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The Association of Vitamin D Deficiency and Incident Frailty in Older Women: The Role of Cardiometabolic Diseases

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Abstract

OBJECTIVES—Evidence suggests vitamin D deficiency is associated with developing frailty.

However, cardiometabolic factors are related to both conditions and may confound and/or mediate the vitamin D—frailty association. We aimed to determine the association of vitamin D

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concentration with incidence of frailty, and the role of cardiometabolic diseases (cardiovascular disease, diabetes, hyperlipidemia, hypertension) in this relationship.

DESIGN—Prospective longitudinal cohort study (seven visits from 1994–2008).

SETTING—Baltimore, Maryland.

PARTICIPANTS—Three hundred sixty-nine women from Women's Health and Aging Study II aged 70–79 years, free of frailty at baseline.

MEASUREMENTS—Serum circulating 25-hydroxyvitamin D [25(OH)D] concentration was assessed at baseline and categorized as: <10; 10–19.9; 20–29.9; and ≥30 ng/mL. Frailty incidence was determined based on presence of three or more criteria: weight loss, low physical activity, exhaustion, weakness, slowness. Cardiometabolic diseases were ascertained at baseline. Analyses included Cox regression models adjusted for key covariates.

RESULTS—Incidence rate of frailty was 32.2 per 1,000 person-years in participants with 25(OH)D<10 ng/mL, compared to 12.9 per 1000 person-years in those with 25(OH)D ≥30 ng/mL (mean follow-up=8.5±3.7 years). In cumulative incidence analyses, those with lower 25(OH)D exhibited higher frailty incidence, though differences were non-significant (p=0.057). In regression models adjusted for demographics, smoking, and season, 25(OH)D<10 ng/mL (vs ≥30 ng/mL) was associated with nearly three-times greater frailty incidence (hazard ratio (HR)=2.77, 95% CI=1.14,6.71, p=0.02). After adjusting for BMI, the relationship of 25(OH)D <10 ng/mL (vs ≥30 ng/mL) with incident frailty persisted, but was attenuated after further accounting for cardiometabolic diseases (HR=2.29, 95% CI=0.92,5.69, p=0.07).

CONCLUSION—Low serum vitamin D concentration is associated with incident frailty in older women; interestingly, the relationship is no longer significant after accounting for the presence of cardiometabolic diseases. Future studies should explore mechanisms to explain this relationship.

Keywords

aging; vitamin D; frailty; cardiometabolic diseases

INTRODUCTION

Vitamin D deficiency, or a low concentration of serum circulating 25-hydroxyvitamin D [25(OH)D], can result from insufficient sunlight exposure, inadequate skin absorption of sunlight, and inadequate diet.¹ Almost half of U.S. community-dwelling adults ages 65 years and older are estimated to have 25(OH)D concentrations <20 ng/mL.² The associations of vitamin D deficiency with bone diseases and poor muscle function have been well described,^{3,4} but its relationship to syndromes such as frailty is not fully understood.

Frailty has been described as a state of increased vulnerability to develop adverse health outcomes when encountering a stressor.^{5,6} Frailty is more prevalent among older adults with low vitamin D levels when compared to those with higher levels.^{7,8} However, moderate but non-significant associations between 25(OH)D concentration and incident frailty among older women have been found,^{9,10} and studies with both genders have reported mixed results.^{11,12} Inconsistent findings may be due to methodological differences (e.g., length of

follow-up, visit intervals, and operational definitions used), demographic characteristics of different study populations, and/or a lack of consistent accounting for the presence of important factors such as cardiometabolic diseases.

Meta-analyses have demonstrated an association between vitamin D levels and cardiometabolic factors, though mostly cross-sectional.¹³ Cardiometabolic diseases are also associated with the development of frailty in older adults.^{14,15} The role of cardiometabolic diseases as a contributing factor to the relationship between vitamin D deficiency and incident frailty has not been explored and may provide insight into this relationship.

We sought to examine the association of serum vitamin D concentrations with the incidence of frailty, accounting for the presence of cardiometabolic diseases at baseline. Our hypotheses were: 1) low 25(OH)D is associated with incident frailty; and 2) the relationship of vitamin D with incident frailty may be potentially confounded and/or mediated by cardiometabolic diseases. We performed analyses in a cohort of community-dwelling older women with follow-up over many years and validated measures of vitamin D and frailty.

METHODS

Subjects

The Women's Health and Aging Study II (WHAS II) is an observational cohort study that followed women aged 70 to 79 years at baseline who represented the two-thirds least disabled community-dwelling women.¹⁶ WHAS II enrolled 436 baseline participants and conducted seven scheduled study assessment visits from 1994 to 2008, which occurred at regular 18-month intervals, except for a three-year interval between visits 3 and 4. Of these, 417 participants were frailty-free at baseline (visit 1) and had at least one blood draw; we excluded others from consideration. We further excluded participants based on: incident frailty before or at first blood draw (n=6), no study follow-up beyond baseline (n = 24), not African American or Caucasian race (n=1); missing smoking status (n=1); and missing vitamin D data measure (n = 16). These exclusions left 369 participants available for the present analysis. Among these 369 frailty-free participants, 343 (93%) had their first blood draw at visit 1; 24 (6.5%) had their first blood draw at visit 2; and 2 (0.5%) had their first blood draw at visit 3.

Vitamin D Assessment

Serum 25-hydroxyvitamin D (25[OH]D) was measured using a radioreceptor assay (Nichols Institute Diagnostics, San Juan Capistrano, CA) with interassay and intrassay coefficients of variation <10% similar to methods previously described.¹⁷

Frailty Assessment

Frailty was defined as presence of at least three of five criteria: weight loss (body mass index (BMI) <18.5 kg/m² or 10% weight loss since age 60), weakness (measured grip strength), exhaustion (self-reported), slowness (measured walking speed), and low physical activity (self-reported).^{5,18} Participants who had no criteria were categorized as nonfrail, and with one or two criteria as prefrail. We excluded frail participants at baseline. At follow-up visits,

we examined those who became frail versus a combined group of those who remained non- and pre-frail.

Other Covariates and Cardiometabolic Measures

Demographic information and season of blood collection were obtained using a standardized questionnaire. Height and weight were measured to calculate BMI. Smoking status was categorized as either non-smoker, former smoker, or current smoker.

Cardiometabolic diseases included a set of four common cardiovascular and metabolic diseases: cardiovascular disease (CVD) and diabetes mellitus (DM), hypertension, and hyperlipidemia similar to previous studies.¹⁹ The presence of a history of CVD (angina pectoris, myocardial infarction, or congestive heart failure) was ascertained at baseline.²⁰ Diabetes was defined based on self-reported history and/or use of glucose-lowering medication. Hyperlipidemia was defined as total cholesterol ≥ 200 mg/dl or use of lipid-lowering medications. Hypertension was defined as self-reported history, use of anti-hypertension medication, systolic blood pressure ≥ 140 mmHg, and/or diastolic blood pressure ≥ 90 mmHg.

Statistical Analysis

We classified serum circulating 25(OH)D levels as follows: <10 ng/mL (severely deficient); $10\text{--}19.9$ ng/mL (deficient); $20\text{--}29.9$ ng/mL (insufficient); and ≥ 30 ng/mL (sufficient).¹ Baseline participant characteristics were compared across vitamin D categories using analysis of variance for continuous variables and chi-square tests for categorical variables. Cumulative incidence for frailty, treating frailty-free mortality (i.e., death before observation of frailty onset) as a competing risk, was estimated using the R CMPRSK package and compared using the method of Gray.²¹ Time to development of frailty was subject to left truncation. Subjects who had not developed frailty by the end of the study follow-up were subsequently censored. A likelihood ratio test was performed to evaluate the global null hypothesis of equal hazard across the vitamin D categories for the outcome of frailty. We analyzed the association between categories of serum vitamin D concentration at baseline and frailty outcomes using Cox regression models (comparing lower categories of vitamin D to vitamin D ≥ 30 ng/mL as the reference) as follows: Model A was unadjusted; Model B adjusted for age, race, education, season of blood collection, and smoking; Model C adjusted for variables in model B and BMI; Model D adjusted for variables in Model C and cardiometabolic diseases (CVD, DM, hyperlipidemia, and hypertension).

A sensitivity analysis was performed by adding hemoglobin A1c (HbA1c) $\geq 6.5\%$ to Model D. This cutoff accounts for those with undiagnosed diabetes.²² A second sensitivity analysis was performed to explore the interaction of prefrailty status and vitamin D level at baseline on the incidence of frailty. Another sensitivity analysis was performed to explore the potential mediating role of inflammation by adding interleukin (IL)-6 to Model D.

The statistical program used was R (Version 3.2.3 GUI 1.66 Mavericks build).²³ A two-tailed p-value of <0.05 was considered statistically significant.

RESULTS

Across vitamin D categories at baseline, the 369 frailty-free women were similar with respect to age, education, and smoking status (Table 1). At baseline, a greater proportion of African American women were in the lowest vitamin D group than in other vitamin D categories ($p = 0.001$). Significant differences were also found across the vitamin D groups for season of blood collection ($p=0.003$) and continuous BMI ($p = 0.001$). However, interestingly, there were no significant differences across vitamin D groups for CVD, DM, hyperlipidemia or hypertension.

Eighty-eight of 369 women (23.8%) developed frailty during a mean follow-up of 8.5 ± 3.7 years. The mean number of visits was 5.3 ± 1.8 . The overall incidence rate for frailty during follow-up was 18.1 per 1,000 person-years. Among women with $25(\text{OH})\text{D} < 10\text{ng/mL}$, the incidence rate of frailty was 32.2 per 1,000 person-years, compared to 12.9 per 1,000 person-years in those with $25(\text{OH})\text{D} \geq 30\text{ng/mL}$. The frailty incidence rate was 21.3 per 1,000 person-years in those with $25(\text{OH})\text{D} 10\text{--}19.9\text{ng/mL}$, and 15.1 per 1,000 person-years among those with $25(\text{OH})\text{D} 20\text{--}29.9\text{ng/mL}$. In competing risks analyses (Figure 1), cumulative incidence of frailty across categories of serum vitamin D was heightened among those with vitamin D deficiency ($p\text{-value}=0.057$). Results of the likelihood ratio test for the global effect of vitamin D suggested reasonably equal hazard in all vitamin D categories with a trend toward significance (Model A:0.04, Model B:0.12, Model C:0.17, Model D:0.23).

The association between low $25(\text{OH})\text{D}$ and incident frailty was further investigated in Cox regression models (Table 2). The crude hazard ratio for the low ($<10\text{ng/mL}$) versus the reference ($\geq 30\text{ng/mL}$) vitamin D category was 3.06 (95% CI=1.32,7.08, $p=0.009$; Model A). Adjusting for demographics, smoking, and season of blood draw, those with severely deficient $25(\text{OH})\text{D} < 10\text{ng/mL}$ (vs those with sufficient concentration $\geq 30\text{ng/mL}$) were significantly associated with nearly three-times greater risk of incident frailty ($p = 0.02$; Model B). Further adjusting for BMI, the association remained significant ($p = 0.04$; Model C). However, in a fully-adjusted model also accounting for the presence of CVD, DM, hyperlipidemia, and hypertension, serum $25(\text{OH})\text{D}$ concentration $< 10\text{ng/mL}$ (vs $\geq 30\text{ng/mL}$) remained associated with incident frailty, but statistical significance was attenuated ($p=0.07$; Model D).

In a sensitivity analysis, no significant interaction of vitamin D and prefrailty on the outcome of frailty was found ($p=0.36$). In an additional sensitivity analysis that further adjusted for HbA1c $\geq 6.5\%$ ($n=323$ with HbA1c available) in the fully adjusted model (Model D), $25(\text{OH})\text{D} < 10\text{ng/mL}$ (vs $\geq 30\text{ng/mL}$) was associated with incident frailty, but this relationship was attenuated and not statistically significant (HR=1.86, 95% CI=0.67,5.16, $p=0.23$). After adjustment for IL-6 ($n=334$) in a sensitivity analysis, the relationship of $25(\text{OH})\text{D} < 10\text{ng/mL}$ (vs $\geq 30\text{ng/mL}$) with incident frailty was attenuated and not statistically significant (HR=1.67, 95% CI=0.59,4.75, $p=0.34$).

There was no statistically significant association for deficient (10–19ng/mL) or insufficient (20–29.9ng/mL) vitamin D levels with incident frailty compared to sufficient levels in regression models.

DISCUSSION

Our study found that women in the lowest category of serum vitamin D concentration (25(OH)D level of <10ng/mL) had a three-fold increased risk of developing frailty up to a decade or more later after adjustment for demographics, smoking, and season of blood collection when compared to those in the highest category (≥30ng/mL). However, the association between severe vitamin D deficiency and incident frailty was attenuated such that it was no longer significant after accounting for the presence of cardiometabolic diseases.

The association between hypovitaminosis D and incident frailty in older U.S. women has been reported as modest but statistically non-significant in previous studies of shorter duration (<5 years) with no or limited adjustment for cardiometabolic diseases.^{9,10} In comparison, our study followed healthy, community-dwelling older women up to 8.5 years or more, and reported a significant association of 25(OH)D <10 ng/mL with incident frailty over this relatively longer follow-up. Furthermore, in our study, this relationship was no longer significant after adjusting for cardiometabolic diseases -- a finding consistent with previous studies that have demonstrated associations of cardiometabolic factors with both vitamin D deficiency¹³ and with frailty.^{14,15} Inconsistent findings have been reported in studies with mixed sex populations.^{11,12}

Measurement issues may also factor into these reported differences. Our categorization of vitamin D was based on the recommendations of The Endocrine Society¹; previous studies have selected other Vitamin D deficiency cut-points, likely due to differing consensus guidelines.^{1,24} Here, we separated 25(OH)D 20–29.9ng/mL from 10–19.9ng/mL and <10ng/mL in order to examine the association across the continuum, and a significant association between low 25(OH)D and incident frailty was only found at very low levels (<10ng/mL). Another methodological consideration is the determination of frailty, which may vary greatly depending on which instrument is used.²⁵ Our study used the most common assessment instrument, the frailty phenotype, which has been well-validated.²⁵ Two previous studies among older women have also used the frailty phenotype.^{9,10} Additionally, our study and the previous ones may have had differential power to detect associations.

In addition to the presence of cardiometabolic diseases, the association between low vitamin D and incident frailty may be due to several factors. Previously reported associations of low vitamin D on muscle function provide a potential mechanistic link to the clinical manifestation of frailty.⁴ The active vitamin D₃ metabolite plays a role in regulating mitochondrial function in skeletal muscle cells and may be related to frailty development.^{26,27} Elevated glucose levels, independent of history of diabetes, may also contribute to the relationship of vitamin D and incident frailty.²² Additionally, studies have found an inverse relationship between vitamin D and inflammatory markers,²⁸ which in turn have been linked to both muscle function and frailty.²⁹ Indeed, the results of our sensitivity analyses suggest a potential mediating role of inflammation in the relationship of vitamin D and incident frailty.

Strengths of the current study include the well-characterized cohort and the use of standardized protocols and a validated frailty assessment instrument. We assessed temporal relationships using longitudinal analyses, accounting for potential covariates. WHAS II had a large sample size and a greater length of follow-up than some previous studies.¹⁶ We uniquely explored whether cardiometabolic diseases contributed to the relationship between vitamin D and frailty incidence compared to previous studies. We accounted for BMI as a measure of adiposity since cut-points for obesity may be different in an older population.³⁰ We employed competing risks analysis to generate a cumulative incidence plot; the more commonly used Kaplan Meier plot does not account for mortality as a competing risk for frail older adults. We also performed multiple sensitivity analyses to explore potential mediators of the relationship of vitamin D deficiency with incident frailty.

Study limitations include the relatively smaller number of participants in the lowest vitamin D category (<10 ng/mL) compared to other categories. Our study was in community-dwelling women and may not be generalizable to other populations. Vitamin D levels were explored at baseline only, though changes in vitamin D levels or initiation of vitamin D supplementation during over time may contribute to frailty status and should be further explored. Our study used self-reported history as part of the definitions for cardiometabolic diseases, and may not have been able to fully account for untreated cardiometabolic disease, which could have led to potential misclassification or residual confounding. The presence of cardiometabolic diseases may have contributed to vitamin D deficiency since both were ascertained at baseline; thus, reverse causation is possible and should be investigated further. Vitamin D levels were not available at visit 1 for a few participants and their levels may have been different if collected at baseline. We adjusted for cardiometabolic diseases as a confounder in our regression models, but given limited evidence to date, it is possible that cardiometabolic diseases could represent a confounder and/or a mediator of the vitamin D—incident frailty relationship. Formal mediation analysis may be useful in a future study, especially given the attenuation of the vitamin D—frailty relationship in our cardiometabolic regression model. Additionally, this relationship is complex and may be impacted by the effects of standard treatments for the cardiometabolic diseases studied.

Our study adds to growing evidence of the relationship between vitamin D levels and the development of frailty. It extends previous findings by demonstrating that this relationship is no longer significant after accounting for the presence of cardiometabolic diseases in older women, suggesting that these diseases may contribute to the association of vitamin D with incident frailty. Serum circulating vitamin D may partially predict frailty onset and could represent a practical biomarker for the identification of individuals at high risk for the development of frailty and other adverse outcomes. Future studies investigating the pathogenesis of frailty can better elucidate whether vitamin D may be a driving factor or a marker of frailty. Well-designed intervention studies are ultimately required to investigate whether treatment of hypovitaminosis D may delay or prevent the development of frailty in older adults and can further inform the management of vitamin D deficiency.

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Figure 1.

Cumulative incidence curves for frailty according to baseline levels of 25-hydroxyvitamin D among 369 women who were not frail at baseline. Women's Health and Aging Study II, 1994–2008. The figure shows stepwise associations between lower levels of vitamin D and greater cumulative frailty incidence (p-value of the log-rank test = 0.057).

Table 1

Baseline Characteristics of Study Participants in WHAS II by Vitamin D Category*

Characteristic	Total	<10	10–19.9	20–29.9	30	p-value**
<i>n</i>	369	28	135	141	65	
<i>Demographics</i>						
Age (years)	73.8 ± 2.8	73.7 ± 3.0	73.7 ± 2.7	73.9 ± 2.8	73.7 ± 2.7	0.95
White race (%)	83.2	60.7	74.8	90.8	93.9	<0.001
High school education (%)	74.8	78.6	74.1	70.2	84.6	0.14
<i>Smoking (%)</i>						
Non-smoker	56.6	53.6	57.0	58.9	52.3	0.33
Former smoker	34.4	32.1	31.9	32.6	44.6	
Current smoker	8.9	14.3	11.1	8.5	3.1	
<i>Season of vitamin D blood collection (%)</i>						
February–April	24.9	17.9	25.2	27.7	21.5	0.003
May–July	20.9	7.1	14.8	25.5	29.2	
August–November	33.5	35.7	34.1	29.8	41.5	
December–January	20.3	39.3	25.9	17.0	7.7	
<i>Physical exam</i>						
BMI (kg/m ²)	26.5 ± 5.0	30.3 ± 5.8	26.6 ± 4.9	26.1 ± 5.1	25.5 ± 4.0	<0.001
<i>Cardiometabolic diseases</i>						
CVD (%)	14.4	17.9	14.8	14.9	10.8	0.79
Diabetes Mellitus (%)	8.1	14.3	7.4	9.2	4.6	0.43
Hypertlipidemia (%)	80.0	67.9	76.3	84.4	83.1	0.13
Hypertension (%)	83.5	78.6	87.4	79.4	86.2	0.26

* Mean ±SD shown unless otherwise indicated. SD = standard deviation; BMI = body mass index; CVD = cardiovascular disease.

** p-value was determined by analysis of variance (ANOVA) for continuous variables and chi-square test for categorical variables.

Table 2

Adjusted Hazard Ratios and 95% Confidence Intervals for Incident Frailty in WHAS II, According to Vitamin D Category at Baseline^a

Vitamin D Category (ng/mL)	Model A	Model B	Model C	Model D
30 (reference)	1.00	1.00	1.00	1.00
20–29.9	1.34 (0.67,2.69)	1.18 (0.58,2.40)	1.16 (0.57,2.38)	1.08 (0.52,2.22)
10–19.9	1.86 (0.95,3.66)	1.57 (0.77,3.19)	1.54 (0.76,3.14)	1.44 (0.71,2.94)
<10	3.06 (1.32,7.08) *	2.77 (1.14,6.71) *	2.55 (1.04,6.29) *	2.29 (0.92,5.69)

^aModel A unadjusted

Model B adjusted for age, race, education, smoking status, and season of blood draw.

Model C adjusted for variables in Model A and body mass index.

Model D adjusted for variables in Model B and cardiovascular disease, diabetes mellitus, hyperlipidemia, and hypertension.

*
p-value <0.05