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Sex-specific differences in the association of vitamin D with low lean mass and frailty: Results from the Berlin Aging Study II

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ABSTRACT

Background: Sex-specific differences in factors associated with aging and lifespan, such as sarcopenia and disease development, are increasingly recognized. The study aims to assess sex-specific aspects of the association between vitamin D insufficiency and low lean mass as well as between vitamin D insufficiency and the frailty phenotype.
Methods: A total of 1102 participants (51% women) from the Berlin Aging Study II were included in this cross-sectional study. Vitamin D insufficiency was defined as a 25(OH)D level <50 nmol/L. Lean mass was assessed with dual-energy x-ray absorptiometry and corrected by body mass index. Low lean mass was defined according to the Foundations for the National Institutes of Health Sarcopenia Project criteria (appendicular lean mass/body mass index <0.789 in men and <0.512 in women) and frailty defined according to the Fried criteria.
Results: In a risk factor–adjusted analysis, the association of vitamin D insufficiency was significantly influenced by sex (P for interaction < 0.001). Men with vitamin D insufficiency had 1.8 times higher odds of having low lean mass, with no association between vitamin D insufficiency and low lean mass in women. Participants with vitamin D insufficiency had 1.5 higher odds of being prefrail/frail with no significant effect modification by sex.
Conclusions: We found notable sex-specific differences in the association of vitamin D insufficiency with low lean mass but not of vitamin D insufficiency with frailty. Vitamin D might play a relevant role in the loss of lean mass in men but not women and might be a biological marker of an unfavorable aging process associated with early development of frailty regardless of sex.

Introduction

The prevalence of vitamin D insufficiency is high in a wide range of countries worldwide including Germany [1]. Older people, and especially those who are institutionalized, are at a particular high risk for a poor vitamin D status [2,3]. This is of clinical importance because low 25-hydroxyvitamin D (25(OH)D) levels have been found to be associated with low lean or muscle mass [4], low muscle strength [5], frailty [6], and falls [7,8], thus linking a biomarker to changes in body composition and to a geriatric syndrome and a functional outcome. Eliciting the specific role of vitamin D in muscle metabolism is still challenging, although it has been suggested that low levels of active vitamin D (1,25[OH]D) could play a causal role in the development of low muscle mass,

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strength, and functional decline [9]. Frailty is a multidimensional syndrome characterized by diminished reserve capacity and increased vulnerability to stressors [10], which is distinct from both multimorbidity, a potential risk factor of frailty, and disability, a potential outcome of frailty [11]. Sarcopenia, the loss of muscle mass and strength associated with aging, might present a link between a biomarker, 25(OH)D, and a complex multidimensional syndrome, frailty [12,13], which can ultimately be viewed as reflective of unhealthy aging.

Of note, there are clear sex-specific differences not only regarding body composition and muscle strength but also with respect to lifestyle factors such as physical activity, dietary habits, and sun exposure, which all have an effect on vitamin D status, muscle health, and frailty.

Although the literature about the potential impact of sex differences on the relationship among 25(OH)D levels, lean mass, and frailty to date is scarce, sex differences in lifespan and aging are well known [14].

Therefore the goal of this study was to assess potential sex-specific aspects of the association between vitamin D insufficiency, defined as serum 25(OH)D level $<$ 50 nmol/L, and low lean mass as well as between vitamin D insufficiency and the frailty phenotype.

Methods

Participants

Altogether, 1102 participants from the Berlin Aging Study II (BASE-II) recruited between 2009 and 2014 were included in this cross-sectional analysis. BASE-II is a prospective epidemiologic study to investigate factors associated with "healthy" or "unhealthy" aging in the residents of the greater metropolitan area of Berlin, Germany, as described previously in detail [15,16]. In short, eligibility criteria at the time of recruitment were comparably healthy, community-dwelling, well-functioning older participants aged between 60 and 82 y. Participants were excluded if they 1) reported difficulty walking one-quarter of a mile without assistance; 2) suffered from Parkinson disease or had experienced stroke or myocardial infarction; 3) had undergone head, heart, or vascular surgery; or 4) suffered from dementia or malignant disease.

For this analysis, we excluded 83 participants using vitamin D supplements to avoid potential confounding as a result of short-term effects on vitamin D concentrations. All participants gave written informed consent and the Ethics Committee of the Charité Universitätsmedizin Berlin approved the study (approval number EA2/029/09). The medical part of the Berlin Aging Study II is officially registered with the trial registry DRKS (DRKS00009277).

Anthropometric measurements

Body weight was measured in light clothes with a portable electronic scale to the nearest 0.1 kg, and height was determined with removed shoes in stretched stature to the nearest 0.1 cm by using an electronic weighing and measuring station (seca 764, seca, Hamburg, Germany). Weight and height were used for calculating the body mass index (BMI) (weight [kg]/height [m]^2).

Body composition

Body composition was assessed with dual-energy x-ray absorptiometry (QDR Discovery (Hologic Inc., Bedford, MA, USA). A trained technician performed the dual-energy x-ray absorptiometry measurement protocol [17]. Total non-bone lean mass was determined from the difference between total lean mass and bone mineral content. Appendicular lean mass (ALM) in kilograms was calculated as the sum of the lean mass of the four limbs. ALM was then corrected for BMI (ALM/BMI). The definition of low lean mass was based on cutoff values for low ALM/BMI ($<$0.789 in men and $<$0.512 in women) chosen according to the lean mass thresholds associated with likelihood of weakness as identified within the Foundations for the National Institutes of Health Sarcopenia Project [18].

Frailty

Frailty was defined according to the physical phenotype proposed by Fried et al. [10] based on five criteria: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed, and low physical activity [10,19]. Some adjustments of the original methodology had to be made because not all assessment methods used by Fried et al. were available in the BASE-II study. In detail, the changes included the following:

(1) Weight loss was defined as unintentional loss of at least 5% of the body weight in the least year.
(2) Self-reported exhaustion was identified by two questions from the Center for Epidemiological Studies depression (CES-D) scale [20].
(3) Weakness was assessed by measuring hand grip strength with a Smedley Dynamometer (Scandidact, Odder, Denmark). The participants were standing upright, shoulders adducted and neutrally rotated, and elbows flexed with the forearm in a 90° position. Participants were then instructed to perform a maximal isometric contraction. The test was performed three times for each hand, and the highest value was chosen. The cutoff values stratified by gender and BMI as suggested by Fried et al. [10] were used to identify reduced grip strength reflecting weakness.
(4) Slow walking speed was judged by using the timed up and go test [21]. The time in seconds taken to stand up from a chair, walk a distance of 3 m, turn, walk back to the chair, and sit down again was measured for the participants. Participants unable to complete the test in less than 10 s were considered to have a slow walking speed.
(5) Low physical activity was based on the question "Are you seldom or never physically active?" If the participant answered "yes," the criterion was fulfilled.

According to how many criteria were met, participants were ranked as frail (3–5), prefrail (1–2), or not frail (0). Given the objective of BASE-II to study the early onset of age-associated disorders and impairments, we considered prefrailty as a precursor of frailty in our analyses. For statistical analysis, prefrail and frail were combined into one variable.

Vitamin D

Fasting blood samples were collected from participants on the morning of their visit. Blood samples were collected throughout the year with no preference for any season. Serum 25(OH)D concentrations were measured using quantitative chemiluminescence technology (IDS-iSYS Multi-Discipline Automated Analyzer and DiaSorin Liaison Analyzer).

Vitamin D insufficiency was defined as a concentration of 25(OH)D $<$ 50 nmol/L based on a recommendation by the Institute of Medicine of a serum 25-hydroxyvitamin D level of at least 50 nmol/L [22].

Covariables

Potential confounders that have been described in the literature previously were included in the regression models: age, regular strength training (dichotomous variable), inflammation (reflected by serum C-reactive protein [CRP] concentrations measured by immunoturbidimetric assay [CRPL3; Roche Diagnostics, Basel, Switzerland]), parameters of body composition, and morbidity. Morbidity was assessed with a morbidity index based on most of the categories of the comorbidity index originally described by Charlson and collaborators [23], which is a weighted sum of moderate to severe, mostly chronic illnesses, including cancer (e.g., lymphoma) and cardiovascular (e.g., congestive heart failure) and metabolic diseases (e.g., diabetes mellitus). The morbidity index used in BASE-II has been described previously in detail [24].

Statistics

Statistical analyses were carried out using SPSS version 21 Software (IBM Corp., Armonk, NY, USA). Data are given in percentage or as mean and standard deviation. Student's t test was performed to compare means between groups. A χ^2 test was used to compare percentages between groups in relation to categorical variables. Binary logistic regression models controlling for potential confounders were performed to calculate odds ratios (95% confidence intervals) of being sarcopenic, being prefrail/frail (combined variable), or fulfilling particular frailty criteria in case of vitamin D insufficiency. An acceptable level of statistical significance was established a priori at $P < 0.05$.

Results

A total of 1102 community-dwelling participants with a mean age of 68.0 ± 3.6 y were included in this analysis. General characteristics of the study population are shown in Table 1. A total of 562 participants (51.0%) were female, which reflects an almost even distribution of men and women. As can be expected, women had a lower lean mass and a lower grip strength than men. The prevalence of low lean mass was higher in men, whereas the

Table 1
General characteristics of the study population

Parameters	Total (N = 1102)	Women (n = 562)	Men (n = 540)	P
Age (y)	68.0 ± 3.6	67.7 ± 3.4	68.4 ± 3.7	0.003
Height (cm)	169.3 ± 8.8	163.0 ± 6.0	175.8 ± 6.1	<0.001
Weight (kg)	76.9 ± 14.2	69.8 ± 12.1	84.3 ± 12.3	<0.001
Waist circumference (cm)	96.1 ± 11.8	91.8 ± 11.5	100.6 ± 10.2	0.049
BMI (kg/m^2)	26.76 ± 4.13	26.28 ± 4.53	27.27 ± 3.61	<0.001
ALM/BMI	0.75 ±0.17	0.62 ± 0.10	0.89 ± 0.12	<0.001
Grip strength (kgf)	34.49 ± 9.59	27.08 ± 4.99	42.19 ± 6.74	<0.001
TUG	7.82 ± 1.71	7.68 ± 1.64	7.98 ± 1.76	0.003
25(OH)D (nmol/L)	55.2 ± 25.6	53.9 ± 24.0	56.6 ± 27.1	0.080
Vitamin D insufficiency n (%)	518 (47.0)	257 (45.7)	261 (48.3)	0.210
Low lean mass (ALM/BMI) n (%)	163 (14.8)	64 (11.4)	99 (18.3)	0.001
Frailty, n (%)				0.520
Frail	10 (0.9)	6 (1.1)	4 (0.7)	
Prefrail	329 (29.9)	160 (28.5)	169 (31.3)	
Not frail	763 (69.2)	396 (70.5)	367 (68.0)	
Smoking, n (%)				<0.001
Current	110 (10.0)	52 (9.3)	58 (10.7)	
Former	463 (42.0)	179 (31.9)	284 (52.6)	
Never	529 (48.0)	331 (58.9)	198 (36.7)	
Arterial hypertension	510 (46.3)	250 (44.5)	260 (48.1)	0.205
Diabetes	143 (14.1)	57 (10.7)	86 (17.9)	0.001
Morbidity index	1.2 ± 1.3	1.3 ± 1.3	1.3 ± 1.3	0.013

ALM, appendicular lean mass; BMI, body mass index; TUG, timed up and go.
Variables are presented as mean and standard deviation or in n and percentage.

prevalence of vitamin D insufficiency and prefrailty/frailty did not differ between men and women.

The mean serum level of 25(OH)D was 55.2 nmol/L. Participants with vitamin D insufficiency had lower ALM/BMI and a higher total fat mass and were more likely to be prefrail or frail. Vitamin D–insufficient men had also experienced a significantly greater number of falls in the previous 12 mo than vitamin D–insufficient women. Table 2 shows the characteristics of the study population stratified according to sex and vitamin D status.

Vitamin D and low lean mass

Vitamin D insufficiency was investigated with regard to low lean mass, defined as ALM/BMI less than the sex-specific cutoff values. The unadjusted results are displayed in Figure 1. In a logistic regression analysis controlling for age, sex, regular strength training, CRP, and the morbidity index (model 1), vitamin D insufficiency was positively associated with low lean mass. These associations remained after additionally adjusting for total fat mass (model 2). The results are shown in Table 3. Because sex proved to be a significant effect modifier for the association between vitamin D insufficiency and low lean mass (P for interaction = 0.003 and <0.001 in model 1 and model 2, respectively), we stratified the analyses by sex to detect possible sex-specific associations between vitamin D insufficiency and low lean mass. In the risk factor–adjusted model stratified by sex, vitamin D insufficiency was no longer significantly associated with low lean mass in women but remained significantly associated with low lean mass in men, as can be seen in Table 4.

Table 2
Characteristics of the study population, stratified according to sex and vitamin D status

	Women (n = 562)			Men (n = 540)		
	25(OH)D		P	25(OH)D		P
Parameters	≥50 nmol/L	<50 nmol/L		≥50 nmol/L	<50 nmol/L	
N (%)	305 (54.3)	257 (45.7)		279 (51.7)	261 (48.3)	0.398
Age (y)	67.5 ± 3.3	68.0 ± 3.5	0.136	68.7 ± 3.5	68.0 ± 3.9	0.019
BMI (kg/m^2)	25.8 ± 3.9	26.8 ± 5.1	0.010	27.0 ± 3.5	27.5 ± 3.7	0.079
Smoking, n(%)			0.653			0.373
Current	27 (51.9)	25 (48.1)		25 (0.7)	33 (56.9)	
Former	93 (52.0)	86 (48.0)		151 (27.5)	133 (46.8)	
Never	185 (55.9)	146 (44.1)		103 (71.8)	95 (48.0)	
Total fat mass (kg)	27.1 ± 7.7	28.9 ± 8.6	0.009	24.6 ± 6.9	26.4 ± 7.1	0.003
ALM (kg)	16.2 ± 2.3	16.1 ± 2.4	0.511	24.2 ± 2.9	23.8 ± 2.8	0.084
ALM/BMI	0.64 ± 0.1	0.61 ± 0.1	0.001	0.91 ± 0.1	0.87 ± 0.1	0.001
Grip strength (kgf)	27.1 ± 4.8	27.0 ± 5.2	0.803	42.0 ± 6.5	42.4 ± 6.8	0.514
TUG time (s)	7.7 ± 1.5	7.7 ± 1.8	0.892	8.0 ± 1.6	8.0 ± 1.9	0.873
Falls*	1.7 ± 0.5	1.6 ± 0.5	0.473	1.8 ± 0.4	1.7 ± 0.5	0.008
Frailty, n (%)			0.003			0.029
Frail	3 (1.0)	3 (1.2)		0 (0.0)	4 (1.5)	
Prefrail	69 (22.6)	91 (35.4)		79 (28.3)	90 (34.5)	
Not frail	233 (76.4)	163 (63.4)		200 (71.7)	167 (64.0)	
Morbidity index	1.1 ± 1.2	1.2 ± 1.1	0.283	1.3 ± 1.3	1.4 ± 1.3	0.541

25(OH)D, 25-hydroxyvitamin D; ALM, appendicular lean mass; BMI, body mass index; TFM, total fat mass; TUG: timed up and go.
Variables are presented as mean and standard deviation or in n and percentage.
*Number of falls in the last 12 mo.

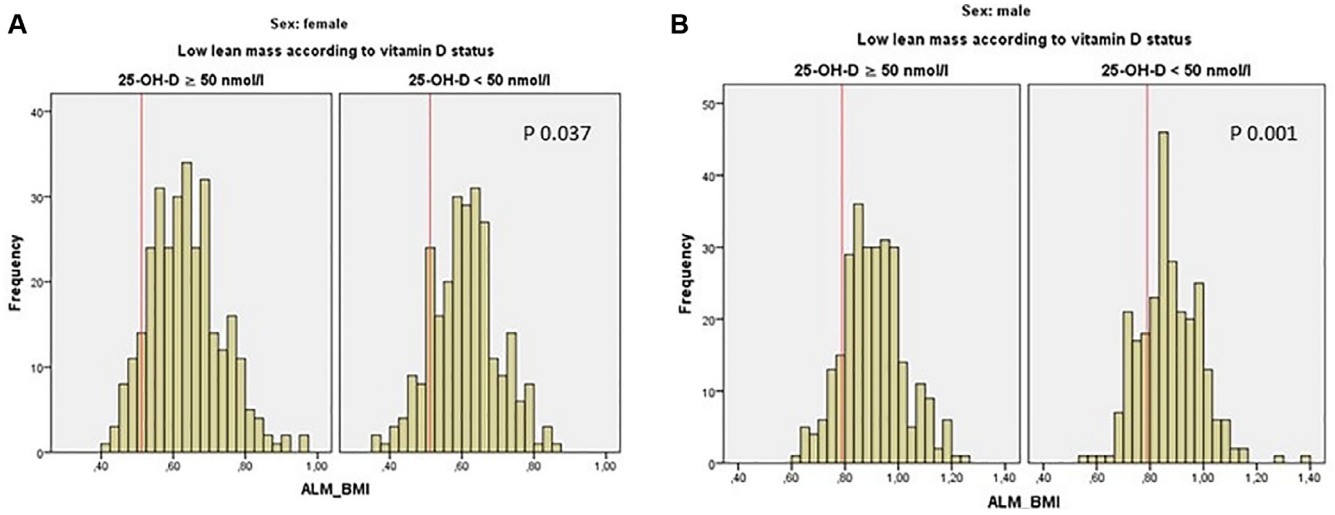

Fig. 1. The prevalence of low lean mass defined by ALM/BMI according to vitamin D status for female (A) and male (B) participants. The red lines indicate the cutoff values for low lean mass. ALM, appendicular lean mass; BMI, body mass index.

Table 3
Risk factor–adjusted logistic regression displaying the association of vitamin D insufficiency with low ALM/BMI*

	25(OH)D < 50 nmol/L		
	OR	95% CI	*P*
Model 1*			
Low ALM/BMI	1.826	1.291–2.584	0.001
Model 2*			
Low ALM/BMI	1.558	1.072–2.266	0.020

25(OH)D, 25-hydroxyvitamin D; ALM, appendicular lean mass; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; OR, odds ratio.
Model 1: Logistic regression adjusted for age, regular strength training, CRP, and morbidity index.
Model 2: Logistic regression adjusted for age, regular strength training, CRP, morbidity index and total fat mass.
*Reference group 25(OH)D ≥ 50 nmol/L.

Vitamin D and frailty

To examine the association of vitamin D insufficiency with prefrailty/frailty and the individual frailty criteria, a risk factor–adjusted logistic regression analysis was conducted controlling for age, sex, inflammation (CRP), and the morbidity index (model 1). Because low ALM/BMI was found to be associated with a higher risk for being prefrail or frail [13], this parameter was additionally considered in model 2 of the regression analysis. The results are shown in Table 5.

Overall, vitamin D insufficiency was significantly associated with prefrailty/frailty status, regardless of adjusting for low ALM/BMI or not. Sex was not a significant effect modifier for the association between vitamin D insufficiency and prefrailty/frailty (*P* for interaction = 0.666 and 0.958 in model 1 and model 2, respectively). Therefore these analyses were not stratified by sex.

Regarding the separate frailty criteria, vitamin D insufficiency was significantly associated with low physical activity and slow walking speed in both models. For all other criteria—weight loss, exhaustion, and weakness—no association with vitamin D insufficiency was found.

Table 4
Risk factor adjusted logistic regression displaying the association of vitamin D insufficiency with low ALM/BMI in women and men*

	Women			Men		
	25(OH)D < 50 nmol/L			25(OH)D < 50 nmol/L		
	OR	95% CI	*P*	OR	95% CI	*P*
Model 1*						
Low ALM/BMI	1.634	0.954–2.799	0.074	1.936	1.228–3.050	0.004
Model 2*						
Low ALM/BMI	1.268	0.710–2.266	0.422	1.762	1.072–2.895	0.025

25(OH)D, 25-hydroxyvitamin D; ALM, appendicular lean mass; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; OR, odds ratio.
Model 1: Logistic regression adjusted for age, regular strength training, CRP, and morbidity index.
Model 2: Logistic regression adjusted for age, regular strength training, CRP, morbidity index, and total fat mass (TFM).
*Reference group 25(OH)D ≥ 50 nmol/L.

Table 5
Risk factor adjusted logistic regression displaying the association of vitamin D insufficiency with prefrailty/frailty and the individual frailty criteria*

	25(OH)D < 50 nmol/L		
	OR	95% CI	*P*
Model 1*			
Prefrailty/frailty	1.611	1.239–2.096	<0.001
Weight loss	0.930	0.394–2.195	0.869
Exhaustion	1.161	0.800–1.686	0.433
Weakness	1.581	0.874–2.858	0.130
Slow walking speed	1.602	1.052–2.439	0.028
Low physical activity	1.881	1.240–2.854	0.003
Model 2*			
Prefrailty/frailty	1.535	1.177–2.003	0.002
Weight loss	0.927	0.391–2.198	0.864
Exhaustion	1.154	0.793–1.680	0.454
Weakness	1.420	0.778–2.592	0.253
Slow walking speed	1.532	1.003–2.341	0.048
Low physical activity	1.761	1.156–2.684	0.008

25(OH)D, 25-hydroxyvitamin D; ALM, appendicular lean mass; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; OR, odds ratio.
Model 1: Logistic regression adjusted for age, sex, CRP, and morbidity index.
Model 2: Logistic regression adjusted for age, sex, CRP, morbidity index, and low ALM/BMI.
*Reference group 25(OH)D ≥ 50 nmol/L.

Discussion

In this analysis we examined the association between vitamin D insufficiency and low lean mass and the association between vitamin D insufficiency and prefrailty/frailty status, with a special focus on effect modification by sex.

As one major finding, we detected that vitamin D status was associated with low lean mass in men only, whereas vitamin D status was associated with frailty regardless of sex. In general, the prevalence of vitamin D insufficiency and of prefrailty/frailty had no sex-specific differences, whereas the prevalence of low lean mass was higher in men.

Because our study was cross-sectional, any conclusion of causal relationships is of course not possible. But although a positive relationship between vitamin D status and muscle is reasonable because we know of direct and indirect effects of vitamin D on muscle tissue [25] and its role in the regulation of skeletal muscle tropism and contraction, the sex-specific differences are more difficult to explain. Although sex-specific differences in muscle mass are generally expected, sarcopenia was already defined by sex-specific cutoffs, thus being adjusted for this premise. Most likely, different rates of decline of anabolic hormones such as testosterone and estrogen in different life stages in men and women, which could not be adjusted for in the present analyses, play a significant role in the development of sarcopenia [26]. Because our study participants had a mean age of roughly 68 y, the hormonal changes of female menopause may outweigh the effect of a low vitamin D level on muscle mass. In men, however, in whom a decline of testosterone usually occurs at an older age, a low vitamin D level might be more crucial concerning the loss of lean mass and the onset of sarcopenia.

Moreover, methodological aspects have to be considered as well. When studying the relationship between vitamin D concentration and muscle mass, it is very important to take whole-body composition into account because a higher BMI—and thus most often a higher fat mass, as seen in our cohort—leads to lower 25 (OH)D concentrations, whereas a reverse effect is unlikely [27]. The responsible mechanism might be due to sequestration of the fat-soluble vitamin D in body fat tissue and therefore decreased bioavailability of vitamin D_3 [28]. Women had a higher total fat mass than men, and the highest total fat mass overall was found in vitamin D–insufficient women. Hence fat mass likely might be a moderator of the effect size of the assumed exposure (vitamin D insufficiency) on the possible outcome (low lean mass) as well as a mediator lying on the pathway between exposure and outcome, and this effect could be more pronounced in women than in men.

The results of our study regarding the association between vitamin D insufficiency and low lean mass differ from previously reported findings. Marantes et al. [29] found no association between 25(OH)D concentrations and muscle mass or strength, with the exception of a subgroup of women younger than age 65 y. Their sample was younger overall (mean age 56 and 57 y for men and women, respectively [range 21–97 y]) than the BASE-II sample, which hampers comparison. In a large sample in the Korean National Health and Nutrition Examination Survey, Park et al. [30] found that vitamin D deficiency (defined as levels <37.5 nmol/L) was positively associated with sarcopenia in women only.

The results of our study illustrate that the potential role of sex-specific effects on the association between vitamin D status and low lean mass remain somewhat controversial, and further studies are needed to elucidate this mechanism.

In our study, vitamin D insufficiency was associated with prefrailty/frailty regardless of sex. However, other studies found sex-specific differences. In a recent meta-analysis by Zhou et al. [31], which also examined the association between low 25(OH)D concentrations and frailty, sex-specific differences were found; low vitamin D concentrations were significantly associated with the risk of frailty in women only. Overall, evidence for sex-specific differences in factors associated with frailty is just beginning to emerge [32]. However, sex differences in biological factors, such as inflammatory cytokines, sarcopenia, or abdominal adiposity, seem to account for sex differences in disease development, disability, mortality, and also frailty [33,34], and a low 25(OH)D level might be one such sex-specific factor, although the exact mechanism and whether there is even a causal role are unclear.

Although the method of measuring frailty and the consideration of sex-specific aspects vary considerably among studies, the majority of those studies have found an association between vitamin D status and frailty [35]. However, only a few studies have investigated the association between vitamin D and each individual criteria of the frailty phenotype. Tajar et al. [36] described an association of low vitamin D concentrations with weakness, low walking speed, exhaustion, and low activity but not sarcopenia (based on measurement of mid-upper arm muscle circumference). We found an association between vitamin D insufficiency and slow walking speed as well as low physical activity. The cross-sectional association with the latter could be explained by reduced outdoor activities and sun exposure. The different assessment methods between studies most likely contribute to the differing results concerning the individual frailty criteria. Of note, our data suggest that there is an association between vitamin D insufficiency and frailty independent of low lean mas. Although the loss of lean or muscle mass is a key risk factor for frailty, the pathogenesis of frailty is multifactorial and therefore factors not affecting muscle mass or affecting only muscle strength but not mass may still favor the development of frailty. It is plausible that the association of vitamin D status with frailty is modified by the presence of certain diseases. For instance, in a study by Buta et al. [37] the relationship between vitamin D levels and incident frailty was no longer significant after adjusting for the presence of cardiometabolic diseases. Vitamin D is also hypothesized to be a marker of resilience to potentially fatal diseases or conditions, which means that vitamin D insufficiency may not be a risk factor for major chronic diseases but for fatal outcomes of these diseases, such as death as a result of myocardial infarction in participants with cardiovascular disease [38]. It can be hypothesized that there is a common pathway between this resilience to fatal outcomes and a resilience to withstand the process of becoming frail with increasing age. Vitamin D insufficiency might be an early marker of a process of unhealthy aging characterized by decreased resilience as well functional decline leading toward frailty, disability, and death. This, of course, cannot be answered in a cross-sectional study, which is one of the limitations of the present analysis. Further longitudinal analyses regarding these factors will be necessary in the future. Another potential problem lies in the BASE-II recruitment criteria that excluded participants if they reported difficulty walking one-quarter of a mile without assistance. Thus our cohort might be composed of viewer participants who could have fulfilled the frailty criterion "slow walking speed," and this might also have resulted in an overall smaller percentage of frail participants in this study. Further limitations include the adjustments that had to be made for defining frailty compared with the original assessment methods by Fried et al. [10]. Moreover, the immunoassays used for the 25(OH)D measurement are not the current gold standard (which is mass spectrometry), meaning comparability to other studies is hampered methodologically.

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