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Association of Low Vitamin D Levels With the Frailty Syndrome in Men and Women

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Background. Although both vitamin D (25-hydroxyvitamin D [25(OH)D]) insufficiency and the frailty syndrome are more prevalent in women than men, sex-specific associations have not been explored. We estimated sex-specific associations of low 25(OH)D with frailty. Vitamin D insufficiency can result in hyperparathyroidism, and thus, parathyroid hormone (PTH) was explored as a potential mediator in the relationship between 25(OH)D levels and frailty.

Methods. The sample included 444 male and 561 female participants aged 65 years and older from the InCHIANTI study for whom 25(OH)D levels and frailty information were available. Frailty was defined as the presence of at least three of the five following criteria: slowness, weakness, low energy expenditure, exhaustion, and weight loss. Logistic regression models estimated the association between serum levels of 25(OH)D and PTH with frailty, controlling for potential confounders.

Results. Independent of covariates, men with 25(OH)D <50 nmol/L had greater odds of frailty than those with 25(OH)D ≥50 nmol/L (odds ratio [OR] = 4.94, 95% confidence interval [CI] = 1.80–13.61). In women, the adjusted OR for frailty (95% CI) was 1.43 (0.58–3.56). The 25(OH)D ORs differed between men and women ($p = .041$). ORs changed little after controlling for PTH. However, when low energy expenditure was excluded from the frailty definition, adjusted OR for frailty in men (95% CI) was 2.18 (0.59–8.04); controlling for PTH attenuated this OR by 32%. In women, the OR (95% CI) for frailty (low energy expenditure excluded) was 1.54 (0.31–7.58) and was attenuated by 6% after controlling for PTH.

Conclusions. Vitamin D insufficiency was associated with frailty in men, but not in women. Results suggest that PTH mediates the relationship between 25(OH)D and nonenergy expenditure aspects of frailty.

Key Words: Vitamin D—Frailty syndrome—Parathyroid hormone—InCHIANTI.

FRAILTY has been described as "a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems and causing vulnerability to adverse outcomes" (1). The syndrome is associated with incident falls, functional limitation, disability, and mortality (1,2); thus, preventing frailty may help slow progression of the disablement process in older persons.

Low 25-hydroxyvitamin D [25(OH)D] levels are common in older adults (3,4) and have been linked to falls (5,6), fractures (5), pain (3,5,7), sarcopenia (4), poor physical function (8,9), disability (3), and frailty (10). Further, vitamin D supplementation has been shown to improve physical function (11,12).

The importance of vitamin D in maintaining calcium homeostasis is well known. Cholecalciferol is synthesized in the skin in response to ultraviolet light or is ingested through food (eg, fatty fish, eggs, fortified dairy products) and hydroxylated into 25(OH)D in the liver. Older persons often have low 25(OH)D levels owing to age-related decreased efficiency of hydroxylation and reduced sunlight exposure (3,13). When 25(OH)D levels are low, active metabolite 1,25-dihydroxyvitamin D [1,25-$(OH)_2$D] and calcium absorption decrease. The reduced serum calcium causes parathyroid hormone (PTH) levels to rise to stimulate 1,25-$(OH)_2$D production, resulting in increased bone turnover and hip fracture risk (3,13). Emerging research suggests that vitamin D affects muscle strength and function (4,8), both directly and indirectly through PTH regulation and inflammation (3,4,9,14,15).

Many sequelae of low 25(OH)D (3,4,8–10) are considered dimensions of the frailty syndrome (1,2); thus, low 25(OH)D may be a reversible cause of frailty. Also, low vitamin D may affect men and women differently. Age-related levels of 25(OH)D decline earlier and faster in women than in men (16), which may explain the greater prevalence of frailty in women versus men. Whether the pathway to frailty differs by sex is unknown.

In this study, we examined sex-specific associations between low 25(OH)D and prevalent frailty in community-dwelling men and women aged 65 years and older. We also explored PTH as a potential mediator in the pathway between low 25(OH)D and frailty.

Methods

Study Population

InCHIANTI is an epidemiological study with participants enrolled from residents of two Italian towns (Bagno a Ripoli in Tuscany, Greve in Chianti). The Italian National Research Council of Aging Ethical Committee approved the study. All participants provided informed consent. Details regarding design and sampling are available elsewhere (17). Participants responded to a home interview, participated in a medical examination, provided blood samples, and underwent functional performance tests.

The study randomly sampled 1,260 men and women aged 65 years and older (and additionally oversampled those aged ≥90 years), of whom 1,154 (91.6%) participated. Analyses presented here utilized data from 1,005 individuals who provided blood samples and information on at least one frailty criterion. Among included participants, 980 provided complete frailty information, whereas the remaining 25 provided partial information.

Frailty

Frailty phenotype was defined according to five dimensions proposed by Fried and colleagues (1): "shrinking," "exhaustion," "low energy expenditure," "slowness," and "weakness." Each dimension was operationalized using previously published methods (18). "Shrinking" was measured as self-reported unintentional weight loss more than 4.5 kg (10 lbs) within the past year. Presence of exhaustion was indicated by a response of "occasionally" or "often/always" to the statement, "I felt that everything was an effort." This statement is an item from the Center for Epidemiological Studies—Depression scale, which was validated in Italian (19). Participants reported their level of daily leisure physical activity in the past year; "low energy expenditure" was defined as either complete inactivity or performing low-intensity activities less than 1 h/wk. "Slowness" was defined as usual walking speed in the slowest quintile within groups defined by sex and height. Walking speed was measured on a 4-m course using photocell recordings at the course start and finish. The final measure averaged two walks. Grip strength was measured using a handheld dynamometer (Nicholas Muscle Tester; Sammon Preston, Inc., Chicago, Ill) by a standard method; "weakness" was defined as grip strength in the lowest quintile within groups defined by sex and body mass index (BMI). "Frailty," "intermediate frailty," and "robustness" were defined, respectively, as presence of at least three, one or two, and zero of the five criteria.

Biological Markers

Fasting blood samples were drawn and were processed and stored at −80°C until analysis. Serum 25(OH)D was measured by radioimmunoassay (RIA kit; DiaSorin, Stillwater, Minn). Intra- and interassay coefficients of variation (CVs) were 8.1% and 10.2%, respectively. Serum intact PTH was measured with a two-site immunoradiometric assay kit (N-tact PTHSP; DiaSorin). Intra- and interassay CVs were less than 3.0% and 5.5%, respectively. The samples were not measured in duplicate. Impaired renal function can affect 25(OH)D levels; therefore, creatinine clearance, calculated using the Cockcroft-Gault formula, was included in statistical analyses. Serum creatinine for this calculation was measured using a standard Jaffe method (Roche Diagnostics, GmbH, Mannheim, Germany).

Other Covariates

The following covariates were included in statistical analyses: age (years), education (years of schooling), blood collection season, smoking (pack-years), alcohol consumption, cognitive function, comorbidities, and BMI. Alcohol consumption was measured as number of drinks per week using the European Prospective Investigation into Cancer and Nutrition (EPIC) questionnaire (20). The Mini-Mental State Examination (MMSE) (21) was used to measure cognitive function. Presence of comorbidities was based on adjudicated measures combining information from self-report, medical records, and clinical examination. Comorbidities considered were congestive heart failure, peripheral arterial disease, hypertension, diabetes mellitus, osteoarthritis, myocardial infarction, angina, and chronic obstructive pulmonary disease. These conditions were previously found to be associated with low 25(OH)D and/or frailty and, hence, may be confounders (10).

Statistical Analysis

Vitamin D insufficiency for analyses was defined as 25(OH)D less than 50 nmol/L, consistent with published reports (3,14). Additional analyses included 25(OH)D as a continuous variable because no consensus on a cutoff exists, and recent research suggests that 25(OH)D levels needed to prevent secondary hyperparathyroidism may depend on age (16). High PTH was defined as the upper quartile of PTH concentrations (>32.4 ng/L).

Descriptive analysis included χ^2 or Fisher exact tests for categorical variables and *t* tests or Wilcoxon rank-sum tests for continuous variables. Multinomial logistic regression was used to estimate covariate-adjusted odds ratios (ORs) of frailty category by 25(OH)D status and assess the interaction between sex and 25(OH)D status. Two sex-stratified models were estimated. In addition to covariates, Model 1 included 25(OH)D and Model 2 included 25(OH)D and PTH. Additionally, logistic regression was used to estimate adjusted ORs of each frailty criterion by 25(OH)D and PTH status.

Results

The study included 561 women (55.8%) and 444 men (44.2%) with average (standard deviation) age 75.6 (7.6)

and 74.2 (7.0) years, respectively. Prevalence of frailty was 11.8% in women and 8.9% in men; 43.6% of women and 35.6% of men were intermediate frail. The median (interquartile range) of 25(OH)D for women and men were 33.4 (22.7–49.4) nmol/L and 48.5 (34.1–73.1) nmol/L, respectively.

Table 1 shows study sample characteristics. Frail participants were older; had fewer years of education, lower MMSE scores, lower creatinine clearance and 25(OH)D, higher serum PTH; and were more likely to have congestive heart failure and chronic obstructive pulmonary disease compared with those of the same sex who were not frail. Frail women consumed less alcohol and were more likely to have peripheral arterial disease, hypertension, and angina than robust women. The most common frailty criterion for frail men and women was slowness.

Table 2 shows adjusted sex-specific associations of 25(OH)D with frailty. In men, ORs (95% confidence intervals [CIs]) of frailty and intermediate frailty, respectively, versus robustness [low vs high 25(OH)D] were

Table 1. Characteristics of InCHIANTI Participants Included in This Study

	Men				Women			
Characteristic	Robust (*N* = 242)	Intermediate Frail (*N* = 151)	Frail (*N* = 39)	*p*	Robust (*N* = 243)	Intermediate Frail (*N* = 237)	Frail (*N* = 64)	*p*
Age (yrs), mean (*SD*)	71.7 (5.5)	76.2 (7.1)	80.8 (7.8)	<.001	72.9 (6.1)	76.1 (7.5)	82.3 (7.4)	<.001
Education (yrs), mean (*SD*)	6.5 (3.6)	5.9 (3.7)	4.6 (2.7)	.003	5.1 (2.7)	4.5 (2.8)	4.2 (2.8)	.025
Season of blood collection, number (%)								
Spring (March–May)	40 (16.5)	30 (19.4)	8 (20.5)		63 (25.9)	34 (14.4)	18 (28.1)	
Summer (June–August)	27 (11.2)	20 (12.9)	9 (23.1)		18 (7.4)	27 (11.4)	9 (1.6)	
Fall (September–November)	70 (28.9)	50 (32.3)	13 (33.3)		71 (35.7)	102 (43.0)	26 (40.6)	
Winter (December–February)	105 (43.4)	55 (35.5)	9 (23.1)	.17	91 (37.4)	74 (31.2)	11 (17.2)	<.001
Smoking (pack-years), mean (*SD*)	22.7 (23.5)	25.8 (24.2)	29.0 (31.2)	.22	2.0 (6.4)	3.3 (9.0)	4.4 (15.4)	.095
Alcohol consumption (drinks/wk), mean (*SD*)	14.0 (13.4)	12.4 (14.2)	8.8 (9.0)	.075	4.2 (5.7)	3.0 (4.7)	3.3 (5.5)	.030
BMI (kg/m^2), mean (*SD*)	27.0 (3.4)	27.2 (3.3)	26.7 (2.8)	.61	27.5 (4.3)	27.8 (4.5)	28.3 (6.1)	.42
MMSE score, mean (*SD*)	26.4 (2.7)	24.2 (5.3)	20.9 (7.6)	<.001	25.2 (3.6)	23.8 (5.0)	21.6 (5.4)	<.001
Congestive heart failure, number (%)	8 (3.3)	11 (7.1)	7 (18.0)	.003	1 (0.4)	17 (7.2)	11 (17.2)	<.001
Peripheral arterial disease, number (%)	15 (6.2)	15 (9.7)	6 (15.4)	.11	3 (1.2)	13 (5.5)	7 (10.9)	.001
Hypertension, number (%)	103 (42.6)	78 (50.3)	17 (43.6)	.31	120 (49.4)	111 (46.8)	42 (65.6)	.027
Diabetes, number (%)	29 (12.0)	20 (12.9)	7 (18.0)	.54	19 (7.8)	27 (11.4)	9 (14.1)	.21
Osteoarthritis, number (%)	131 (54.1)	76 (49.0)	20 (51.3)	.60	135 (55.6)	147 (62.0)	37 (57.8)	.36
Myocardial infarction, number (%)	11 (4.6)	11 (7.1)	5 (12.8)	.11	5 (2.1)	11 (4.6)	3 (4.7)	.21
Angina, number (%)	14 (5.8)	13 (8.4)	3 (7.7)	.51	0 (0)	11 (4.6)	4 (6.2)	<.001
Chronic obstructive pulmonary disease, number (%)	30 (12.4)	32 (20.6)	12 (30.8)	.006	0 (0)	4 (1.7)	5 (7.8)	<.001
Creatinine clearance (mL/min), median (IQR)	70.5 (61.0–85.0)	68.5 (54.4–82.2)	57.8 (43.8–67.9)	<.001	62.4 (50.4–73.2)	59.5 (47.0–70.7)	48.3 (37.3–61.8)	<.001
Serum PTH (ng/L), median (IQR)	19.2 (14.5–25.2)	24.2 (16.5–35.8)	23.6 (19.1–38.3)	<.001	22.7 (16.2–32.0)	23.4 (15.4–35.8)	29.4 (20.2–44.1)	.002
Serum PTH >32.4 ng/L, number (%)	28 (11.6)	46 (29.7)	12 (30.8)	<.001	58 (23.9)	71 (30.0)	27 (42.2)	.014
25(OH)D (nmol/L), median (IQR)	61.5 (41.7–78.4)	43.2 (30.0–69.6)	35.7 (23.5–48.4)	<.001	36.2 (27.2–56.2)	34.2 (21.7–47.7)	26.4 (17.2–35.9)	<.001
25(OH)D <50.0 nmol/L, number (%)	96 (39.7)	97 (62.6)	30 (76.9)	<.001	172 (70.8)	180 (76.0)	56 (87.5)	.017
Frailty criteria, number (%)								
Weight loss	0	13 (8.7)	13 (35.1)		0	13 (5.7)	15 (26.3)	
Exhaustion	0	29 (20.1)	20 (62.5)		0	84 (38.0)	35 (64.8)	
Low energy expenditure	0	29 (18.7)	30 (76.9)		0	87 (36.7)	56 (87.5)	
Slowness	0	66 (46.2)	33 (97.1)		0	68 (31.0)	53 (91.4)	
Weakness	0	72 (46.4)	34 (87.2)		0	73 (30.8)	50 (79.4)	

Notes: The *p* values compare variables across frailty status, within gender. The χ^2 or Fisher exact test for categorical variables; analysis of variance or Kruskal-Wallis test for continuous variables.

SD = standard deviation, IQR = interquartile range. 25(OH)D = 25-hydroxyvitamin D; PTH = parathyroid hormone; BMI = body mass index; MMSE = Mini-Mental State Examination.

Table 2. Multinomial Logistic Regression Assessing the Association of 25(OH)D With Frailty

	Men				Women			
	Frail vs Robust		Intermediate Frail vs Robust		Frail vs Robust		Intermediate Frail vs Robust	
Biomarkers	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Model 1*								
25(OH)D (low vs high)	4.94 (1.80–13.61)	.002	2.52 (1.56–4.07)	<.001	1.43 (0.58–3.56)	.44	1.18 (0.75–1.88)	.47
Model 2*								
25(OH)D (low vs high)	4.13 (1.45–11.80)	.008	2.13 (1.30–3.50)	.003	1.36 (0.54–3.43)	.52	1.17 (0.73–1.87)	.51
PTH (high vs low)	2.40 (0.84–6.87)	.10	2.42 (1.31–4.48)	.005	1.37 (0.65–2.89)	.41	1.16 (0.74–1.83)	.52

Notes: 25(OH)D = 25-hydroxyvitamin D; PTH = parathyroid hormone; OR = odds ratio; CI = confidence interval.

*Model 1: 25(OH)D + covariates; Model 2: 25(OH)D + PTH + covariates; Low 25(OH)D: <50.0 nmol/L; High PTH: >32.4 ng/L. Covariates included age (years), education (years of schooling), blood collection season, smoking (pack-years), alcohol consumption (drinks/wk), cognitive function (Mini-Mental State Examination), comorbidities (congestive heart failure, peripheral arterial disease, hypertension, diabetes mellitus, osteoarthritis, myocardial infarction, angina, and chronic obstructive pulmonary disease), body mass index (kg/m^2), and creatinine clearance (mL/min).

4.94 (1.80–13.61) and 2.52 (1.56–4.07). Men's OR for intermediate frailty, controlling for PTH, was attenuated by 16%, and high PTH was associated with intermediate frailty (OR = 2.42, 95% CI = 1.31–4.48). Among women, ORs (95% CI) of frailty and intermediate frailty, respectively, versus robustness were 1.43 (0.58–3.56) and 1.18 (0.75–1.88). OR for frailty for women was attenuated by 5% after controlling for PTH. Sex was an effect modifier of the association between low 25(OH)D and frailty ($p = .041$).

Covariate-adjusted analyses with continuous 25(OH)D showed that a 10 nmol/L difference in 25(OH)D (lower vs higher) was associated with ORs (95% CI) for frailty of 1.35 (1.10–1.66) and 1.04 (0.92–1.17) among men and women, respectively. Controlling for continuous PTH and covariates, ORs (95% CI) for frailty were 1.33 (1.08–1.64) and 1.02 (0.90–1.14) among men and women, respectively, (not shown).

Sex-specific associations of 25(OH)D with individual frailty criteria are shown in Table 3. After adjustment for covariates, men with low 25(OH)D had elevated odds of low energy expenditure (OR = 6.83, 95% CI = 2.62–17.82) and slowness (OR = 2.52, 95% CI = 1.39–4.59). After controlling for PTH, the OR for low energy expenditure in men increased by 9%, and men's OR for slowness decreased by 13%. Women with low 25(OH)D had elevated adjusted odds of low energy expenditure (OR = 2.28, 95% CI = 1.41–4.93), which remained unchanged after controlling for PTH.

After refitting the model using continuous 25(OH)D, the ORs (95% CI) for each 10 nmol/L difference (lower vs

Table 3. Covariate-Adjusted Associations of 25(OH)D and PTH With Individual Frailty Criteria

	Weight Loss	Exhaustion	Low Energy Expenditure	Slowness	Weakness
			OR (95% CI)		
Men					
Model 1*					
25(OH)D (low vs high)	1.01 (0.38–2.73)	1.56 (0.78–3.12)	6.83 (2.62–17.82)	2.52 (1.39–4.59)	1.29 (0.75–2.23)
	$p = .98$	$p = .20$	$p < .001$	$p = .002$	$p = .36$
Model 2*					
25(OH)D (low vs high)	1.08 (0.39–2.99)	1.19 (0.57–2.49)	7.47 (2.79–19.98)	2.20 (1.17–4.11)	1.04 (0.58–1.86)
	$p = .89$	$p = .64$	$p < .001$	$p = .014$	$p = .89$
PTH (high vs low)	0.70 (0.20–2.48)	2.92 (1.34–6.39)	0.70 (0.29–1.70)	1.75 (0.88–3.45)	2.40 (1.27–4.55)
	$p = .58$	$p = .007$	$p = .44$	$p = .11$	$p = .007$
Women					
Model 1*					
25(OH)D (low vs high)	1.45 (0.44–4.72)	0.76 (0.78–3.12)	2.28 (1.20–4.32)	1.23 (0.57–2.67)	0.79 (0.45–1.40)
	$p = .54$	$p = .30$	$p = .012$	$p = .55$	$p = .42$
Model 2*					
25(OH)D (low vs high)	1.56 (0.47–5.14)	0.79 (0.47–1.34)	2.28 (1.19–4.37)	1.12 (0.59–2.14)	0.72 (0.40–1.29)
	$p = .47$	$p = .39$	$p = .013$	$p = .72$	$p = .27$
PTH (high vs low)	0.58 (0.19–1.75)	0.88 (0.52–1.48)	0.97 (0.57–1.63)	1.51 (0.88–2.58)	1.65 (0.99–2.76)
	$p = .33$	$p = .62$	$p = .90$	$p = .13$	$p = .055$

Notes: 25(OH)D = 25-hydroxyvitamin D; PTH = parathyroid hormone; OR = odds ratio; CI = confidence interval.

*Model 1: 25(OH)D + covariates; Model 2: 25(OH)D + PTH + covariates; Low 25(OH)D: <50.0 nmol/L; High PTH: >32.4 ng/L. Covariates included age (years), education (years of schooling), blood collection season, smoking (pack-years), alcohol consumption (drinks/wk), cognitive function (Mini-Mental State Examination), comorbidities (congestive heart failure, peripheral arterial disease, hypertension, diabetes mellitus, osteoarthritis, myocardial infarction, angina, and chronic obstructive pulmonary disease), body mass index (kg/m^2), and creatinine clearance (mL/min).

Table 4. Sensitivity Analysis: Multinomial Logistic Regression Assessing the Association of 25(OH)D and PTH With Four-Category Frailty (Excluding Low Energy Expenditure)

	Men				Women			
	Frail vs Robust		Intermediate Frail vs Robust		Frail vs Robust		Intermediate Frail vs Robust	
Biomarkers	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Model 1*								
25(OH)D (low vs high)	2.18 (0.59–8.04)	.24	1.86 (1.15–3.00)	.011	1.54 (0.31–7.58)	.60	0.84 (0.53–1.33)	.45
Model 2*								
25(OH)D (low vs high)	1.47 (0.37–5.76)	.58	1.55 (0.94–2.55)	.086	1.44 (0.28–7.29)	.66	0.79 (0.50–1.27)	.33
PTH (high vs low)	5.63 (1.62–19.55)	.006	2.53 (1.38–4.63)	.003	1.47 (0.50–4.38)	.49	1.44 (0.92–2.25)	.11

Notes: 25(OH)D = 25-hydroxyvitamin D; PTH = parathyroid hormone; OR = odds ratio; CI = confidence interval.

*Model 1: 25(OH)D + covariates + low energy expenditure; Model 2: 25(OH)D + PTH + covariates + low energy expenditure; Low 25(OH)D: <50.0 nmol/L; High PTH: >32.4 ng/L. Covariates included age (years), education (years of schooling), blood collection season, smoking (pack-years), alcohol consumption (drinks/wk), cognitive function (Mini-Mental State Examination), comorbidities (congestive heart failure, peripheral arterial disease, hypertension, diabetes mellitus, osteoarthritis, myocardial infarction, angina, chronic obstructive pulmonary disease), body mass index (kg/m^2), and creatinine clearance (mL/min).

higher) for men were 1.50 (1.23–1.83) and 1.10 (0.99–1.22) for low energy expenditure and slowness, respectively. For women, the OR for low energy expenditure was 1.07 (95% CI = 0.99–1.16). Weak associations between continuous 25(OH)D and other frailty criteria were found ($p > .05$) among both sexes (not shown).

Low 25(OH)D levels were most strongly associated with low energy expenditure, possibly due to reverse causality via limited sunlight exposure. To assess the relationship of low 25(OH)D with nonenergy expenditure aspects of frailty, multinomial regression was performed using a four-component frailty measure (where low energy expenditure is omitted) while controlling for covariates and low energy expenditure. Among men, 15 participants previously classified as intermediate frail were classified as robust using the four-component measure, and 19 men were reclassified from frail to intermediate frail. Similarly, 29 women previously classified as intermediate frail were classified as robust using the four components, and 40 women were reclassified from frail to intermediate frail. Regression results are shown in Table 4. Among men, the adjusted ORs (95% CI) for frailty and intermediate frailty were 2.18 (0.59–8.04) and 1.86 (1.15–3.00), respectively. After controlling for PTH, the frailty OR was attenuated by 32%. Among women, the adjusted ORs (95% CI) for frailty and intermediate frailty were 1.54 (0.31–7.58) and 0.84 (0.53–1.33). After controlling for PTH the frailty OR was attenuated by 6%. For both sexes, associations of PTH with frailty were stronger using the four-component frailty measure than when using the five-component measure.

Discussion

In this study, we found strong independent associations of low 25(OH)D with frailty measured using the widely accepted five components in men and weak evidence for association in women. Low 25(OH)D was independently associated with low energy expenditure in both sexes and with slowness in men. The evidence of association using a modified four-component measure of frailty (excluding low energy expenditure) in men was much weaker. One explanation for this attenuation is the smaller number of men classified as frail using the four-component measure; however, we cannot rule out reverse causality of low physical activity with low 25(OH)D as an explanation of this result.

Sex-stratified analyses controlled for biological and social differences between men and women that may have obscured associations in studies that included both sexes in one analysis. These results were robust to modeling of 25(OH)D (continuous and dichotomous). The 25(OH)D results were attenuated when low energy expenditure was removed from the frailty measure and included as a covariate; however, the PTH results were strengthened.

Although low physical activity may lead to low 25(OH)D, low 25(OH)D may be associated with frailty through several other biological pathways, including effects on bone, muscle, and immunity. Effects of vitamin D on bone health are well known (13). Low 25(OH)D levels are associated, both directly and mediated through elevated PTH, with osteoporotic fractures and osteomalacia, a condition whereby new bone matrix is not properly mineralized (3). These conditions, along with poor balance, (22) may result in bodily pain (7) (eg, via progression of osteoarthritis) (23,24) and fear of falling, which may contribute to sedentariness (3,13,25). This pathway may also explain the strong associations between low 25(OH)D and low energy expenditure for both sexes found in this study.

Additionally, low 25(OH)D may affect frailty via effects on muscle strength. Vitamin D receptors (VDRs) are located in skeletal muscle cells (26), and low 25(OH)D may result in decreased muscle strength from both decreased muscle synthesis and altered contractile properties of muscle (27). Muscle protein synthesis is initiated by binding 1,25-$(OH)_2$D to its nuclear receptor. The influence of 1,25-$(OH)_2$D on calcium homeostasis is believed to influence

contractile properties of muscle cells via both a VDR-mediated genomic pathway and a nongenomic rapid mechanism (28). Thus, the association between low 25(OH)D and frailty may be explained by associations of insufficient 25(OH)D with sarcopenia and muscle weakness because both are central to the frailty syndrome (1). Previous studies found associations of low 25(OH)D with low muscle strength (4), poor balance (22,29), and falls (6). Additionally, associations between elevated PTH and sarcopenia have been reported (4). In this study, a moderate association was found between low 25(OH)D and weakness in men.

A third pathway through which low 25(OH)D may affect frailty stems from hypothesized anti-inflammatory properties of vitamin D (13). The VDR has been identified on most immune system cells (30,31). Active metabolite 1,25-$(OH)_2$D inhibits secretion by antigen-presenting cells of cytokine interleukin-12 (IL-12). Since IL-12 stimulates development of $CD4^+$ helper T cells subtype 1 (T_H1) and inhibits development of $CD4^+$ helper T cells subtype 2 (T_H2), 1,25-(OH)2D actions result in a shift away from a proinflammatory T_H1-like profile toward an anti-inflammatory T_H2-like profile (31). Low 25(OH)D has been associated with increased risk of T_H1 cytokine-mediated autoimmune diseases including inflammatory bowel disease, rheumatoid arthritis, and type 1 diabetes mellitus (32).

Associations between serum markers of inflammation with functional decline, slowness, and frailty have been reported (33–39). Effects of low 25(OH)D on muscle may be mediated by proinflammatory cytokines, which are believed to adversely affect muscle strength and function (33,34,36,40). Recent research (9) hypothesized that low 25(OH)D may affect physical function via secondary hyperparathyroidism resulting in elevated cytokine levels, which have been linked to sarcopenia (39). In this study, an association between low 25(OH)D and slowness was found among men.

Sex differences in the relationship of 25(OH)D with frailty found in this study may have biologic and methodologic origins. Women in this study had lower 25(OH)D levels than men; thus, relationships were estimated for different ranges of 25(OH)D in men and women. In particular, only 29.2% of robust women compared with 60.3% of robust men had adequate 25(OH)D levels. Differences in the 25(OH)D distribution may be compounded by age differences (women were older), because higher 25(OH)D levels may be needed for older individuals to avoid secondary hyperparathyroidism (16). Lastly, comorbidities with differing prevalence between sexes were included in our analyses, which may be an important part of the pathway linking low 25(OH)D to frailty in women compared with men (32). To avoid extrapolation problems, the results should be interpreted as "sex-specific associations" of 25(OH)D with frailty for the 25(OH)D distributions encountered in this study rather than "sex comparisons."

An advantage of this study is the large population-based sample with plasma 25(OH)D, the best clinical indicator of vitamin D body stores. The cross-sectional design precludes determining temporality of 25(OH)D and frailty; therefore, observed associations may be due to noncausal relationships (eg, unmeasured confounders). Although insufficient 25(OH)D leading to progression of the frailty syndrome is biologically plausible, frail persons are possibly more likely to limit their outdoor activities, leading to decreased sunlight exposure and low 25(OH)D. This explanation is consistent with the strong association between low 25(OH)D and low energy expenditure found in this study. Also, the temporal relationship between 25(OH)D and PTH cannot be established; thus, reverse causality cannot be excluded as an explanation. Further longitudinal studies should evaluate whether low 25(OH)D is associated with onset or progression of frailty and its individual dimensions in older, community-dwelling adults.

In conclusion, results suggest that, independent of PTH, men with low 25(OH)D have elevated odds of frailty and intermediate frailty compared with men with adequate 25(OH)D, with evidence suggesting different associations with individual frailty criteria. The odds of frailty among women with low 25(OH)D were moderately elevated. Also, elevated PTH was strongly associated with nonenergy expenditure aspects of frailty in men with a moderate association in women. Three biologic pathways (bone, muscle, and inflammation) may explain the association between low 25(OH)D and frailty, and the relative contribution of each pathway may depend on sex. These results exemplify the need for longitudinally examining the disablement process separately in men and women and for assessing the relationship between vitamin D and frailty in populations of women with a broader distribution of 25(OH)D levels.

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