 65, but employ an alternate definition of frailty that bears little resemblance to the Fried criteria [20]. Shardell *et al.* demonstrated an association between low serum 25-hydroxyvitamin D and frailty amongst persons older than 65 in a general population cohort, but only amongst men. Moreover, this study made no apparent attempt to control for season of blood collection [22].

Our study's strengths include analysis of a nationally representative sample of US adults with robust recruitment of persons older than 80 years. We also adjusted for a wide array of sociodemographic factors, comorbid conditions and environmental factors that might have confounded the vitamin D-frailty relation. Our study also carries a few important limitations. First, NHANES III data are primarily cross-sectional and we were unable to follow serum 25-hydroxyvitamin D concentrations over time. Secondly, 25-hydroxyvitamin D data were missing in more than half of home-examined participants and were therefore excluded from our primary analysis. Since these home-examined participants tended to have more comorbidity than participants examined in mobile units, we have probably underestimated the population prevalence of frailty (and 25-hydroxyvitamin D deficiency).

An additional challenge of our study was the complexity of the NHANES sampling scheme whereby northern dwelling survey participants were sampled primarily in the summer months and residents of southern states were sampled year-round with an emphasis on the winter months. This sampling scheme had the potential to increase misclassification of 25-hydroxyvitamin D insufficient and deficient participants. We were reassured that the results of our two sensitivity analyses, aimed at addressing this potential misclassification, qualitatively confirmed the results from our primary analysis. Using seasonally adjusted 25-hydroxyvitamin D concentrations, we found a nearly threefold increase in the odds of frailty amongst whites with 25-hydroxyvitamin D deficiency and a greater than twofold increase in the odds of frailty amongst non-whites with 25-hydroxyvitamin D insufficiency. The slightly lower odds of frailty in the seasonally adjusted analysis as compared to the primary analysis may appear counter intuitive if, as we expect, seasonal adjustment of 25-hydroxyvitamin D concentrations reduces misclassification of 25-hydroxyvitamin D deficiency and insufficiency. However, because persons living in northern states were sampled in the summer, those persons classified as 25-hydroxyvitamin D deficient using 25-hydroxyvitamin D concentrations not corrected for season were the most ‘deficient of the deficient.’ For this reason, the association between 25-hydroxyvitamin D deficiency and frailty appeared stronger in the primary analysis. In effect, some participants at the upper end of the deficient range were misclassified as ‘insufficient’ in the base case analysis. With re-classification in the seasonally adjusted analysis, the odds of frailty associated with 25-hydroxyvitamin D deficiency were attenuated.

It is also relevant to note that our seasonally adjusted analysis applied an adjustment based exclusively on residents of the southern census region on other census regions. This method for seasonal adjustment has an obvious limitation, namely that southern seasonal adjustment may introduce novel bias to 25-hydroxyvitamin D measurements in participants living in other census regions. This bias could take several potential forms. For example, residents in the hot, more humid south may plausibly spend less time outside during the summer months (rather, choosing indoor air-conditioned settings) than residents of more northern latitudes where the weather is more temperate. Therefore, the relative increase in summer sun exposure may be attenuated in the south compared with other regions. Unfortunately, it was not possible to create a model for seasonal adjustment based on data from all four census regions.

Similarly, our secondary analysis in the subset of participants for whom latitude of residence was available also qualitatively confirmed the results of our primary analysis. The latitude adjusted analysis showed a greater than fivefold increase in the odds of frailty amongst whites with 25-hydroxyvitamin D deficiency and a greater than threefold increase in the odds of frailty amongst non-whites with 25-hydroxyvitamin D deficiency. Whilst we believe that our sensitivity analyses suggest a robust association between vitamin D deficiency and frailty, there is likely to be residual confounding by several factors for which we could not adjust, including dietary 25-hydroxyvitamin D intake, sun exposure (beyond that accounted for by month of evaluation and latitude), melanin content in skin (beyond what is accounted for by self-reported race), and the use (and type) of sunscreen.

The intersection of 25-hydroxyvitamin D deficiency and ageing is an important area of research with much that remains to be studied. In the future, researchers should focus on longitudinal data that demonstrate how 25-hydroxyvitamin D status changes over time in older adults who are ageing well and in those who are ageing poorly. In addition, further studies should investigate whether interventions to correct deficiency and insufficiency of 25-hydroxyvitamin D status, such as supplementation and/or sun exposure, could reduce frailty or improve physical functioning in frail persons.

References

1. Jones DM, Song X, Rockwood K. Operationalizing a frailty index from a standardized comprehensive geriatric assessment. J Am Geriatr Soc 2004;52:1929–33. [PubMed: 15507074]
2. Morley JE, Haren MT, Rolland Y, et al. Frailty. Med Clin North Am 2006;90:837–47. [PubMed: 16962845]
3. Slaets JP. Vulnerability in the elderly: frailty. Med Clin North Am 2006;90:593–601. [PubMed: 16843764]
4. Fried LP, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146–56. [PubMed: 11253156]
5. Hoogerduijn JG, et al. A systematic review of predictors and screening instruments to identify older hospitalized patients at risk for functional decline. J Clin Nurs 2007;16:46–57. [PubMed: 17181666]
6. Morley JE. Diabetes, sarcopenia, and frailty. Clin Geriatr Med 2008;24:455–69. [PubMed: 18672182]
7. Ginde MC, Liu AA, Camargo CA Jr. Demographic differences and trends of vitamin D insufficiency in the US population, 1988-2004. Arch Intern Med 2009;169:626–32. [PubMed: 19307527]
8. Yetley EA. Assessing the vitamin D status of the US population. Am J Clin Nutr 2008;88:558S–64S. [PubMed: 18689402]
9. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266–81. [PubMed: 17634462]
10. Wilhelm-Leen ER, et al. Frailty and chronic kidney disease: The Third National Health and Nutrition Evaluation Survey. Am J Med 2009;122:664–71. [PubMed: 19559169]

11. Scragg R, et al. Serum 25-hydroxyvitamin D3 levels decreased in impaired glucose tolerance and diabetes mellitus. Diabetes Res Clin Pract 1995;27:181–8. [PubMed: 7555599]
12. Scragg R, Sowers M, Bell C. Serum 25-hydroxyvitamin D, ethnicity, and blood pressure in the Third National Health and Nutrition Examination Survey. Am J Hypertens 2007;20:713–9. [PubMed: 17586404]
13. Judd SE, et al. Optimal vitamin D status attenuates the age-associated increase in systolic blood pressure in white Americans: results from the third National Health and Nutrition Examination Survey. Am J Clin Nutr 2008;87:136–41. [PubMed: 18175747]
14. Melamed ML, et al. 25-hydroxyvitamin D levels and the risk of mortality in the general population. Arch Intern Med 2008;168:1629–37. [PubMed: 18695076]
15. de Boer IH, et al. 25-hydroxyvitamin D levels and albuminuria in the Third National Health and Nutrition Examination Survey (NHANES III). Am J Kidney Dis 2007;50:69–77. [PubMed: 17591526]
16. Wortsman J, et al. Decreased bioavailability of vitamin Din obesity. Am J Clin Nutr 2000;72:690–3. [PubMed: 10966885]
17. Wang TJ, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation 2008;117:503–11. [PubMed: 18180395]
18. Parekh N, et al. Association between vitamin D and age-related macular degeneration in the Third National Health and Nutrition Examination Survey, 1988 through 1994. Arch Ophthalmol 2007;125:661–9. [PubMed: 17502506]
19. Bolland MJ, et al. The effects of seasonal variation of 25-hydroxyvitamin D and fat mass on a diagnosis of vitamin D sufficiency. Am J Clin Nutr 2007;86:959–64. [PubMed: 17921371]
20. Puts MT, et al. Endocrine and inflammatory markers as predictors of frailty. Clin Endocrinol (Oxf) 2005;63:403–11. [PubMed: 16181232]
21. Boxer RS, et al. The association between vitamin D and inflammation with the 6-minute walk and frailty in patients with heart failure. J Am Geriatr Soc 2008;56:454–61. [PubMed: 18194227]
22. Shardell M, et al. Association of low vitamin D levels with the frailty syndrome in men and women. J Gerontol A Biol Sci Med Sci 2009;64:69–75. [PubMed: 19164273]
23. Plan and operation of the Third National Health and Nutrition Examination Survey (Government document), 1988–1994. Vital Health Stat 1994;32:1–407.
24. Rule AD, et al. Measured and estimated GFR in healthy potential kidney donors. Am J Kidney Dis 2004;43:112–9. [PubMed: 14712434]
25. Rule AD, et al. Using serum creatinine to estimate glomerular filtration rate: accuracy in good health and in chronic kidney disease. Ann Intern Med 2004;141:929–37. [PubMed: 15611490]
26. National Center for Health Statistics. Reference Manual Physician Examiner's Training Manual. Rockville, MD: National Center for Health Statistics; 1991.
27. Lenfant C, et al. Seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7): resetting the hypertension sails. Hypertension 2003;41:1178–9. [PubMed: 12756222]
28. SAS Institute. Introduction to Survey Sampling and Analysis Procedures, in SAS OnlineDoc 9.1.3. Cary, NC: SAS Institute; 2002–2008.
29. Visser M, et al. Low serum concentrations of 25-hydroxyvitamin D in older persons and the risk of nursing home admission. Am J Clin Nutr 2006;84:616–22. quiz 671–2. [PubMed: 16960177]
30. Chonchol M, Scragg R. 25-Hydroxyvitamin D, insulin resistance, and kidney function in the Third National Health and Nutrition Examination Survey. Kidney Int 2007;71:134–9. [PubMed: 17082756]
31. Glerup H, et al. Hypovitaminosis D myopathy without biochemical signs of osteomalacic bone involvement. Calcif Tissue Int 2000;66:419–24. [PubMed: 10821877]
32. Janssen HC, Samson MM, Verhaar HJ. Vitamin D deficiency, muscle function, and falls in elderly people. Am J Clin Nutr 2002;75:611–5. [PubMed: 11916748]
33. Bischoff HA, et al. *In situ* detection of 1,25-dihydroxyvitamin D3 receptor in human skeletal muscle tissue. Histochem J 2001;33:19–24. [PubMed: 11352397]

34. Endo I, et al. Deletion of vitamin D receptor gene in mice results in abnormal skeletal muscle development with deregulated expression of myoregulatory transcription factors. Endocrinology 2003;144:5138–44. [PubMed: 12959989]

35. Bischoff-Ferrari HA, et al. Effect of Vitamin D on falls: a metaanalysis. JAMA 2004;291:1999–2006. [PubMed: 15113819]

36. Moreira-Pfrimer LD, et al. Treatment of vitamin D deficiency increases lower limb muscle strength in institutionalized older people independently of regular physical activity: a randomized double-blind controlled trial. Ann Nutr Metab 2009;54:291–300. [PubMed: 19729890]

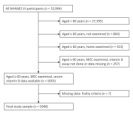

Fig. 1. Study flow diagram for NHANES III sample

Fig. 2. Census regions and 40° latitude line

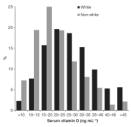

Fig. 3. Vitamin D levels for white and non-white persons, age ≥60 years

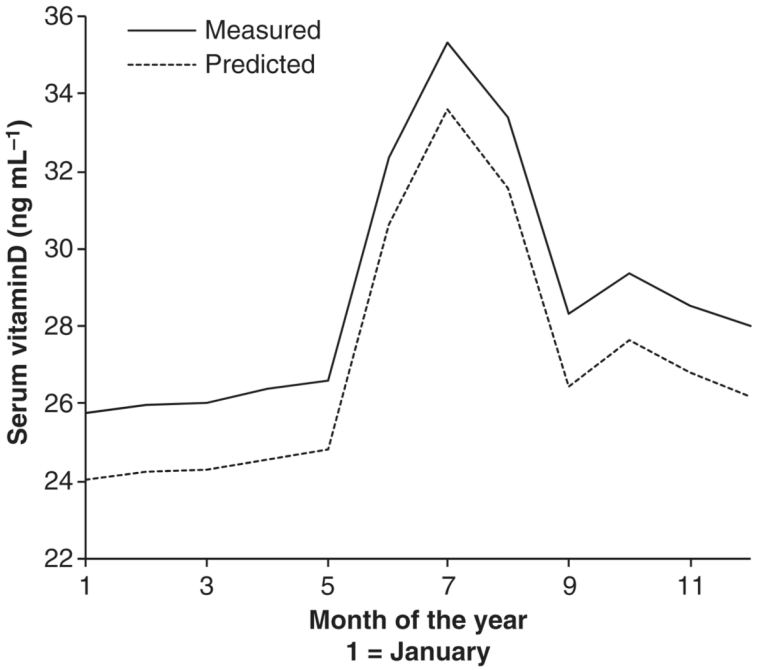

Fig. 4. Model for seasonally adjusted vitamin D

Table 1
Characteristics of participants with and without vitamin D deficiency by race

	Percentage of vitamin D deficient[a] (SE)	
	Non-white (*n* = 1080)	**White (*n* = 3968)**
Age, years		
60–69 (*n* = 2216)	24.6 (2.3)	7.6 (0.8)
70–79 (*n* = 1667)	25.3 (3.1)	6.7 (0.8)
≥80 (*n* = 1165)	31.9 (5.0)	10.8 (1.1)
Sex		
Female (*n* = 2579)	28.8 (2.7)	10.7 (0.9)
Male (*n* = 2469)	21.6 (2.8)	3.9 (0.6)
Census region		
Northeast (*n* = 801)	24.9 (2.3)	6.1 (1.1)
Midwest (*n* = 1085)	26.1 (5.1)	6.2 (0.8)
South[b] (*n* = 2178)	27.0 (3.6)	9.0 (1.3)
West (*n* = 984)	23.5 (5.4)	9.8 (0.6)
Season		
January–March (*n* = 1248)	38.4 (4.4)	12.3 (1.9)
April–June (*n* = 1242)	24.6 (4.5)	8.1 (0.9)
July–September (*n* = 1334)	24.1 (3.1)	5.6 (0.8)
October–December (*n* = 1224)	19.6 (2.1)	7.7 (1.3)
Socioeconomic status		
PIR <2 (*n* = 2360)	27.3 (2.4)	7.1 (0.6)
PIR ≥2 (*n* = 2688)	23.0 (2.9)	8.1 (0.7)
Body mass index		
<18.5 (*n* = 109)	33.3 (9.1)	10.9 (4.3)
18.5–24.9 (*n* = 1693)	20.6 (2.6)	7.7 (1.0)
25–29.9 (*n* = 2024)	26.3 (2.7)	7.1 (0.8)
≥30(*n* = 1222)	30.5 (4.3)	8.8 (1.0
Comorbidity		
Arthritis (*n* = 2273)	24.8 (2.6)	7.9 (0.9)
Cancer, nonskin (*n* = 408)	17.1 (6.2)	8.1 (1.7)
Chronic liver disease (*n* = 287)	20.8 (5.5)	8.6 (2.6)
Chronic lung disease (*n* = 537)	36.3 (7.7)	12.3 (1.5)
Chronic kidney disease (*n* = 1403)	29.7 (2.5)	10.5 (1.3)
Cardiovascular disease (*n* = 1310)	31.3 (4.3)	7.5 (1.0)
Diabetes (*n* = 1483)	24.5 (2.6)	8.0 (1.1)

[a] [25-Hydroxyvitamin D] <15 ng mL^{-1}.

[b] includes Texas.

PIR, poverty to income ratio.

Table 2

Adjusted odds ratios for frailty amongst white participants aged ≥60 years who were mobile evaluation center examined (*C* = 0.767)

	Odds ratio	95% confidence interval
Vitamin D (ng mL^{-1})		
≥30	Reference	—
15–<30	1.0	0.6–1.7
<15	3.7	2.1–6.8
Age (years)		
60–69	Reference	—
70–79	1.9	1.3–2.8
≥80	2.5	1.4–4.5
Sex		
Male	Reference	—
Female	1.2	0.8–1.8
Poverty to income ratio (PIR)		
PIR ≥2	Reference	—
PIR <2	1.9	1.3–2.6
Comorbidity		
Arthritis	3.8	2.2–6.5
Cancer, nonskin	1.9	1.2–2.9
Chronic liver disease	1.4	0.7–2.7
Chronic lung disease	1.4	0.8–2.3
Chronic kidney disease	1.7	1.1–2.6
Cardiovascular disease	1.8	1.2–2.6
Diabetes	1.6	1.1–2.3

Table 3

Adjusted odds ratios for frailty amongst non-white participants aged ≥60 years who were mobile evaluation center examined (*C* = 0.755)

	Odds ratio	95% confidence interval
Vitamin D (ng mL^{-1})		
≥30	Reference	—
15–<30	2.7	1.2–6.0
<15	4.0	1.7–9.2
Age (years)		
60–69	Reference	—
70–79	1.8	1.1–3.0
≥80	3.4	1.8–6.2
Sex		
Male	Reference	—
Female	0.9	0.5–1.6
Poverty to income ratio (PIR)		
PIR ≥2	Reference	—
PIR <2	1.5	0.9–2.3
Comorbidity		
Arthritis	3.8	2.2–6.5
Cancer, nonskin	1.3	0.3–5.6
Chronic liver disease	2.8	1.1–7.1
Chronic lung disease	1.0	0.5–2.3
Chronic kidney disease	1.5	0.9–2.6
Cardiovascular disease	2.8	1.8–4.3
Diabetes	1.0	0.6–1.6

Table 4
Comparison of odds ratios from four models

	Non-white		White	
	Odds ratio[a]	95% CI	Odds ratio[a]	95% CI
Measured vitamin D	4.0	1.7–9.2	3.7	2.1–6.8
Seasonally adjusted vitamin D	2.4	0.9–6.3	2.7	1.6–4.6
Latitude adjusted analysis	3.7	1.5–8.8	5.3	2.6–11.1
Seasonally and latitude adjusted	2.8	1.0–8.3	3.3	1.6–6.8

Measured vitamin D model, $n = 5048$.

Seasonally adjusted vitamin D model, $n = 5048$.

Latitude adjusted model, $n = 2193$.

Seasonally and latitude adjusted model, $n = 2193$.

[a]Odds ratio for frailty associated with vitamin D deficiency (serum vitamin D < 15ng mL^{-1}).