Final report, General Research Fund

1. **Title:** The effect of low vitamin D status and frailty on morbidity and mortality among US older adults

2. **Investigator:** Ellen Smit, Program of Epidemiology, School of Biological and Population Health Sciences

3. **Award:** GFR, Fall 2010, $9,966

4. **Summary of the hypothesis or goals and the scholarly work/activities performed using the GRF support:**

While both frailty and low vitamin D, as measured by low serum 25-hydroxyvitamin D (25(OH)D) levels, have been separately associated with an increased risk for adverse health, their independent effects on morbidity and mortality have not been reported. This research proposal aims to examine the effects of frailty and serum 25(OH)D levels on the incidence of diabetes and mortality in US adults (age ≥60 years) who participated in The Third National Health and Nutrition Examination Survey (NHANES III).

Specifically, we set out to determine:
1. The relationship between serum 25(OH)D and frailty in adults age 60 yrs and older.
2. The independent and joint effects of frailty and serum 25(OH)D levels on incidence of diabetes and all cause mortality in US adults 60 years and older.

We analyzed the NHANES data, gained access the restricted data files through the Center for Health Statistics Research Data Center, and determined the association between serum 25(OH)D and frailty (aim 1) and their joint effects on all cause mortality (aim 2). We submitted a manuscript on the relationship between serum 25(OH)D and frailty, and serum 25(OH)D, frailty and mortality, which has been accepted for publication in the European Journal of Clinical Nutrition (see attached). We further examined the Medicare enrollment and claims record data to determine feasibility of establishing the incidence of diabetes. We determined the need for additional resources to continue this effort and subsequently wrote a proposal for external funding (see item 7 below).

5. **Summary of any additional scholarly activities the GRF funding made possible for the investigator**

We were able to examine the role of dietary intake, nutritional status, and food security in frailty in older adults and have a submitted a manuscript for publication to the British Journal of Nutrition. We further explored the role of vitamin D in pre-diabetes and wrote a proposal to examine this in relation to the incidence of diabetes and mortality (see item 7 below).

6. **How and/or on what were the GRF funds expended?**
    1. Data programmer/research assistant ($3532.59): Responsibilities include: to assist with data analysis, programming in SAS and SUDAAN, manuscript writing, reference collection. Because of the specialized skills needed to do the programming for complex survey analysis and turn-over of data programmer, we were limited by their availability.

2. SAS ($50)/SUDAAN ($1060) /STATA ($395): Purchase of licenses of SAS, and SAS callable SUDAAN, and STATA for analysis of data from large complex multi-staged stratified sample design and to be able to remotely access the data at the Research Data Center (RDC) at the National Center for Health Statistics (NCHS). Without SAS/SUDAAN, access would have to be onsite at RDC in Hyattsville, MD, increasing costs significantly.

3. RDC access ($3000): NCHS-RDC fees for accessing restricted NHANES III files

7. List all external funding requests *(i.e. proposals)* that have been developed and submitted as a result of the GRF Funding.

We submitted a R21 to NIH entitled: "Vitamin D and the risk of diabetes and mortality in adults with prediabetes." The proposal was to determine the role of vitamin D deficiency in reducing the risk of diabetes and mortality in populations at high risk for diabetes i.e., Non-Hispanic Blacks (Blacks), Mexican Americans, and adults 65 years and older with pre-diabetes. Although scored, it did not receive funding and we are currently considering submission to other funding agencies.

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ORIGINAL ARTICLE

The effect of vitamin D and frailty on mortality among non-institutionalized US older adults

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BACKGROUND/OBJECTIVES: Although both frailty and low vitamin D have been separately associated with an increased risk for adverse health, their joined effects on mortality have not been reported. The current study examined prospectively the effects of frailty and vitamin D status on mortality in US older adults.

SUBJECTS/METHODS: Participants aged ⩾60 years in The Third National Health and Nutrition Examination Survey with 12 years of mortality follow-up were included in the analysis ($n = 4731$). Frailty was defined as meeting three or more criteria and pre-frailty as meeting one or two of the five frailty criteria (low body mass index (BMI), slow walking, weakness, exhaustion and low physical activity). Vitamin D status was assessed by serum 25-hydroxyvitamin D (25(OH)D) and categorized into quartiles. Analyses were adjusted for gender, race, age, smoking, education, latitude and other comorbid conditions.

RESULTS: Serum 25(OH)D concentrations were lowest in participants with frailty, intermediate in participants with pre-frailty and highest in participants without frailty. The odds of frailty in the lowest quartile of serum 25(OH)D was 1.94 times the odds in the highest quartile (95% confidence interval (CI): 1.09–3.44). Mortality was positively associated with frailty, with the risk among participants who were frail and had low serum 25(OH)D being significantly higher than those who were not frail and who had high concentrations of serum 25(OH)D (hazards ratio 2.98; 95% CI: 2.01–4.42).

CONCLUSION: Our results suggest that low serum 25(OH)D is associated with frailty, and there is additive joint effects of serum 25(OH)D and frailty on all-cause mortality in older adults.

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Keywords: vitamin D; serum 25(OH)D; frailty; mortality

INTRODUCTION

Geriatric syndromes are a loosely defined group of conditions highly prevalent in the elderly but not considered as discrete diseases; these include frailty, among others.[1] Frailty is a state of decreased physical functioning and a significant complication related with aging that increases the risk for incident falls, fractures, disability, comorbidity, health care expenditure and premature mortality.[2–4] In 2010, the proportion of US adults 65 years of age and older was 13%; however, by 2030 it is projected that about 20% of the population will be older than 65 years of age, a 54% increase. This shift in age structure will have a substantial impact on the prevalence of frailty and highlights the need for identifying clinical and population-based strategies to decrease the prevalence and consequences of frailty.[5,6]

Vitamin D assists in maintaining adequate blood calcium and phosphorous levels to maintain strong bones, regulates cell growth and differentiation, assists in immune system activity, and influences muscle phosphate metabolism.[7] Vitamin D deficiency is associated with increased risks for falls, fractures and poor physical function.[2,8–10] Several epidemiologic studies have shown muscle weakness in the elderly with vitamin D deficiency,[11,12] including lower leg extension power,[13] lower grip strength[14] and shorter walking distance.[15] In addition, cross-sectional results have shown low vitamin D status to be associated with frailty in older adults.[16,17] Other studies have shown frailty to be predictive of mortality.[18–20] Conversely the effects of frailty status with low vitamin D status with premature mortality in a diverse cohort of US adults have not been reported. Thus, the purpose of this study is to examine the independent and joint effects of frailty and vitamin D on all cause mortality in a national sample of US adults 60 years and older.

METHODS

Study participants

The study population consists of adults aged 60 years and older who took part in the Third National Health and Nutrition Examination Survey (NHANES III). Briefly, the NHANES III is a nationally representative sample of the population that used a stratified random sample of the civilian non-institutionalized population, drawn from 50 states in the United States and the District of Columbia during 1988–1994.[21] The analytic sample for this study consists of older adults (60+ years) with complete data on frailty and serum 25-hydroxyvitamin D (25(OH)D) concentrations ($n = 4731$).

Frailty

A clinical definition of the frailty phenotype has been developed by Fried *et al.*[3] for the general aging population and is widely used and validated by others.[4,22–24] The definition is based on meeting three of following five criteria: unintentional weight loss, slowness, muscle weakness, exhaustion and low physical activity. We defined frailty based on a modification of the Fried *et al.*[3,25] criteria, adhering to the five frailty domains previously

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established and applied to the NHANES III data. These are: (1) low body mass index (BMI); (2) slow walking; (3) muscular weakness; (4) exhaustion; and (5) low physical activity. Participants were classified as frail if they met three of these five criteria. Participants who met one or two of the five criteria were classified as pre-frail, and participants meeting none of the criteria were classified as not frail.

Height and weight were measured and used to calculate BMI as weight in kilograms divided by height in meters squared (kg/m^2). Low BMI was defined defined as BMI $\leqslant$18.5 kg/m^2. A timed 8-foot walk test was performed twice, and the best time for the 8-foot walk was used for each participant. A participant was classified as a slow walker if their best time for the 8-foot walk was within the slowest quintile adjusted for sex. Participants were asked whether they had no difficulty, some difficulty, much difficulty or were unable to lift or carry something as heavy as 10 pounds (like a sack of potatoes or rice) at all when they were by themselves and without the use of aids. Participants who responded to this question as having some or much difficulty or unable to lift or carry that amount were classified as experiencing muscular weakness. Participants were also asked whether they had no difficulty, some difficulty and much difficulty or were unable to walk from one room to another on the same level. Participants who responded to this question as having some or much difficulty or unable to walk form room to room were classified as experiencing exhaustion. Low physical activity, defined as considering themselves as less active when compared with most (men/women) of the same age.

Vitamin D

Vitamin D is metabolized in the liver and extrarenal tissues to 25(OH)D and converted in the kidneys to the active form 1,25-dihydroxyvitamin D ($1,25(OH)_2D$). Concentrations of serum 25(OH)D are a good indicator of vitamin D status.[26] Measurement of 25(OH)D was done during the mobile examination center visit on all participants over 12 years of age. A radioimmunoassay (RIA) kit (Diosorin, formerly INCSTAR, Stillwater, MN, USA) was used at the National Center for Environmental Health, Centers for Disease Control and Prevention (Atlanta, GA, USA). The 25(OH)D assay consisted of a two-step procedure. The first procedure involved a rapid extraction of 25(OH)D and other hydroxylated metabolites from serum or plasma with acetonitrile. Following extraction, the treated sample was assayed by using an equilibrium RIA procedure. The RIA method is based on an antibody with specificity to 25(OH)D. The sample, antibody and tracer are incubated for 90 min at 20–25 °C. Phase separation is accomplished after a 20-min incubation at 20–25 °C with a second antibody-precipitating complex, as previously described.[21] The coefficient of variation for the 25(OH)D assay was evaluated on pooled quality control samples and in duplicate for each batch. The coefficient of variation ranged from 10 to 25% for lower values (20–62.5 nmol/l)) and from 12 to 18% for higher values (85–147.5 nmol/l).[27]

Serum 25(OH)D was treated as continuous and categorized into four quartiles ($<$49.5, 49.5–66.4, 66.5–84.1 and $>$84.1 nmol/l). The cutoffs of the quartiles are in line with published cutoffs for serum 25(OH)D,[28–32] with quartile 1 reflecting low concentrations and quartile 4 reflecting sufficient concentrations.

Mortality

The NHANES III Linked Mortality File contains information based on the results from a probabilistic match between NHANES III participants aged 17 years and older and National Death Index (NDI) death certificate records. The NDI is a central computerized database of all certified deaths in the United States since 1979. The NDI system matches death records based on seven established matching criteria: (1) Social Security Number; (2) first and last name, exact month of birth and year of birth within 1 year; (3) last name, first initial and middle initial, exact month of birth and year of birth within 1 year; (4) first and last name, exact month of birth and exact day of birth; (5) last name, first initial and middle initial, exact month of birth and exact day of birth; (6) first name, father's surname, exact month of birth and exact year of birth; and (7) for females only, first name, exact month and year of birth and last name from the user's record matching birth surname on the NDI record (for females who change their name after marriage, but do not supply a birth surname). For each match, a score is assigned based on probabilistic weights allocated to the identifying information linking NHANES III and NDI records. A match was deemed true or false based on pre-set cutoff scores.[33] The NHANES III Linked Mortality File provides mortality follow-up data from the date of NHANES III survey participation (1988–1994) through December 31, 2006.

Covariates

Self-reported race and ethnicity were used to classify participants as non-Hispanic white, non-Hispanic black or Mexican American (that is, persons of Mexican origin living in the United States). Age was defined as the age in years at the time of the household interview. Education was based on number of years the participant attended and completed school, and coded as less than high school, high school and more than high school. During the medical examination, height was measured using a stadiometer and weight was measured on a balance beam scale. Height and weight data were then used to calculate BMI (weight (kg) divided by the square of height (m)). BMI was categorized into underweight (BMI $<$18.5 kg/m^2), normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI 25–29.9 kg/m^2) and obese (BMI $\geqslant$30 kg/m^2). Smoking history was assessed during the interview and classified into current, former or never smokers. NHANES examinations are performed in southern latitudes during the winter months and northern latitudes during the summer months. Latitude and month of blood draw have been shown to influence serum 25(OH)D levels.[27] To evaluate the potential impact of latitude and month of blood collection on serum 25(OH)D we gained access to these variables from the restricted access data sets through the Research Data Center at the National Center for Health Statistics. Latitude and month of blood draw were subsequently evaluated as potential confounders in the analysis. An index of chronic diseases related to physical function was created as the sum of affirmative responses to the following physician diagnosed self-reported chronic conditions: asthma, stroke, congestive heart failure, emphysema, heart attack, limp, scoliosis, rheumatoid arthritis, dysplasia, osteoporosis, cancer, back pain, diabetes and angina. The chronic disease index was categorized as none, 1, 2 and 3 or more chronic diseases.

Analysis

Total and adjusted means, variances and prevalences were calculated using multivariate linear and logistic regression models. Sample weights, provided by the National Center for Health Statistics, were used to correct for differential selection probabilities and to adjust for non-coverage and non-response. Logistic regression models with frailty as the outcome were used to obtain adjusted odds ratios. Potential confounding variables were evaluated for use in multivariate models, and the following variables were included in final multivariate models: age, BMI, race–ethnicity, gender, smoking, education, chronic disease index and latitude. For trend tests, a continuous variable was created by assigning each participant the median value for the category in which they belonged and modeling this to evaluate its significance. Multivariate proportional hazards models were used to assess the association between frailty and mortality stratified by serum 25(OH)D quartiles. The joint effect of frailty (frail, not frail) and serum 25(OH)D (quartile 1 and quartile 4) on mortality was examined by entering into the model terms for the combination of the two variables; the reference category was not frail and quartile 4 of serum 25(OH)D. Multiplicative interaction was tested by including a cross-product term for frailty and serum 25(OH)D along with the main effect terms for each in the regression model, and using the Wald statistic to calculate the *P*-value. Additive interaction was tested by calculating the attributable portion (AP) due to interaction and the relative excess risk due to additive interaction (RERI) using the methods described by Andersson *et al.*[34] Statistical significance was evaluated with 95% confidence intervals (CIs) with AP and RERI $>$0 indicating additive interaction. All analyses were completed using SUDAAN (Release 9.01, Research Triangle Institute, Durham, NC, USA).

RESULTS

Cross-sectional results

Among adult participants aged 60 years and older in NHANES III, 9.6% were frail, 40.5% were pre-frail and 50% were not frail. A description of the characteristics of the population by frailty status is shown in Table 1. Frail participants tended to be older, female non-white and less educated than participants who were not frail. Frail participants were also more likely to be current smokers, obese and diagnosed with chronic diseases than participants who were not frail. Serum 25(OH)D concentrations were lowest in frail participants, intermediate in pre-frail participants and highest in participants who were not frail.

The prevalences of the five frailty criteria are shown in Table 2. The most common criterion in frail participants was muscle

Table 1. Characteristics of adult participants (⩾60 years) in NHANES III according to frailty status[a,b]

	Frail (n = *453*)	*Pre-frail* (n = *1915*)	*Not frail* (n = *2363*)
Age (years)[c1]	73.6 ± 0.6	72.0 ± 0.4	69.4 ± 0.3
Gender[c2]			
Male	31.2	36.8	46.5
Female	68.9	63.2	53.5
Race–ethnicity[c,c2]			
White	72.1	81.0	87.8
Black	16.8	10.7	6.0
Mexican	4.4	2.9	1.7
Other	6.7	5.4	4.5
Education[c3]			
Less than HS	65.7	46.3	35.5
HS	22.0	30.2	31.7
More than HS	11.0	22.7	32.6
Smoking[c3]			
Never	49.7	46.1	43.1
Past smoker	31.6	36.0	43.6
Current smoker	18.8	17.9	13.3
BMI[c2]			
Underweight	8.4	4.7	0
Normal weight	24.8	35.2	36.2
Overweight	29.2	34.5	42.3
Obese	37.6	25.7	21.5
Chronic disease index[d,c2]	94.6	77.6	63.8
None	6.1	19.7	33.4
One chronic disease	15.0	24.4	29.8
Two chronic diseases	21.8	22.4	19.0
Three or more chronic diseases	57.2	33.5	17.9
Serum 25(OH)D (nmol/l)[c1]	60.4 ± 2.3	65.6 ± 1.1	71.9 ± 0.9

Abbreviations: BMI, body mass index; HS, high school; NHANES III, Third National Health and Nutrition Examination Survey; 25(OH)D, 25-hydroxyvitamin D. Data are denoted as mean ± s.e.m. or percentage (%). *P*-values were obtained using *t*-tests for continuous variables and Wald χ^2-tests for categorical variables: [c1]$P = 0.001$; [c2]$P < 0.00001$; and [c3]$P = 0.0036$. [a]Paticipants were defined as frail, they met three of the following five criteria: (1) low BMI, defined as BMI ⩽18.5 kg/m^2; (2) slow walking, defined as the slowest quintile adjusted for sex, in a timed 8-foot walk; (3) muscular weakness, defined as having some or much difficulty or unable to lift or carry something as heavy as 10 pounds; (4) exhaustion, defined as some or much difficulty, or unable to walk from one room to the other on the same level; and (5) low physical activity, defined as considering themselves as less active when compared with most (men/women) of the same age. Participants who met one or two of the above five criteria were classified as pre-frail and participants meeting none of the criteria were classified as not frail. [b]Weighted estimates. [c]White = non-Hispanic white; black = non-Hispanic black; Mexican = Mexican American; Other = other race–ethnic groups. [d]Sum of the following reported chronic diseases: asthma, stroke, congestive heart failure, emphysema, heart attack, limp, scoliosis, rheumatoid arthritis, dysplasia, osteoporosis, cancer, back pain, diabetes and angina.

weakness, followed by slow walking, low physical activity and exhaustion. Common criteria in pre-frail participants were muscle weakness, slow walking and low physical activity.

Participants with low concentrations of serum 25(OH)D (quartile 1) were more likely to be frail (odds ratio 1.67, 95% CI: 1.00–2.82) and pre-frail (odds ratio 1.54, 95% CI: 1.10–2.15) compared with participants with higher concentrations of serum 25(OH)D (quartile 4) (Table 3).

Table 2. Prevalence (%) of each of the criterion of frailty in adult participants (⩾60 years) in NHANES III according to frailty status

	Frail	*Pre-frail*	*Not frail*
Low BMI[a]	8.5	5.0	0
Slow walking[b]	89.5	41.9	0
Muscle weakness[c]	97.7	44.6	0
Exhaustion[d]	63.4	4.2	0
Low physical activity[e]	77.9	31.8	0

Abbreviations: BMI, body mass index; NHANES III, Third National Health and Nutrition Examination Survey. [a]BMI ⩽18.5 kg/m^2. [b]Slowest quintile adjusted for sex, in a timed 8-foot walk. [c]Having some or much difficulty or unable to lift or carry something as heavy as 10 pounds. [d]Having some or much difficulty, or unable to walk from one room to the other on the same level. [e]Considering themselves as less active when compared with most (men/women) of the same age.

Longitudinal results

The median follow-up time for mortality was 12.6 years. The multivariate hazards ratio (HR) for all cause mortality was 1.27 (95% CI: 1.09–1.47) for participants with serum 25(OH)D concentrations in quartile one, 1.10 (95% CI: 0.93–1.30) for quartile 2 and 1.04 (95% CI: 0.85–1.26) for quartile 3 compared with quartile 4. The HRs for frail and pre-frail participants are provided in Table 4 and show that both frail and pre-frail participants are at increased risk for death than participants who were not frail. Table 4 also displays the results of the joint effect of frailty and serum 25(OH)D on mortality based on the combination of the two variables with the reference category being not frail and quartile 4 of serum 25(OH)D. The risk of death for participants who were not frail but had low serum 25(OH)D concentrations was not significantly higher (HR 1.25, 95% CI: 0.97–1.60) compared with participants with no frailty and high concentrations of serum 25(OH)D. Similarly, the risk of death for participants who had high serum 25(OH)D concentrations but who were frail was not significantly higher (HR 1.43, 95% CI: 0.83–2.46) than participants with no frailty and high concentrations of serum 25(OH)D. However, the risk of death among participants who were frail and had low serum 25(OH)D was significantly higher than among participants who were not frail and who had high concentrations of serum 25(OH)D was 2.98 (95% CI: 2.01–4.42). Among pre-frail participants the increased risk of death was similar between quartiles of serum 25(OH)D. The cross-product term for serum 25(OH)D and frailty to evaluate multiplicative interaction was not significant when added to the final model along with the main effect terms ($P = 0.18$). The RERI comparing participants who were frail and had low serum 25(OH)D to participants who were not frail and had high serum (25(OH)D was 1.16 (95% CI: 0.07–2.25) and the AP was 0.46 (95% CI: 0.13–0.79) indicating presence of additive interaction (that is, RERI and AP > 0).

DISCUSSION

Among US adults ages 60 years and older, close to 1 in 10 were frail and the prevalence of pre-frailty was a high 40.5% in 1988–1994. The most common symptoms of frailty included muscle weakness, slow walking, exhaustion and low physical activity. Among pre-frail older adults the most common frailty indicators were muscle weakness, slow walking and low physical activity. It is noteworthy that exhaustion was reported only by 4% of pre-frail older adults, but among frail older adults it was reported by 63.4%. Boxer *et al.*[35] also found exhaustion and weight loss to be less consistently correlated with frailty than other measures of physical function such as muscular strength, physical activity and walk time. Frail participants were also more likely to report a larger percent of chronic conditions related to physical functioning. Given the aging US population, the close to 1

Table 3. Odds ratios (95% confidence intervals)[a] of frailty and pre-frailty by quartile of serum 25(OH)D concentrations in adult participants (⩾60 years) in NHANES III

	Quartile 1, <49.5 nmol/l	*Quartile 2, 49.5–66.4 nmol/l*	*Quartile 3, 66.5–84.1 nmol/l*	*Quartile 4, >84.1 nmol/l*	P *for trend*
Pre-frail	1.54 (1.10–2.15)	1.17 (0.88–1.55)	1.34 (1.02–1.76)	1.0	0.01
Frail	1.67 (1.00–2.82)	1.18 (0.72–1.95)	1.07 (0.49–2.32)	1.0	0.02

Abbreviations: NHANES III, Third National Health and Nutrition Examination Survey; 25(OH)D, 25-hydroxyvitamin D. [a]Adjusted for age, BMI, race–ethnicity, gender, smoking, education, chronic diseases index and latitude.

Table 4. Hazards ratios (95% confidence intervals) of mortality comparing frail and pre-frail to not frail participants in adult participants (⩾60 years) in NHANES III

	Frail	*Pre-frail*	*Not frail*
Overall model[a]	2.19 (1.78–2.70)	1.59 (1.43–1.77)	1.0
	Joined effect of frailty and serum 25(OH)D on mortality[b]		
	Frail[c]	*Pre-frail*[d]	*Not frail*[e]
Quartile 1 (<49.5 nmol/l)	2.98 (2.01–4.42)	1.97 (1.61–2.40)	1.25 (0.97–1.60)
Quartile 2 (49.5–66.4 nmol/l)	2.37 (1.44–3.89)	1.62 (1.29–2.03)	1.20 (0.96–1.49)
Quartile 3 (66.5–84.1 nmol/l)	2.50 (1.48–4.21)	1.51 (1.16–1.97)	1.11 (0.88–1.40)
Quartile 4 (>84.1 nmol/l)	1.43 (0.83–2.46)	1.82 (1.41–2.35)	1.0

Abbreviations: NHANES III, Third National Health and Nutrition Examination Survey; serum 25(OH)D, serum 25-hydroxyvitamin D. [a]Overall model: dependent = mortality, independent = frailty, adjusted for [b]. [b]Adjusted for age, BMI, race–ethnicity, gender, smoking, education, chronic diseases index and latitude. [c]Unweighted sample sizes: quartiles 1–4: 171, 91, 60 and 51, respectively. [d]Unweighted sample sizes: quartiles 1–4: 597, 471, 376 and 303, respectively. [e]Unweighted sample sizes: quartiles 1–4: 561, 606, 534 and 579, respectively.

in 2 older adults with frail or pre-frail symptoms is of great public health concern with the potential to impact health care delivery and independent living.

Similar to the findings by Wilhelm-Leen *et al.*,[16] the cross-sectional results showed that participants with low serum 25(OH)D concentrations were 1.7 times more likely to be frail and 1.5 times more likely to be pre-frail, indicating a strong association between frailty and serum 25(OH)D. Given that the data are cross-sectional it can not be determined if low serum 25(OH)D contributes to the development of frailty or if frailty results in low serum 25(OH)D. For example, low physical activity may result in lower sun exposure and a lower serum 25(OH)D. Nonetheless, several mechanisms by which low vitamin D contributes to frailty have been proposed. Vitamin D metabolites can affect muscle metabolism by mediating gene transcription, via rapid pathways not involving DNA, and via allelic polymorphisms of the vitamin D receptor found in the muscle.[36] Inflammatory measures have also been linked to frailty. A higher frailty phenotype score was associated with higher high-sensitivity C-reactive protein, Interleukin-6 and lower serum 25(OH)D concentrations in congestive heart failure patients.[35] There is clear evidence for a role of vitamin D in bone health, while the role of vitamin D on falls or physical performance is less.[32,37–39] Several studies on vitamin D supplementation and criteria of frailty have shown mixed results.[40,41] A supplementation trial of deficient elderly women showed improvement in knee extension strength and walking distance.[40] Supplementation with vitamin D when replete did not improve knee extension strength, however.[41]

The longitudinal results presented here examine the potential joint effect of low serum 25(OH)D concentrations and frailty at baseline on mortality in older adults after 12.6 years of follow-up. Although all frail participants were at greater risk of death than participants who were not frail at baseline, the data suggest that participants who were frail and had low serum 25(OH)D concentrations were at greater risk of death than participants who were frail and had higher concentrations of serum 25(OH)D. In fact, the risk of death among frail older adults was somewhat higher, though not significantly, than older adults who were not frail among those with high concentrations of serum 25(OH)D (quartile 4). In addition, participants who were frail and who had low serum 25(OH)D concentrations were at a much greater risk of death than participants who were not frail and who had higher concentrations of serum 25(OH)D. Although this joint effect was not significant on the multiplicative level, the results do show additive joint effects of low serum 25(OH)D and frailty on mortality. This suggests that serum 25(OH)D status may be especially important among frail older adults for the prevention of premature mortality. The effect modification was not evident for older adults who were pre-frail with the risk being similarly elevated in all quartiles of serum 25(OH)D.

Strengths of our study include serum 25(OH)D and frailty measures on a representative sample of the civilian, non-institutionalized older US adults, detailed data on important covariates and a 12.6-year follow-up for mortality. Limitations include that the definition of frailty was based on a modification of the Fried *et al.*[3] criteria to fit the available NHANES data, including a low BMI in place of unintentional weight loss. However, this definition is consistent with the definition of frailty applied to the NHANES III data by others and adhered to the original five frailty domains.[3,25] Because of potential effect of extreme temperature variations to the mobile examination center and its impact on instrument sensitivity and response rate, the interviews and examinations were conducted in the southern states in winter months and northern states in the summer months. Thus, low serum 25(OH)D may be more prevalent in winter months for the northern states, suggesting the conservative nature of these estimates. Using quartiles of serum 25(OH)D, rather than a specific cutoff, and evaluating latitude and month of blood draw limits the impact on the risk estimates.

In conclusion, results suggest that among older US adults, low vitamin D is associated with frailty, and there is additive interaction between low vitamin D and frailty on all cause mortality. This highlights the importance of assessing vitamin D status among older adults. More research is needed on the potential effect that vitamin D supplementation may have on

improving frailty and mortality. Also, additional research is needed to investigate how improvement in physical fitness in older adults through physical training may be combined with nutritional interventions that target optimization of serum 25(OH)D concentrations thereby potentially reducing frailty and premature mortality.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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