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Low Serum 25-Hydroxyvitamin D as a Risk Factor for Frailty in Community-Dwelling Older Men: A Korean Nationwide Study

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Background: Despite the critical role of vitamin D in various biological processes, its impact on frailty—a condition closely linked to biological age—remains inconclusive. This study aimed to explore the association between serum 25-hydroxyvitamin D (25[OH]D) levels and frailty status in older Korean adults, utilizing a comprehensive frailty index (FI) and a nationally representative dataset.

Methods: This cross-sectional study included 6,589 participants aged ≥65 years from the Korea National Health and Nutrition Examination Survey (2008–2012). Frailty was assessed using a deficit accumulation FI based on 38 physical, cognitive, psychological, and social items.

Results: After adjusting for potential confounders, frail men showed 6.8% lower serum 25(OH)D concentrations compared to non-frail controls (P=0.007). Men in the lowest serum 25(OH)D quartile (≤39.3 nmol/L) exhibited a 5.3% higher FI (P=0.047) and 1.71-fold increased odds of frailty (P=0.005), compared to those in the highest quartile (>63.3 nmol/L). Similarly, men with vitamin D deficiency (<30 nmol/L) exhibited a 9.6% higher FI compared to those with sufficient vitamin D levels (≥50 nmol/L; P=0.004). However, no significant association between serum 25(OH)D concentration and frailty was observed in women across any analysis.

Conclusion: These findings suggest that low serum 25(OH)D concentrations are a potential risk factor for frailty, particularly in men. Further research is warranted to determine whether vitamin D supplementation in such high-risk older adults could help mitigate frailty.

Keywords: Frailty; 25-Hydroxyvitamin D; Aging; Biomarkers

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INTRODUCTION

Frailty is a complex clinical syndrome characterized by a decline in physiological reserves across multiple organ systems, resulting in reduced resilience and increased vulnerability to adverse health outcomes [1]. It is a major concern in aging populations as it contributes to falls, hospitalization and mortality and significantly burdens healthcare systems worldwide [2]. However, assessing frailty accurately remains a challenge due to its complex and multidimensional nature. Although there is no gold standard, frailty is commonly assessed using two principal models: the Fried frailty phenotype (FFP) and the frailty index (FI). The FFP, introduced by Fried et al. [3], conceptualizes frailty as a physical phenotype characterized by five criteria: unintentional weight loss, weakness, exhaustion, slowness, and low physical activity. FFP is simple and practical for clinical use but it does not fully capture the cognitive, psychological, and social aspects of frailty. In contrast, the FI developed by Rockwood et al. [4] offers a more comprehensive assessment by incorporating deficits across health domains, including comorbidities, functional impairments, and symptoms, providing a detailed and sensitive measure of frailty. This multidimensional approach allows the FI to provide a more detailed and sensitive measure of frailty. By assessing frailty on a continuous scale, the FI allows for the identification of subtle health declines and the accurate prediction of critical outcomes.

Identifying modifiable risk factors contributing to frailty is crucial for developing effective prevention and management strategies. Among these potential factors, vitamin D is an important factor due to its vital role in musculoskeletal health, immune function, and overall physiological homeostasis [5]. Vitamin D plays a critical role in skeletal aging by regulating calcium absorption and bone remodeling, which helps maintain bone density and reduces the risk of fractures [6]. Additionally, vitamin D is essential for maintaining muscle strength and function, as it promotes muscle cell proliferation and differentiation while mitigating muscle atrophy through anti-inflammatory and antioxidative pathways [7]. A vitamin D deficiency exacerbates sarcopenia by impairing neuromuscular signaling and reducing physical performance [8]. Beyond its musculoskeletal effect, vitamin D also exerts systemic effects by modulating immune responses, suppressing chronic low-grade inflammation through cytokine inhibition, and enhancing mitochondrial efficiency to reduce oxidative stress, thereby mitigating cellular and systemic aging [9,10]. Serum 25-hydroxyvitamin D (25[OH]D) is widely regarded as a reliable marker for assessing vitamin D status [11]. Low serum 25(OH)D levels have been widely reported in older populations and are associated with a variety of negative health outcomes [12-14]. Given these well-documented associations, vitamin D deficiency may reflect or influence frailty.

Although numerous studies have examined the relationship between vitamin D levels and frailty, most have focused on small populations, or single-sex cohorts, or have relied on phenotypic frailty assessments [15-17]. These limitations have led to inconclusive evidence regarding the role of vitamin D as a potential biomarker for frailty. Furthermore, there has been limited research utilizing the FI to investigate the relationship between serum 25(OH)D levels and frailty in a nationally representative cohort, including both men and women. Therefore, we aimed to investigate the relationship between serum 25(OH)D levels and frailty using the comprehensive FI, which captures deficits across multiple health domains using nationally representative data from the older Korean adults. Additionally, our study included both sexes, enabling the assessment of sex-specific differences in this relationship.

METHODS

Participants and data collection

This cross-sectional study utilized data from the Korea National Health and Nutrition Examination Survey (KNHANES IV and V), conducted from 2008 to 2012. The KNHANES is a nationally representative survey conducted by the Korea Centers for Disease Control and Prevention, providing comprehensive data on the health and nutritional status of the Korean population. The survey consists of health interviews, health examinations, and nutritional assessments [18]. A stratified, multistage sampling design was employed to ensure proportional representation across various demographic and geographic groups. Detailed information regarding the survey's methodology and database is available at https://knhanes.cdc.go.kr.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Eunpyeong St. Mary's Hospital, Catholic Medical Center, The Catholic University of Korea (IRB approval No. PC25ZISI0012). As the study utilized previously collected anonymized data, the requirement for written informed consent was waived.

Of the 8,036 older adults (aged ≥65 years) who participated in KNHANES from 2008 to 2012, 6,589 were included in the analysis after applying the following exclusion criteria: (1) more than 20% missing data in the frailty assessment (>7 items) (*n*=

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181) and (2) missing serum vitamin D measurements (n=1,266). The final analysis included 6,589 participants (Supplemental Fig. S1).

Laboratory analyses

Blood samples were obtained from participants following an overnight fast of at least 8 hours. Samples were collected in the morning, promptly processed through centrifugation and aliquoting, and transported to the Central Testing Institute in Seoul, Korea, for analysis within 24 hours. Serum fasting glucose, total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) were enzymatically measured using a commercial kit (Sekisui, Osaka, Japan) with a Hitachi Automatic Analyzer 7600 (Hitachi, Tokyo, Japan). Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula: LDL-C=TC–HDL-C–(TG/5). Spot urine sampling was performed in fasting state and the first-morning midstream urine was collected in most of the population. Serum 25(OH)D levels were measured using a 1470 WIZARD gamma counter (PerkinElmer, Turku, Finland) using the 25(OH)D ^{125}I RIA Kit (DiaSorin, Stillwater, MN, USA). The 25(OH)D levels were retrospectively standardized, as the institute participated in the Vitamin D External Quality Assessment Scheme (DEQAS) to ensure the accuracy and reliability of external quality controls [19].

Classification of serum 25(OH)D levels

Serum 25(OH)D levels were categorized into sex- specific quartiles (men: Q1 ≤39.3 nmol/L to Q4 >63.3 nmol/L; women: Q1 ≤33.5 nmol/L to Q4 >57.0 nmol/L) and sufficiency categories based on clinical thresholds: deficient (<30 nmol/L), insufficient (30 to 50 nmol/L), and sufficient (≥50 nmol/L).

Covariates related to frailty

During the study period, blood pressure (BP) was measured by trained nurses using a mercury sphygmomanometer (Baumanometer Wall Unit 33[0850], W.A. Baum, Copiague, NY, USA) and an appropriately sized cuff. Prior to the measurement, participants were instructed to remain seated and rest quietly for at least 5 minutes in a comfortable position to ensure stable readings. BP was measured three times on the right arm, with a 30-second interval between each measurement. The final systolic and diastolic BP values were determined as the average of the second and third measurements, following standard protocols to enhance reliability and precision [20]. Household income, education levels, and lifestyle such as smoking status were determined based on participants' responses to related questions. Household income was divided into four quartiles: low (<680 United States dollar [USD]/month), mid-low (680–1,359 USD/month), mid-high (1,360–2,229 USD/month), and high (≥2,230 USD/month). Education levels were categorized as elementary school or lower, middle school, high school, and college or higher. Smoking was defined as having smoked at least five packs of cigarettes in a lifetime and currently smoking. Participants were identified as having specific diseases, such as hypertension, dyslipidemia, or cardiovascular disease, if they reported a physician-confirmed diagnosis. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2).

Assessment of frailty

Frailty in this study was assessed using a FI developed based on standardized methodologies [21] and adapted from prior frailty indices utilizing KNHANES data [22-25]. The FI included 38 items commonly surveyed in KNHANES, encompassing comorbidities, functional abilities, signs and symptoms, and laboratory results. Comorbidities included anemia, arthritis, bronchial asthma, cancer, cardiovascular disease, cataracts, chronic obstructive pulmonary disease, depression, diabetes, dyslipidemia, hypertension, and stroke. Functional abilities were assessed based on physical inactivity, reduced exercise capacity, limitations in activities of daily living, social activity restrictions, inability to self-care, hearing impairment, and chewing difficulty. Signs and symptoms evaluated included pain or discomfort, weight loss, depression or anxiety, suicidal ideation, and stress. Laboratory measurements incorporated into the FI were systolic BP, diastolic BP, heart rate regularity, pulmonary function, hemoglobin, blood urea nitrogen, creatinine, TC, TG, HDL-C, fasting glucose, and urine protein. Additionally, current smoking status and BMI were included as part of the index calculation.

This index quantifies frailty on a continuous scale ranging from 0 (optimal health) to 1 (severe frailty). Participants were classified into three categories according to their FI score: non-frail (FI ≤0.15), pre-frail (0.15< FI ≤0.25), and frail (FI >0.25), consistent with established criteria.

Statistical analysis

Statistical analyses were conducted to account for the complex sampling design and weighting of KNHANES, ensuring nationally representative estimates. Data from the annual surveys were pooled and analyzed, treating each year's sample as independent. Continuous variables were expressed as mean±standard

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Table 1. Baseline Characteristics of the Study Participants according to Frailty Status

Variable	Men (*n*=2,815)				Women (*n*=3,774)			
	Non-frail (*n*=1,284)	Pre-frail (*n*=997)	Frail (*n*=534)	*P* value	Non-frail (*n*=975)	Pre-frail (*n*=1,426)	Frail (*n*=1,373)	*P* value
Age, yr	71.1±0.1	71.9±0.2	72.5±0.3	<0.001[a]	71.8±0.2	72.2±0.2	73.2±0.2	<0.001[a]
Income quartile, %				<0.001[a]				<0.001[a]
Low	40.4	47.1	61.1		46.8	55.5	62.0	
Mid-low	27.1	30.9	23.0		25.4	22.1	20.2	
Mid-high	18.8	11.6	8.5		15.0	12.5	9.9	
High	13.7	10.4	7.5		12.8	9.9	7.8	
Level of education, %				<0.001[a]				<0.001[a]
1st	42.9	49.0	62.5		79.9	84.6	90.5	
2nd	17.3	19.8	15.2		7.8	8.2	5.8	
3rd	21.7	19.9	16.5		9.2	6.3	3.1	
4th	18.1	11.3	5.8		3.1	0.9	0.7	
Smoking	238 (20.2)	296 (30.7)	181 (35.6)	<0.001[a]	24 (2.7)	59 (4.2)	85 (6.9)	<0.001[a]
Hypertension	593 (46.8)	651 (65.8)	363 (68.6)	<0.001[a]	479 (51.0)	933 (67.5)	1,045 (77.7)	<0.001[a]
Dyslipidemia	100 (8.3)	128 (12.6)	86 (16.6)	<0.001[a]	119 (13.2)	235 (16.5)	323 (23.9)	<0.001[a]
Cardiovascular disease (MI, angina)	43 (3.1)	94 (9.2)	72 (13.3)	<0.001[a]	18 (1.5)	60 (4.1)	128 (9.3)	<0.001[a]
BMI, kg/m^2	23.1±0.1	23.4±0.1	23.1±0.2	0.151	23.5±0.1	24.2±0.1	24.9±0.1	<0.001[a]

Values are expressed as mean±standard error or number (%). Continuous and categorial variables were compared using general linear model and cross-tabs analyses in a complex sample analysis method, respectively.
MI, myocardial infarction; BMI, body mass index.
[a]Statistically significant values.

error, while categorical variables were presented as percentages. Baseline characteristics of the participants were analyzed using general linear models for continuous variables and cross-tabulations for categorical variables. Confounding variables were selected based on clinical relevance and statistical significance in univariate analyses and included age, income, level of education, smoking, hypertension, dyslipidemia, cardiovascular diseases, and BMI. Linear regression analysis was conducted to assess the association between serum 25(OH)D levels and the FI, with the FI as the dependent variable and serum 25(OH)D as the independent variable. The risk of pre-frailty and frailty was assessed using multiple logistic regression to calculate odds ratios (ORs) with 95% confidence intervals, based on continuous serum 25(OH)D levels, quartiles of serum 25(OH)D, and sufficiency categories (deficient, insufficient, and sufficient). Differences in the FI across serum 25(OH)D quartiles and sufficiency categories were analyzed using a general linear model, adjusting for potential covariates. Multiple logistic regression was used to assess associations with pre-frailty and frailty. All analyses were two-tailed, with statistical significance set at $P<0.05$. Statistical analyses were performed using SPSS version 21.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

The baseline characteristics of participants, categorized by frailty status, are summarized in Table 1. Among the 6,589 participants aged ≥65 years, the prevalence of frailty was 29.1%. Among 2,815 men, 1,284 (45.6%) were non-frail, 997 (35.4%) were pre-frail, and 534 (19.0%) were frail, with mean ages of 71.1, 71.9, and 72.5 years, respectively ($P<0.001$). Among 3,774 women, 975 (25.8%) were non-frail, 1,426 (37.8%) were pre-frail, and 1,373 (36.4%) were frail, with mean ages of 71.8, 72.2, and 73.2 years, respectively ($P<0.001$). In both men and women, the progression from non-frail to pre-frail and frail status was associated with lower income, less educational attainment, a higher smoking prevalence, and increased prevalence rates of hypertension, dyslipidemia, and cardiovascular diseases (all $P<0.001$). BMI showed no significant differences across frailty groups in men. In women, however, BMI increased pro-

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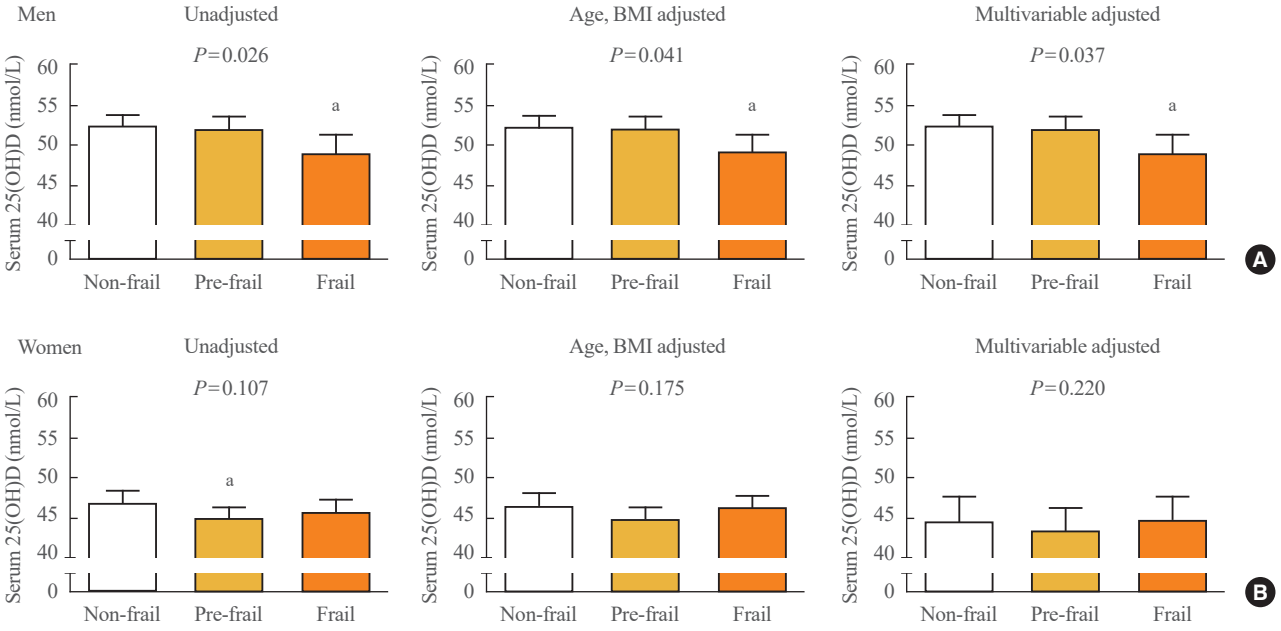

Fig. 1. Differences in serum 25-hydroxyvitamin D (25[OH]D) levels according to the frailty status in men (A) and women (B). The estimated means with 95% confidence intervals were generated and compared using general linear model analysis in a complex sample analysis method. Multivariable adjusted model includes age, income, level of education, smoking, hypertension, dyslipidemia, cardiovascular diseases, and body mass index (BMI) as confounding factors. [a]Statistically significant difference from the non-frail group.

gressively with frailty compared to the control group ($P<0.001$).

The differences in serum 25(OH)D levels by frailty status were analyzed using a general linear model in a complex sample analysis framework (Fig. 1). In men, no significant difference in serum 25(OH)D level was observed between the non-frail and pre-frail groups before adjusting for confounders. However, serum 25(OH)D levels in frail men were reduced by 6.8% compared to in the non-frail controls ($P=0.007$). This significant reduction in serum 25(OH)D levels among frail men remained statistically significant even after adjusting not only for age and BMI but also for income, level of education, smoking, hypertension, dyslipidemia, and cardiovascular diseases ($P=0.013$ and $P=0.014$, respectively). In contrast, no significant differences in serum 25(OH)D levels were observed among the three frailty groups in women, after multivariable adjustment.

The relationship between serum 25(OH)D level and the FI was examined using linear regression analyses (Table 2). In men, unadjusted analyses showed a significant inverse relationship between serum 25(OH)D levels and the FI ($P=0.038$). However, this association lost statistical significance after adjusting for confounding factors like age and BMI. In women, no significant relationship was observed between serum 25(OH)D levels and the FI in any adjustment model.

The risk of pre-frailty and frailty in relation to serum 25(OH)D level was assessed using multiple logistic regression analyses (Table 3). After adjusting for age, income, education level, smoking status, hypertension, dyslipidemia, cardiovascular diseases,

Table 2. Multiple Linear Regression Analysis to Determine whether Serum 25(OH)D Level Is Independently Associated with Frailty Index

Adjustment	Dependent variable: frailty index		
	β	SE	*P* value
Men			
Unadjusted	–0.000668	0.000321	0.038[a]
Age and BMI	–0.000508	0.000313	0.104
Multivariable	–0.000498	0.000285	0.081
Women			
Unadjusted	–0.000338	0.000298	0.258
Age and BMI	–0.000036	0.000288	0.901
Multivariable	0.000064	0.000255	0.802

General linear model analysis was performed with frailty index as a dependent variable, and with serum 25(OH)D as an independent variable. Multivariable adjusted model includes age, income, level of education, smoking, hypertension, dyslipidemia, cardiovascular diseases, and BMI as confounding factors.
25(OH)D, 25-hydroxyvitamin D; β, regression coefficient; SE, standard error; BMI, body mass index.
[a]Statistically significant value.

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and BMI, no significant association was found between serum 25(OH)D level and pre-frailty in either men or women. However, in men, a decrease in the serum 25(OH)D level of standard deviation was associated with an increased crude OR of 1.22 for frailty (P=0.009). This association remained significant in the age- and BMI-adjusted model (20% increased risk; P=0.015)

Table 3. Logistic Regression Analyses to Determine the ORs for Pre-Frail and Frail Status according to Serum 25(OH)D Level

Adjustment	Pre-frail		Frail	
	OR (95% CI)[a]	*P* value	OR (95% CI)[a]	*P* value
Men				
Unadjusted	1.03 (0.93–1.13)	0.586	1.22 (1.05–1.41)	0.009[b]
Age and BMI	1.01 (0.91–1.11)	0.892	1.20 (1.04–1.38)	0.015[b]
Multivariable	1.00 (0.90–1.11)	0.979	1.19 (1.04–1.38)	0.015[b]
Women				
Unadjusted	1.11 (1.01–1.22)	0.033[b]	1.07 (0.96–1.18)	0.213
Age and BMI	1.09 (0.99–1.20)	0.079	1.02 (0.92–1.13)	0.749
Multivariable	1.08 (0.98–1.19)	0.125	1.00 (0.90–1.11)	0.954

Multivariable adjustment model includes age, income, level of education, smoking, hypertension, dyslipidemia, cardiovascular diseases, and BMI as confounding factors.
OR, odds ratio; 25(OH)D, 25-hydroxyvitamin D; CI, confidence interval; BMI, body mass index.
[a]Per standard deviation decrement in serum 25(OH)D level (17.8 nmol/L for men and 17.8 nmol/L for women); [b]Statistically significant values.

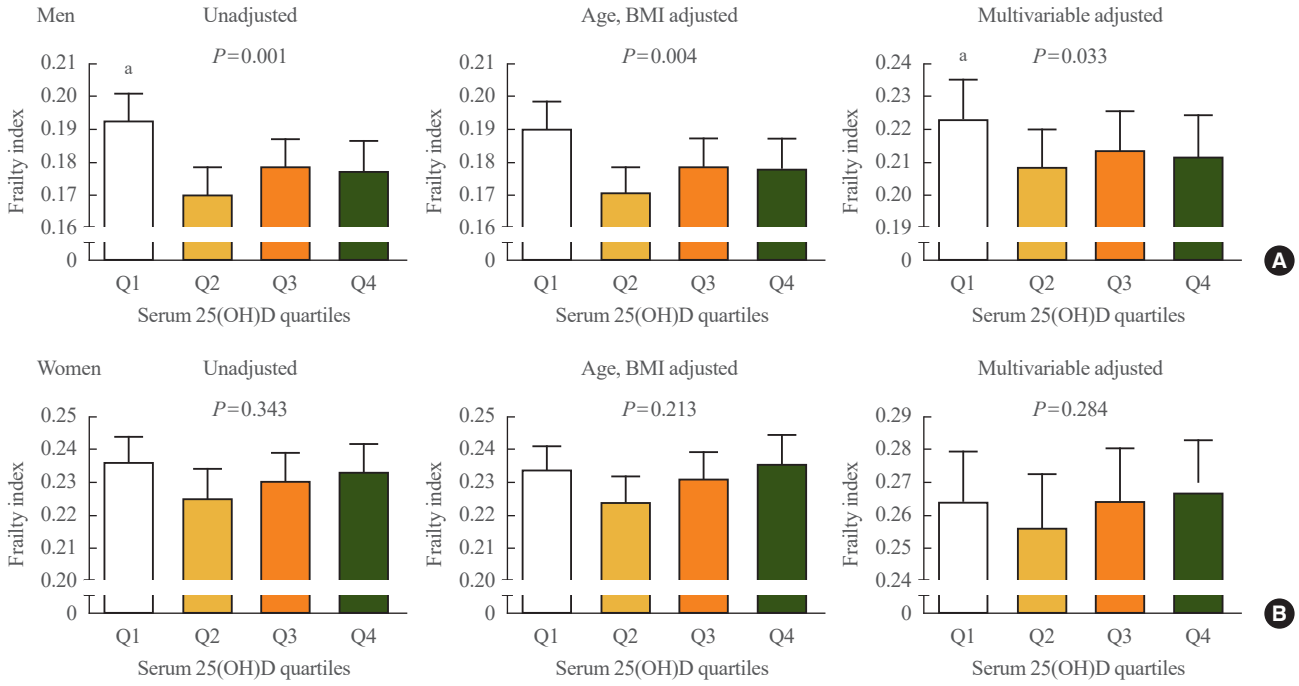

Fig. 2. Differences in frailty index according to serum 25-hydroxyvitamin D (25[OH]D) quartiles in men (A) and women (B). The estimated means with 95% confidence intervals were generated and compared using general linear model analysis in a complex sample analysis method. Multivariable adjusted model includes age, income, level of education, smoking, hypertension, dyslipidemia, cardiovascular diseases, and body mass index (BMI) as confounding factors. Serum 25(OH)D quartiles in men: Q1, serum 25(OH)D ≤39.3 (nmol/L); Q2, 39.3< serum 25(OH)D ≤50.5; Q3, 50.5< serum 25(OH)D ≤63.3; Q4, serum 25(OH)D >63.3. Serum 25(OH)D quartiles in women: Q1, serum 25(OH)D ≤33.5 (nmol/L); Q2, 33.5< serum 25(OH)D ≤44.0; Q3, 44.0< serum 25(OH)D ≤57.0; Q4, serum 25(OH)D >57.0. Q, quartile. [a]Statistically significant difference from the Q4 (highest quartile).

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and the fully adjusted multivariable model (19% increased risk; P=0.015). Conversely, in women, no significant association was identified between serum 25(OH)D level and frailty risk, regardless of adjustment.

To assess potential threshold effects of the serum 25(OH)D levels on the FI, participants were divided into four quartile groups by serum 25(OH)D levels within each sex (Fig. 2). Among men, unadjusted analyses showed that participants in the lowest quartile (Q1, ≤39.3 nmol/L) had an 8.5% higher FI compared to those in the highest quartile (Q4, >63.3 nmol/L) (P=0.016). This difference remained statistically significant after adjusting for all confounding factors, with Q1 showing a 5.3% higher FI compared to Q4 (P=0.047). In women, however, no significant differences in the FI were observed across quartile groups in any adjustment model.

Consistently, in men, the OR for frailty risk in the Q1 group compared to the Q4 group was significantly higher across all models: with a value of 1.74 in the unadjusted model (P=0.002), 1.65 in the age- and BMI-adjusted model (P=0.005), and 1.71 in the fully adjusted multivariable model (P=0.005) (Fig. 3). In women, there were no significant differences in frailty risk across serum 25(OH)D quartile groups, regardless of the adjustment model used.

Lastly, participants were categorized into three groups based on serum 25(OH)D levels, as follows: deficient (<30 nmol/L), insufficient (≥30 but <50 nmol/L), and sufficient (≥50 nmol/L). Differences in FI by vitamin D status were analyzed (Fig. 4). In men, the FI was at least 9.6% higher in the vitamin D deficient group compared to the vitamin D sufficient group, before and after adjusting for potential confounders (P<0.001 to 0.004). However, in women, no significant differences in FI were observed among the three vitamin D status groups, irrespective of adjustment.

DISCUSSION

This study demonstrated an impact of serum 25(OH)D levels on frailty status in older Korean adults using a nationally represen-

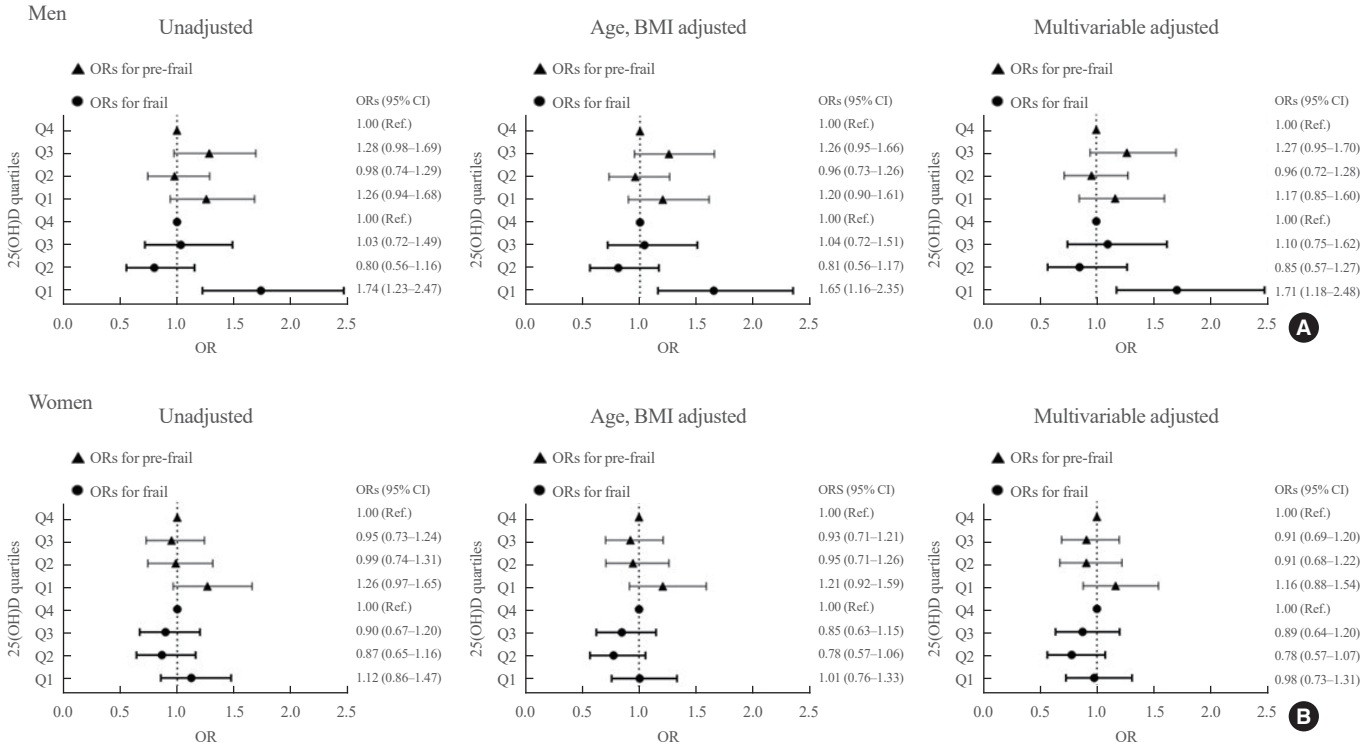

Fig. 3. Logistic regression analyses to determine the odds ratios for pre-frail and frail status according to serum 25-hydroxyvitamin D (25[OH]D) quartiles in men (A) and women (B). Multivariable adjusted model includes age, income, level of education, smoking, hypertension, dyslipidemia, cardiovascular diseases, and body mass index (BMI) as confounding factors. Serum 25(OH)D quartiles in men: Q1, serum 25(OH)D ≤39.3 (nmol/L); Q2, 39.3< serum 25(OH)D ≤50.5; Q3, 50.5< serum 25(OH)D ≤63.3; Q4, serum 25(OH)D >63.3. Serum 25(OH)D quartiles in women: Q1, serum 25(OH)D ≤33.5; Q2, 33.5< serum 25(OH)D ≤44.0; Q3, 44.0< serum 25(OH)D ≤57.0; Q4, serum 25(OH)D >57.0. OR, odds ratio; CI, confidence interval; Q, quartile.

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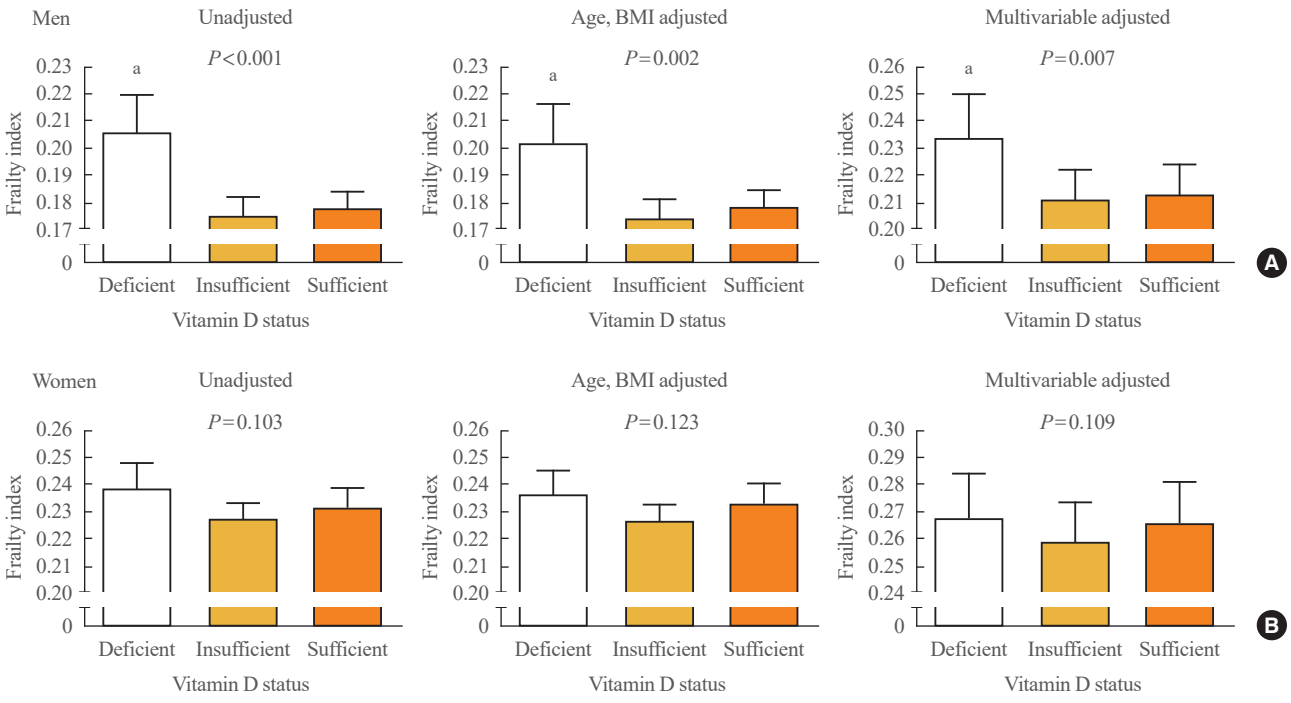

Fig. 4. Differences in frailty index according to serum 25-hydroxyvitamin D (25[OH]D) status in men (A) and women (B). The estimated means with 95% confidence intervals were generated and compared using general linear model analysis in a complex sample analysis method. Multivariable adjusted model includes age, income, level of education, smoking, hypertension, dyslipidemia, cardiovascular diseases, and body mass index (BMI) as confounding factors. Deficient, serum 25(OH)D <30 (nmol/L); Insufficient, 30≤ serum 25(OH)D <50; Sufficient, serum 25(OH)D ≥50. [a]Statistically significant difference from the 'sufficient' status.

tative cohort. The findings showed that low serum 25(OH)D levels were linked to increased FI and frailty risk in men. Additionally, when categorized by vitamin D sufficiency, men with 25(OH)D deficiency showed a significantly higher frail index compared to those with sufficient levels. In contrast, no significant patterns were observed between serum 25(OH)D levels and frailty status or FI in women. These results highlight potential sex differences in the relationship between serum 25(OH)D levels and frailty, underscoring the need for targeted strategies to address frailty in aging populations.

Numerous studies have explored the association between 25(OH)D levels and frailty, but the findings remain inconsistent. According to a previous meta-analysis, while some studies have reported a significant association between low serum 25(OH)D levels and an increased risk of frailty, others have found no association or only modest effects [16]. However, most prior studies relied on the FFP, which primarily evaluates physical frailty based on five physical criteria. Although practical, the FFP may not capture the multidimensional nature of frailty [26-28]. A recent review reported that while observation studies suggest an association between vitamin D levels and frailty, randomized trials of vitamin D supplementation have shown limited benefit in the general population [29]. This discrepancy needs a population-specific and methodologically refined approach. Notably, most of these studies employed the FFP or general summary scales rather than a comprehensive deficit accumulation model. Therefore, its limitations in comprehensively assessing frailty make it difficult to draw definitive conclusions about the role of vitamin D as a biomarker for frailty. In contrast, the FI reflects gradual changes in health status and is effective in predicting adverse health outcomes, such as hospitalization and mortality [30,31]. By applying the FI in a nationally representative cohort, our study addressed the limitations of previous research and provided robust evidence for an association between serum 25(OH)D levels and frailty.

The overall prevalence of frailty based on the FI in this study was 28.9%, which is consistent with previous research showing higher frailty rates when using the FI compared to the FFP [32,33]. The finding of a higher frailty prevalence in women compared to men aligns with previous study, indicating that women are more prone to frailty despite their longer life expectancy [34]. Biologically, women are more susceptible to osteo-

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porosis and sarcopenia due to hormonal changes, particularly the postmenopausal decline in estrogen, which accelerates musculoskeletal deterioration and increases their vulnerability to frailty [35,36]. Social and behavioral factors, such as higher rates of psychological distress, also contribute to frailty in women. Psychological distress has been shown to negatively impact physical and social functioning, further increasing the risk of frailty [37].

Interestingly, while frailty prevalence was higher in women, the association between serum 25(OH)D levels and frailty was more pronounced in men. Men in the lowest serum 25(OH)D quartile (Q1) had a significantly higher FI and a 1.71-fold increased frailty risk compared to those in the highest quartile (Q4). In contrast, women showed no significant association between 25(OH)D levels or status and FI. Our findings are consistent with a previous meta-analysis investigating the association between low serum 25(OH)D levels and frailty [16]. Previous studies have consistently shown that low serum 25(OH)D levels are associated with a high risk of frailty with ORs ranging from 1.7 to 3.7 in participants aged 60 years and older [38,39]. However, these prior studies did not stratify their analyses by sex. One study from Italy, which used the FFP to define frailty, reported significant sex differences, showing that serum 25(OH)D levels (<30 nmol/L) were associated with a 4.94-fold higher frailty risk in men, whereas the association in women was weaker and became nonsignificant after adjustment [40]. These findings align with our results, highlighting the importance of accounting for sex differences.

Vitamin D influences muscle strength through mechanisms such as the activation of vitamin D receptors in muscle cells, promoting protein synthesis and reducing muscle degeneration [41]. A recent study demonstrated that the anabolic effect of vitamin D on muscle strength was significantly moderated by testosterone levels [42]. This interaction suggests that testosterone may amplify the benefit of vitamin D on muscle function, potentially accounting for the stronger association observed between vitamin D levels and frailty in older men. Muscle function and physical performance are critical components of resilience especially in aging men. Furthermore, men tend to exhibit higher baseline muscle mass, which may result to a steeper decline in functional capacity when vitamin D levels are insufficient. The interaction between vitamin D and testosterone is another plausible mechanism [43]. Vitamin D receptors in Leydig cells suggest a direct role for vitamin D in supporting testosterone synthesis. The dual deficiency of vitamin D and testosterone may synergistically impair muscle function, increase inflammation, and exacerbate physical decline, contributing to higher frailty risk in men [44]. In women, no significant association was observed between quartile-based vitamin D levels and frailty outcomes. This aligns with previous research in a U.S. cohort, where no link was found between hypovitaminosis D and frailty in older women, particularly in studies with shorter follow-up periods and limited adjustment for cardiometabolic conditions [45]. While vitamin D plays a crucial role in musculoskeletal health, frailty in women is influenced by multiple factors, including hormonal changes with menopause, psychosocial stressors, and chronic conditions. Postmenopausal estrogen decline accelerates bone and muscle loss, independent of vitamin D levels, possibly masking the impact of vitamin D deficiency on frailty outcomes. Additionally, estrogen enhances the expression of vitamin D receptors, and its reduction may decrease vitamin D bioefficacy [46]. While biological differences are critical factors, potential confounders including vitamin D supplementation in women may also influence this discrepancy. Postmenopausal women are more likely to receive vitamin D and calcium supplementation as part of osteoporosis treatment or prevention strategies, which are commonly recommended in osteoporosis management guidelines to enhance bone health and reduce fracture risk [47]. Socioeconomic status should also be considered in interpreting these sex-specific differences. Compared to men, women in this cohort had significantly lower levels of education and income across all frailty categories. This structural socioeconomic gap, combined with the higher overall prevalence of frailty in women, suggests that frailty in older women may be more strongly influenced by long-standing social disadvantage than by vitamin D status alone. Interestingly, although not statistically significant, a similar inverted J-shaped pattern was observed in women. FI values were slightly higher in the lowest quartile of serum 25(OH)D levels, with minimal differences between the insufficient and sufficient groups. This suggests that a threshold-like association may exist in women as well, but it may be attenuated due to the effects of hormonal decline, supplementation, or socioeconomic disparities.

While previous studies have assumed a linear inverse association between vitamin D deficiency and frailty [17], our findings suggest a threshold effect. FI values were significantly higher in individuals with 25(OH)D deficiency (<30 nmol/L) compared to those with insufficient or sufficient levels, but minimal differences were observed between the insufficient and sufficient groups. This threshold effect was evident, as men with 25(OH)D deficiency had a 1.98-fold higher risk of frailty. These findings indicate that severe vitamin D deficiency has the greatest

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impact on frailty risk in men, underscoring the importance of correcting 25(OH)D levels below this critical threshold. In contrast, the threshold effect was less evident in women. Inconsistent findings on 25(OH)D and frailty may result from differences in study populations, measurement methods, threshold definitions, and frailty criteria. In our study, vitamin D deficiency was defined as serum 25(OH)D levels below 30 nmol/L, a threshold endorsed by multiple expert guidelines for identifying severe deficiency linked to significant health risks, including osteomalacia and nutritional rickets [48-50]. While thresholds <50 nmol/L are often used to define insufficiency or sufficiency [51], our focus on severe deficiency captures individuals at the highest risk of adverse health outcomes.

To the best of our knowledge, this is the first population-based cohort study to examine sex-specific differences in the relationship between serum 25(OH)D levels and frailty status using the well-established FI. Additionally, the large sample size of our study allowed for comprehensive adjustments for multiple confounding factors, enhancing the statistical robustness and reliability of our findings. Our study also extends the previous literature in several ways. First, we identified an inverted J-shaped, threshold-based association in men rather than a simple linear trend. We also demonstrated that this association is sex-specific and may be biologically mediated. Third, we applied a clinically meaningful cut-off for vitamin D deficiency (<30 nmol/L), consistent with expert recommendations. These empirical observations and methodological distinctions clarify the nature of the association between vitamin D and frailty and help contextualize our findings within an aging East Asian population. However, several limitations should be acknowledged. First, the assessment of frailty was based on a combination of self-reported questionnaires and objective health measures. While the use of the FI allowed for a multidimensional assessment of frailty, self-reported components, such as functional limitations and symptoms, introduce the potential for misclassification. Second, the cross-sectional design of this study limits the ability to establish a causal relationship between serum 25(OH)D levels and frailty. Longitudinal studies are needed to clarify whether vitamin D deficiency contributes to frailty or if frailty leads to lower vitamin D levels. Third, this study did not collect detailed data on vitamin D supplementation, which may confound the observed associations, particularly in women. Postmenopausal women are more likely to receive vitamin D and calcium supplementation as part of osteoporosis management, potentially masking the true relationship between vitamin D deficiency and frailty. Additionally, the study did not account for dietary or supplemental sources of vitamin D, which may influence serum 25(OH)D levels. Fourth, potential residual confounding factors, such as physical activity and sun exposure, may have affected the observed associations. Finally, although the nationally representative cohort is a strength, our findings may not be generalizable to populations with different ethnic, cultural, or dietary backgrounds.

In conclusion, our findings suggest that low serum 25(OH)D concentrations are a key contributor to frailty risk, particularly in older men, while no significant association was observed in women. These results underscore the importance of sex-specific interventions, emphasizing the correction of vitamin D deficiency in men and addressing broader, multifactorial determinants of frailty in women. Future longitudinal research is needed to establish causal pathways and develop targeted interventions to address frailty in diverse populations.

CONFLICTS OF INTEREST

Beom-Jun Kim is a deputy editor of the journal. But he was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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AUTHOR CONTRIBUTIONS

Conception or design: B.J.K. Acquisition, analysis, or interpretation of data: J.L., M.K., B.J.K. Drafting the work or revising: J.L., B.J.K. Final approval of the manuscript: J.L., M.K., J.H., Y.J., D.R., H.W.J., K.H.B., B.J.K.

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REFERENCES

1. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013;381:752-62.
2. Gilbert T, Neuburger J, Kraindler J, Keeble E, Smith P, Ariti C, et al. Development and validation of a hospital frailty risk score focusing on older people in acute care settings using electronic hospital records: an observational study. Lancet 2018;391:1775-82.
3. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146-56.
4. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-95.
5. Houston DK, Neiberg RH, Tooze JA, Hausman DB, Johnson MA, Cauley JA, et al. Low 25-hydroxyvitamin D predicts the onset of mobility limitation and disability in community-dwelling older adults: the Health ABC Study. J Gerontol A Biol Sci Med Sci 2013;68:181-7.
6. Mendes MM, Botelho PB, Ribeiro H. Vitamin D and musculoskeletal health: outstanding aspects to be considered in the light of current evidence. Endocr Connect 2022;11:e210596.
7. Girgis CM, Clifton-Bligh RJ, Mokbel N, Cheng K, Gunton JE. Vitamin D signaling regulates proliferation, differentiation, and myotube size in C2C12 skeletal muscle cells. Endocrinology 2014;155:347-57.
8. Remelli F, Vitali A, Zurlo A, Volpato S. Vitamin D deficiency and sarcopenia in older persons. Nutrients 2019;11:2861.
9. Ghaseminejad-Raeini A, Ghaderi A, Sharafi A, Nematollahi-Sani B, Moossavi M, Derakhshani A, et al. Immunomodulatory actions of vitamin D in various immune-related disorders: a comprehensive review. Front Immunol 2023;14:950465.
10. Miao D, Goltzman D. Mechanisms of action of vitamin D in delaying aging and preventing disease by inhibiting oxidative stress. Vitam Horm 2023;121:293-318.
11. Demay MB, Pittas AG, Bikle DD, Diab DL, Kiely ME, Lazaretti-Castro M, et al. Vitamin D for the prevention of disease: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2024;109:1907-47.
12. Kuchuk NO, Pluijm SM, van Schoor NM, Looman CW, Smit JH, Lips P, et al. Relationships of serum 25-hydroxyvitamin D to bone mineral density and serum parathyroid hormone and markers of bone turnover in older persons. J Clin Endocrinol Metab 2009;94:1244-50.
13. Lee SG, Lee YH, Kim KJ, Lee W, Kwon OH, Kim JH, et al. Additive association of vitamin D insufficiency and sarcopenia with low femoral bone mineral density in noninstitutionalized elderly population: the Korea National Health and Nutrition Examination Surveys 2009-2010. Osteoporos Int 2013;24:2789-99.
14. Hill TR, Verlaan S, Biesheuvel E, Eastell R, Bauer JM, Bautmans I, et al. A vitamin D, calcium and leucine-enriched whey protein nutritional supplement improves measures of bone health in sarcopenic non-malnourished older adults: the PROVIDE Study. Calcif Tissue Int 2019;105:383-91.
15. Zhou J, Huang P, Liu P, Hao Q, Chen S, Dong B, et al. Association of vitamin D deficiency and frailty: a systematic review and meta-analysis. Maturitas 2016;94:70-6.
16. Ju SY, Lee JY, Kim DH. Low 25-hydroxyvitamin D levels and the risk of frailty syndrome: a systematic review and dose-response meta-analysis. BMC Geriatr 2018;18:206.
17. Marcos-Perez D, Sanchez-Flores M, Proietti S, Bonassi S, Costa S, Teixeira JP, et al. Low vitamin D levels and frailty status in older adults: a systematic review and meta-analysis. Nutrients 2020;12:2286.
18. Kweon S, Kim Y, Jang MJ, Kim Y, Kim K, Choi S, et al. Data resource profile: the Korea National Health and Nutrition Examination Survey (KNHANES). Int J Epidemiol 2014;43:69-77.
19. Park JH, Hong IY, Chung JW, Choi HS. Vitamin D status in South Korean population: seven-year trend from the KNHANES. Medicine (Baltimore). 2018;26:e11032.
20. Kim HL, Park SM, Cho IJ, Kim YM, Kim DH, Kim SH, et al. Standardized protocol of blood pressure measurement and quality control program for the Korea National Health and Nutrition Examination Survey. Clin Hypertens 2023;29:28.
21. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. BMC Geriatr 2008;8:24.
22. Kang MG, Kim SW, Yoon SJ, Choi JY, Kim KI, Kim CH, et al. Association between frailty and hypertension prevalence, treatment, and control in the elderly Korean population. Sci Rep 2017;7:7542.
23. Kang MG, Jung HW. Association between oral health and frailty in older Korean population: a cross-sectional study. Clin Interv Aging 2022;17:1863-72.
24. Kang MG, Jung HW, Kim BJ. A link between systemic low-grade inflammation and frailty in older adults: clinical evi-

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dence from a nationwide population-based study. Korean J Intern Med 2024;39:1011-20.
25. Kang MG, Baek JY, Jo Y, Ryu D, Jang IY, Jung HW, et al. Higher serum uric acid as a risk factor for frailty in older adults: a nationwide population-based study. J Cachexia Sarcopenia Muscle 2024;15:2134-42.
26. Ensrud KE, Blackwell TL, Cauley JA, Cummings SR, Barrett-Connor E, Dam TT, et al. Circulating 25-hydroxyvitamin D levels and frailty in older men: the osteoporotic fractures in men study. J Am Geriatr Soc 2011;59:101-6.
27. Tajar A, Lee DM, Pye SR, O'Connell MD, Ravindrarajah R, Gielen E, et al. The association of frailty with serum 25-hydroxyvitamin D and parathyroid hormone levels in older European men. Age Ageing 2013;42:352-9.
28. Schottker B, Saum KU, Perna L, Ordonez-Mena JM, Holleczek B, Brenner H, et al. Is vitamin D deficiency a cause of increased morbidity and mortality at older age or simply an indicator of poor health?. Eur J Epidemiol 2014;29:199-210.
29. Kim DH, Rockwood K. Frailty in older adults. N Engl J Med 2024;391:538-48.
30. Blodgett J, Theou O, Kirkland S, Andreou P, Rockwood K. Frailty in NHANES: comparing the frailty index and phenotype. Arch Gerontol Geriatr 2015;60:464-70.
31. Buta BJ, Walston JD, Godino JG, Park M, Kalyani RR, Xue QL, et al. Frailty assessment instruments: Systematic characterization of the uses and contexts of highly-cited instruments. Ageing Res Rev 2016;26:53-61.
32. O'Caoimh R, Sezgin D, O'Donovan MR, Molloy DW, Clegg A, Rockwood K, et al. Prevalence of frailty in 62 countries across the world: a systematic review and meta-analysis of population-level studies. Age Ageing 2021;50:96-104.
33. To TL, Doan TN, Ho WC, Liao WC. Prevalence of frailty among community-dwelling older adults in asian countries: a systematic review and meta-analysis. Healthcare (Basel) 2022;10:895.
34. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. J Am Geriatr Soc 2012;60:1487-92.
35. Scott D, Blizzard L, Fell J, Ding C, Winzenberg T, Jones G, et al. A prospective study of the associations between 25-hydroxy-vitamin D, sarcopenia progression and physical activity in older adults. Clin Endocrinol (Oxf) 2010;73:581-7.
36. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, Staehelin HB, Bazemore MG, Zee RY, et al. Effect of vitamin D on falls: a meta-analysis. JAMA 2004;291:1999-2006.
37. Schnittger RI, Walsh CD, Casey AM, Wherton JP, McHugh JE, Lawlor BA, et al. Psychological distress as a key component of psychosocial functioning in community-dwelling older people. Aging Ment Health 2012;16:199-207.
38. Wilhelm-Leen ER, Hall YN, Deboer IH, Chertow GM. Vitamin D deficiency and frailty in older Americans. J Intern Med 2010;268:171-80.
39. Smit E, Crespo CJ, Michael Y, Ramirez-Marrero FA, Brodowicz GR, Bartlett S, et al. The effect of vitamin D and frailty on mortality among non-institutionalized US older adults. Eur J Clin Nutr 2012;66:1024-8.
40. Shardell M, Hicks GE, Miller RR, Kritchevsky S, Andersen D, Bandinelli S, et al. Association of low vitamin D levels with the frailty syndrome in men and women. J Gerontol A Biol Sci Med Sci 2009;64:69-75.
41. Bollen SE, Bass JJ, Fujita S, Wilkinson D, Hewison M, Atherton PJ, et al. The vitamin D/vitamin D receptor (VDR) axis in muscle atrophy and sarcopenia. Cell Signal 2022;96:110355.
42. Yang A, Lv Q, Han Z, Dai S, Li Y, Hao M, et al. The effects of vitamin D on muscle strength are influenced by testosterone levels. J Cachexia Sarcopenia Muscle 2025;16:e13733.
43. Rafiq R, van Schoor NM, Sohl E, Zillikens MC, Oosterwerff MM, Schaap L, et al. Associations of vitamin D status and vitamin D-related polymorphisms with sex hormones in older men. J Steroid Biochem Mol Biol 2016;164:11-7.
44. Pilz S, Frisch S, Koertke H, Kuhn J, Dreier J, Obermayer-Pietsch B, et al. Effect of vitamin D supplementation on testosterone levels in men. Horm Metab Res 2011;43:223-5.
45. Ensrud KE, Ewing SK, Fredman L, Hochberg MC, Cauley JA, Hillier TA, et al. Circulating 25-hydroxyvitamin D levels and frailty status in older women. J Clin Endocrinol Metab 2010;95:5266-73.
46. Colin EM, Uitterlinden AG, Meurs JB, Bergink AP, van de Klift M, Fang Y, et al. Interaction between vitamin D receptor genotype and estrogen receptor alpha genotype influences vertebral fracture risk. J Clin Endocrinol Metab 2003;88:3777-84.
47. Cosman F, Lewiecki EM, Eastell R, Ebeling PR, Jan De Beur S, Langdahl B, et al. Goal-directed osteoporosis treatment: ASBMR/BHOF task force position statement 2024. J Bone Miner Res 2024;39:1393-405.
48. Munns CF, Shaw N, Kiely M, Specker BL, Thacher TD, Ozono K, et al. Global consensus recommendations on prevention and management of nutritional rickets. J Clin Endocrinol Metab 2016;101:394-415.

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49. Cashman KD. Vitamin D deficiency: defining, prevalence, causes, and strategies of addressing. Calcif Tissue Int 2020; 106:14-29.
50. Holick MF. The vitamin D deficiency pandemic: approaches for diagnosis, treatment and prevention. Rev Endocr Metab Disord 2017;18:153-65.
51. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011; 96:1911-30.

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