RESEARCH ARTICLE

Association between Frailty, Osteoporosis, Falls and Hip Fractures among Community-Dwelling People Aged 50 Years and Older in Taiwan: Results from I-Lan Longitudinal Aging Study

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Abstract

Background

Association of frailty with adverse clinical outcomes has been reported in Western countries, but data from the Asian population are scarce. This study aimed to evaluate the epidemiology of frailty among community-dwelling middle-aged and elderly population and to explore its association with musculoskeletal health in Taiwan.

Methods

I-Lan Longitudinal Aging Study (ILAS) data were retrieved for this study. Frailty was defined by the Fried's criteria; a comparison of demographic characteristics, physical performance, and body composition, including skeletal muscle mass and bone mineral density (BMD), as well as recent falls, history of hip fractures and the functional status of subjects with different frailty statuses were accomplished.

Results

Overall, the data of 1,839 participants (mean age: 63.9±9.3 years, male 47.5%) were obtained for analysis. The prevalence of pre-frailty was 42.3% in men and 38.8% in women, whereas the prevalence of frailty was 6.9% and 6.7% in men and women, respectively. Frailty was significantly associated with older age, the male gender, larger waist circumference, lower skeletal muscle index, lower hip BMD, poorer physical function, poorer nutritional status, and poorer cognitive function. Also, frailty was significantly associated with osteoporosis (OR: 7.73, 95% CI: 5.01–11.90, p<0.001), history of hip fractures (OR: 8.66, 95% CI: 2.47–30.40, p = 0.001), and recent falls (O.R: 2.53, 95% CI: 1.35–4.76, p = 0.004).

Conclusions

Frailty and pre-frailty, in Taiwan, was closely associated with recent falls, history of hip fractures and osteoporosis among community-dwelling people 50 years of age and older. Furthermore, frailty intervention programs should take an integrated approach towards strengthening both and muscle mass, as well as prevention of falls.

Introduction

Frailty is a well-recognized geriatric syndrome,[1] which features the loss of function, loss of physiologic reserve, and an increased vulnerability to diseases and death.[2] In addition, frailty is also associated with cognitive impairment,[3] multimorbidity, impaired functional status,[4] risk of falls and fractures,[5] medical and surgical outcomes,[6,7] hospitalizations, institutionalization and mortality.[8] Moreover, frailty is closely associated with body compositional changes and osteoporosis,[9] and may overlap with the pathogenesis of sarcopenia.[10] Despite extensive reports regarding frailty and related adverse health outcomes, the association of frailty and the changes of body composition has not been well understood.[11]

The prevalence of frailty varies greatly from study to study in its use of different diagnostic criteria in different settings.[2,12,13] Although the epidemiology may vary greatly, the age-related increasing trend of frailty prevalence has been clearly shown indifferent studies. As one of the fastest aging countries in the world, Taiwan needs to face the challenges related to population aging as most Western countries are doing.[14,15] Among all health care challenges, the impact of frailty to health and health care outcomes is of great importance. Previous studies have disclosed that frailty was associated with the decline in lean muscle mass, bone mass and the presence of sarcopenia,[16–18] which may result in a greater negative impact on older people. Although these associations have been reported in previous studies, little is known regarding the association among Asian populations. Therefore, this study aimed to evaluate the prevalence and clinical characteristics of frailty among the community-dwelling middle aged and elderly population in Taiwan, and to explore the associations of frailty and musculoskeletal health.

Materials and Methods

Study subjects

The I-Lan Longitudinal Aging Study (ILAS) is a community-based aging cohort study in I-Lan County of Taiwan, which aimed to evaluate the complex interrelationship between aging, frailty, sarcopenia and cognitive decline. Community-dwelling people aged 50 years and older were randomly selected for study from the I-Lan County of Taiwan.[19] Selected inhabitants were invited via mail or telephone to participate with the research team, and were enrolled when they signed the consent forms as study participations. The inclusion criteria for ILAS were: (1) inhabitants who presently live in I-Lan County without a plan of moving in the near future, and (2) residents 50 years of age or older. Subjects with the following conditions were excluded: (1) those who were unable to adequately communicate with the research nurses, (2) those unable to complete all evaluation tests due to poor functional status, (3) those who had a limited life expectancy due to major illnesses, and (4) current residents in long-term care facilities. Overall, the data of 1,839 participants of ILAS were retrieved for study. All participants

signed a written informed consent. The whole study and the consent procedure had been approved by the Institutional Review Board of National Yang Ming University.

Demography, physical examinations and laboratory examinations

A questionnaire consisting of demographic information, socioeconomic condition, medical history and the burden of chronic diseases was evaluated using Charlson's Comorbidity Index. [20] Tobacco usage was categorized into three classes: non-smoker, ex-smoker (quit in past 6 months) and current smoker. Participants who consumed alcohol were categorized as drinkers and non-drinkers. A comprehensive functional assessment was performed on all participants by using the following: the Functional Autonomy Measurement System for physical function test,[21] the Center for Epidemiologic Studies Depression Scale (CES-D) for measuring the mood status,[22] the Mini-Nutrition Assessment (MNA) for nutritional status measurement, [23] and the Mini–Mental State Examination (MMSE) for cognitive function measurement. [24]

All subjects underwent anthropometric measurements by research nurses, including height and body weight, and the body mass index (BMI) was calculated accordingly. Baseline blood samples were obtained for each participant in the morning after an overnight fasting of at least 10 hours. Serum levels of albumin and total cholesterol were measured using an automatic analyzer (ADVIA 1800, Siemens, Malvern, PA, USA). Whole-blood glycated hemoglobin A1c (HbA1c) was measured by an enzymatic method using the Tosoh G8 HPLC Analyzer (Tosoh Bioscience, Inc., San Francisco, CA, USA). Serum levels of intact-parathyroid hormone (i-PTH) (Siemens Advia Centaur) and 25-hydroxyvitamin D (25(OH)D) (Diasorin Liaison) were also measured by ELISA methods. High-sensitivity C-reactive protein (hs-CRP) was determined by an immunoturbidimetric assay (Siemens Advia 1800) for further analysis.

Muscle strength and physical performance

For all participants, handgrip strength of the dominant hand was measured using digital dynamometers (Smedlay's Dynamo Meter; TTM, Tokyo, Japan), with participants standing in an upright position with both arms down on their sides. The best results of three tests were used for further analysis. Moreover, participants performed a timed 6-meter walk for each participant to evaluate their physical performance.

Bone mineral density (BMD) and body composition

A whole body dual-energy X-ray absorptiometry (DXA) scan was performed on each participant to measure their total body fat mass and fat-free lean body mass (LBM) by using a Lunar Prodigy instrument (GE Healthcare, Madison, WI, USA). Appendicular skeletal muscle mass (ASM) was calculated as the sum of the lean soft tissue mass of all four limbs. In this study, height-adjusted muscle index, or relative appendicular skeletal muscle (RASM),[25] was calculated by appendicular skeletal muscle mass divided by height (m) square (ASM/height^2, kg/m^2). BMD at the lumbar spine and bilateral hip joints were measured for analysis.

Definition of Frailty

In this study, frailty is defined by Fried's criteria, which includes exhaustion, weakness, slowness, physical inactivity and weight loss.[26] Exhaustion was defined using the 2 statements by the Center for Epidemiologic Studies-Depression scale (CES-D). Weakness was defined by low handgrip strength, and slowness was defined by slow gait speed. Physical inactivity was evaluated by using the International Physical Activity Questionnaire (IPAQ).[27,28] Weight loss

was defined as having involuntary weight loss of >5% in the past year or 3kgs within past 3 months. Weakness, slowness and physical inactivity referred to those who performed lower than the gender-specific lowest quintile of the study population. A participant was classified as frail if he/she was positive for three of more items on the Fried's criteria, and those who were positive for one or two items were classified as pre-frail. Those who were negative on all 5 items of Fried's criteria were considered robust.

Statistical analysis

In this study, continuous variables were expressed as the mean ± standard deviation, and the categorical data was expressed by percentages. Comparisons of continuous data between groups were done by Student's t test and comparisons of categorical data were done by Chi square test when appropriate. Comparisons between groups of different frailty statuses were performed by one-way ANOVA. To study the cross-sectional association between bone health, muscle quality and the frailty syndrome, multinomial logistic regression was used, allowing the modeling of the prefrail and frail states by using robust as reference group. Further gender-specific analysis was also performed for the above-mentioned conditions.

The covariates of interest, waist circumference, muscle index, bone mineral density were also analyzed. Other covariates included age, gender, functional status, cognition status, nutrition, and comorbid conditions. Finally, serum 25(OH)D and i-PTH level were added to the model because they were closely related to bone mineral density and fall.

The first sequential model included basic characteristics, bone density and muscle quality. The second model added functional confounders, and the serum markers related to bone and fall were added to the third model.

Results

Overall, data of 1,839 participants 50 years of age and older (mean age: 63.9±9.3 years, 47.5% males) from ILAS were retrieved for study. Table 1 summarized the comparisons of demographic characteristics of study participants between genders. In this study, BMI was similar between men and women, but men had significantly higher lean body mass, appendicular skeletal muscle mass, and skeletal muscle index (RASM) than women. In contrast, the women had higher total body fat percentage and more total body fat mass than men. Also, men had significantly stronger handgrip strength (35.1±8.3 Kg vs. 21.8±5.4 Kg, P<0.001), and faster gait speed (1.6±0.5 vs. 1.4±0.4 m/s, P<0.001) than women. Moreover, men also had significantly higher bone mineral density in both their lumbar spine and femoral neck (Table 1).

Table 2 summarized the comparisons of clinical characteristics between subjects in different frailty statuses. The prevalence of pre-frailty was 42.3% in men and 38.8% in women, while frailty was 6.9% and 6.7% in men and women, respectively. Overall, frail subjects were significantly older but pre-frail and frail participants had higher waist circumference than those robust subjects, although the BMI did not differ significantly between them. Also, smoking was not significantly different between frailty groups but frail people were less likely to consume alcohol habitually.

In the body composition analysis, frail people had significantly lower lean body mass, appendicular skeletal muscle mass, RASM and BMD when compared with other groups. However, the serum levels of total 25-OH vitamin D were similar in robust and pre-frail groups, but significantly lower in the frail group. The serum levels of i-PTH were similar between subjects with different frailty statuses. Comparisons of functional status, depressive symptoms, nutritional status and cognitive function showed a declining trend between different frailty statuses. Also, frail people had the highest CCI scores, followed by pre-frail and robust subjects, which

Table 1. Demographic characteristics of participants of the I-Lan Longitudinal Aging Study.

	Total (N = 1839)	Men (N = 873)	Women (N = 966)	P value
Age (years)	63.9±9.3	65.1±9.7	62.9±8.7	<0.001
Anthropometric measurements				
Height (cm)	158.6±8.0	164.3±6.2	153.5±5.6	<0.001
Weight (Kg)	62.7±11.0	67.4±10.5	58.4±9.6	<0.001
Body mass index (Kg/m^2)	24.9±3.6	24.9±3.3	24.8±3.8	0.433
Dual-energy X-ray absorptiometry				
Lean body mass (Kg)	41.7±8.2	48.6±5.6	35.5±4.3	<0.001
ASM (Kg)	17.9±4.1	21.4±3.0	14.8±2.0	<0.001
RASM (kg/m^2)	7.0±1.1	7.9±0.8	6.3±0.7	<0.001
Total fat mass (Kg)	19.5±7.0	17.2±6.8	21.6±6.6	<0.001
Total body fat percentage (%)	31.6±8.8	25.3±6.6	37.1±6.4	<0.001
Lumbar BMD	1.030±0.182	1.091±0.176	0.976±0.169	<0.001
Hip BMD	0.839±0.140	0.890±0.132	0.793±0.130	<0.001
Physical performance				
Walking speed (m/s)	1.5±0.5	1.6±0.5	1.4±0.4	<0.001
Handgrip strength (Kg)	28.1±9.6	35.1±8.3	21.8±5.4	<0.001
Frailty status (%)				
Robust	52.7	50.9	54.5	0.289
Pre-frail	40.5	42.3	38.8	
Frail	6.8	6.9	6.7	
Cigarette Smoking (%)				
Never smoker	69.5	40.2	96.0	<0.001
Ex-smoker	12.2	24.7	0.9	
Current smoker	18.3	35.1	3.1	
Alcohol drinker (%)	33.0	49.8	17.8	<0.001
Functional status				
SMAF	-0.18±1.63	-0.20±1.79	-0.16±1.47	0.575
CES-D	2.4±4.6	2.0±3.7	2.8±5.2	<0.001
Mini-nutrition assessment	27.2±1.8	27.4±1.7	26.9±1.9	<0.001
MMSE	25.6±4.0	26.2±3.5	25.1±4.4	<0.001
Education(years)	6.2±5.0	7.1±5.0	5.4±4.8	<0.001

ASM = appendicular skeletal muscle mass; RASM = relative appendicular skeletal muscle; BMD = bone mineral density; SMAF = the Functional Autonomy Measurement System; CES-D = the Center for Epidemiologic Studies Depression Scale; MMSE = Mini–mental state examination.

was statistically significant. Comparisons of serum markers for protein-energy nutrition such as albumin and total cholesterol and total lymphocyte counts showed no statistical differences between subjects with different frailty statuses.

Table 3 showed the odds ratios for frailty status in association with poor medical conditions. Frailty was significantly associated with osteoporosis (OR: 7.73, 95% CI: 5.01–11.90, p<0.001), history of hip fractures (OR: 8.66, 95% CI: 2.47–30.40, p = 0.001), and recent falls (O.R: 2.53, 95% CI: 1.35–4.76, p = 0.004). Gender differences were only found in the association between osteoporosis and frailty status. In women, worse frail conditions were found to be at a higher risk of osteoporosis. The odds ratio was 2.62 in the prefrail group and 8.25 in the frail group of women compared with their robust college. Robust and prefrail men had a lower risk of osteoporosis compared with robust women, but the odds ratio increased to 2.85 when it came to frail men.

Table 2. Baseline association of demographic and health characteristics with frailty: the _I-Lan_ Longitudinal Aging Study.

	Total	Robust	Pre-frail	Frail	p
Number (%)	1839	970 (52.7)	744 (40.5)	125 (6.8)	
Age (year)	63.9±9.3	60.7±7.5	66.3±9.3	74.6±9.2	<0.001
Sex (%)					
Women	52.5	54.2	50.4	52.0	0.289
Men	47.5	45.8	49.6	48.0	
BMI (Kg/m^2)	24.9±3.6	24.8±3.5	24.9±3.6	24.7±4.0	0.655
Waist circumference (cm)	84.8±9.8	83.8±9.4	85.5±9.9	88.1±10.8	<0.001
Cigarette Smoking (%)					
Never smoker	67.4	69.3	65.4	60.9	0.359
Ex-smoker	19.7	18.5	21.4	20.3	
Current smoker	12.9	12.2	13.2	18.8	
Alcohol drinker (%)	35.0	38.7	32.1	15.4	<0.001
Dual-energy X-ray absorptiometry					
Lean body mass (Kg)	41.7±8.2	42.3±8.4	41.2±8.0	39.7±7.0	0.001
ASM (Kg)	17.9±4.1	18.3±4.3	17.6±3.9	16.5±3.6	<0.001
RASM (Kg/m^2)	7.0±1.1	7.1±1.1	7.0±1.1	6.7±1.0	<0.001
Total fat mass (Kg)	19.5±7.0	19.7±7.1	19.4±6.9	18.9±7.8	0.463
Total body fat percentage (%)	31.6±8.8	31.5±8.7	31.7±8.6	31.5±10.0	0.917
Physical performance					
Walking speed (m/s)	1.5±0.5	1.7±0.4	1.4±0.4	0.9±0.3	<0.001
Handgrip strength (Kg)	28.1±9.6	30.9±9.0	26.0±9.2	18.8±7.1	<0.001
Bone mineralization					
Lumbar BMD	1.0±0.2	1.0±0.2	1.0±0.2	1.0±0.2	<0.001
Hip BMD	0.8±0.1	0.9±0.1	0.8±0.1	0.7±0.1	<0.001
25(OH)D (ng/ml)	23.4±7.1	23.1±6.5	23.9±7.8	22.7±6.8	0.040
i-PTH (pg/ml)	43.7±43.9	42.4±30.0	44.6±58.4	48.2±32.5	0.283
Osteoporosis (%)	15.3	8.8	19.7	42.6	<0.001
Men	8.4	3.7	10.8	29.8	<0.001
Women	21.4	13.0	28.1	55.2	<0.001
Hip surgery (%)	1.2	0.5	1.7	4.3	0.001
Falls within 3 months (%)					
0	94.8	95.3	95.3	88.8	0.001
1	4.6	4.3	4.3	8.0	
≥ 2	0.6	0.4	0.4	3.2	
Functional status					
SMAF	-0.2±1.6	-0.0±0.2	-0.1±0.5	-2.0±5.8	<0.001
CES-D	2.4±4.6	1.5±2.6	2.7±4.4	8.2±10.0	<0.001
Mini-nutrition assessment	27.2±1.8	27.5±1.6	27.1±1.8	25.3±2.6	<0.001
MMSE	25.6±4.0	26.8±3.0	25.0±4.0	20.8±5.8	<0.001
Education, years	6.2±5.0	7.5±4.8	5.2±4.8	2.6±3.5	<0.001
CCI	1.0±1.3	0.7±1.1	1.2±1.3	2.1±1.4	<0.001
Serum markers of protein-energy nutrition					
Total lymphocyte count (K/uL)	2.0±0.6	2.0±0.6	1.9±0.7	1.8±0.6	0.020
Albumin (mg/dL)	4.5±0.2	4.5±0.2	4.5±0.3	4.4±0.2	<0.001
Total cholesterol (mg/dL)	195.0±35.3	198.8±35.1	191.8±34.8	184.7±35.8	<0.001

(_Continued_)

Table 2. (*Continued*)

	Total	Robust	Pre-frail	Frail	p
HbA1c (%)	6.1±1.0	6.0±0.8	6.2±1.1	6.4±1.3	<0.001
hs-CRP (mg/dL)	0.2±0.5	0.2±0.4	0.2±0.4	0.4±0.9	<0.001

ASM = appendicular skeletal muscle mass; RASM = relative appendicular skeletal muscle; BMD = bone mineral density; 25(OH)D = 25-hydroxyvitamin D; i-PTH = intact-parathyroid hormone; SMAF = the Functional Autonomy Measurement System; CES-D = the Center for Epidemiologic Studies Depression Scale; MMSE = Mini–mental state examination; CCI = Charlson's Comorbidity Index; hs-CRP = high-sensitive C-reactive protein.

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In multinomial logistic regression analysis, we found that older, male, with larger waist circumference, lower muscle mass index, lower hip BMD, lower SMAF scores (poorer functional status), lower MNA score (higher malnutrition or undernutrition risk), and lower MMSE score (poorer cognition) were all independent risk factors for pre-frailty and frailty (Table 4).

Discussion

The prevalence of frailty in different epidemiological studies varied from 4% to 13% by using different diagnostic criteria,[3,29–31] whereas the prevalence of pre-frailty ranged from 28% to 44%.[12,26] In this study, the prevalence of frailty and pre-frailty was 6.8%, and 40.5%, respectively. The results were compatible to the report from the CHS study,[26] and the prevalence was in between the two previous Taiwanese studies.[32,33] However, the inclusion/exclusion criteria of the study participants for ILAS were more similar to the CHS in that both studies focused on otherwise healthy community-dwelling older people. Therefore, we considered the prevalence of frailty in ILAS to be more feasible for international comparisons than those studies carried out Taiwan.

Obesity paradox of older people is a challenging public health issue in the aging society, which should be managed by a life course approach.[34,35] In this study, frailty was not associated with BMI and the percentage of body fat, but the waist circumferences of pre-frail and frail subjects were significantly larger than the robust subjects. Some studies suggested that central obesity and fat redistribution were important predictors of frailty,[36–38] rather than general body mass or fat mass. On the other hand, pre-frail and frail subjects had lower lean body mass, appendicular skeletal mass and lower skeletal muscle index than the robust subjects despite having similar BMI between the groups. Overall, frailty is significantly associated with the decline of physical function and changes of body composition, which may be mainly due to loss of bone and muscle mass without the significant increase in fat mass.

In this study, a strong association between frailty and lower BMD, in both the lumbar spine and hips of older adults, was identified, even after adjusting for age, gender and functional status so that they were compatible with previous studies.[18,39,40] A significant health hazard of frailty was falls and related fragility fractures.[41,42] In this study, frail subjects were more likely to fall, and to have osteoporosis, as well as sarcopenia and a history of hip fractures. Newton et al. demonstrated that the BMD was significantly lower in frail elderly people, especially among those with recurrent falls.[43] Also, the higher fracture risk of frailty was independent of BMD measurements among the elderly population.[44] Hence, a comprehensive survey of the musculoskeletal health and implementation of fall prevention was of great importance while frailty is identified in clinical practice.[45] Similar to previous studies,[46,47] frailty was associated with lower serum levels of vitamin D in this study, but the serum levels of i-PTH were similar between groups. Besides musculoskeletal health, frailty was also associated with

Table 3. Odds ratios for frailty status in association with poor medical conditions.

Participant number/Total number		Odds Ratio	95% CI		p value
			Lower	Upper	
Osteoporosis					
Total					
robust	84/958	Reference			
prefrail	142/722	2.55	1.91	3.40	<0.001
frail	49/115	7.73	5.01	11.90	<0.001
Women					
robust	68/524	Reference			
prefrail	104/370	2.62	1.86	3.69	<0.001
frail	32/58	8.25	4.64	14.69	<0.001
Men					
robust	16/434	0.26	0.15	0.45	<0.001
prefrail	38/352	0.81	0.53	1.24	0.332
frail	17/57	2.85	1.53	5.31	0.001
Hip surgery					
Total					
robust	5/958	Reference			
prefrail	12/722	3.22	1.13	9.19	0.029
frail	5/115	8.66	2.47	30.40	0.001
Women					
robust	4/524	Reference			
prefrail	5/370	1.78	0.48	6.68	0.392
frail	2/58	4.64	0.83	25.92	0.080
Men					
robust	1/434	0.30	0.03	2.70	0.283
prefrail	7/352	2.64	0.77	9.08	0.124
frail	3/57	7.22	1.58	33.12	0.011
Fall					
Total					
robust	46/970	Reference			
prefrail	35/744	0.99	0.63	1.56	0.971
frail	14/125	2.53	1.35	4.76	0.004
Women					
robust	29/526	Reference			
prefrail	20/375	0.97	0.54	1.73	0.907
frail	7/65	2.07	0.87	4.93	0.101
Men					
robust	17/444	0.68	0.37	1.26	0.221
prefrail	15/369	0.73	0.38	1.38	0.326
frail	7/60	2.26	0.95	5.42	0.067

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poorer functional status, poorer cognitive function, higher malnutrition risk, and higher burden of chronic conditions as in some of the previous studies.[4,41,48] Moreover, frail elderly people also had higher serum levels of HbA1c and hs-CRP, which was related to chronic inflammation and insulin resistance.[49–51]

Table 4. Association between frailty, physical performance and body composition as described by Odds Ratios (ORs) for multinomial logistic regression models.

	Model 1[a]		Model 2[b]		Model 3[c]	
	Pre-frail	Frail	Pre-frail	Frail	Pre-frail	Frail
	versus Robust		versus Robust		versus Robust	
Characteristic	OR (95% confidence interval)					
Age(years)	1.065(1.051, 1.079)[†]	1.142(1.109,1.176)[†]	1.043(1.027, 1.060)[†]	1.075(1.038, 1.114)[†]	1.043(1.026, 1.060)[†]	1.077(1.039, 1.116)[†]
Gender						
Women	Reference	Reference	Reference	Reference	Reference	Reference
Men	1.772(1.280, 2.453)[†]	3.312(1.719, 6.382)[†]	1.945(1.387, 2.727)[†]	3.872(1.889, 7.936)[†]	1.896(1.339, 2.686)[†]	4.118(1.983, 8.554)[†]
WC(cm)	1.021(1.008, 1.034)[†]	1.065(1.038, 1.094)[†]	1.023(1.010, 1.037)[†]	1.088(1.058, 1.118)[†]	1.024(1.010, 1.037)[†]	1.086(1.056, 1.117)[†]
RASM(kg/m^2)	0.712(0.605, 0.837)[†]	0.441(0.314, 0.618)[†]	0.721(0.609, 0.852)[†]	0.493(0.338, 0.718)[†]	0.720(0.609, 0.851)[†]	0.504(0.346, 0.735)[†]
Lumbar spine BMD	1.134(0.521, 2.470)	3.634(0.775, 17.054)	1.300(0.589, 2.870)	5.013(0.896, 28.055)	1.293(0.586, 2.856)	5.059(0.915, 27.963)
Hip joint BMD	0.268(0.089, 0.809)[†]	0.002(0.000, 0.022)[†]	0.330(0.107, 1.016)	0.005(0.000, 0.071)[†]	0.327(0.106, 1.008)	0.006(0.000, 0.075)[†]
SMAF			0.621(0.376, 1.026)	0.478(0.284, 0.804)[†]	0.622(0.377, 1.026)	0.482(0.287, 0.809)[†]
MNA			0.927(0.864, 0.995)[†]	0.666(0.586, 0.757)[†]	0.928(0.865, 0.997)[†]	0.662(0.582, 0.754)[†]
MMSE			0.929(0.898, 0.962)[†]	0.842(0.793, 0.894)[†]	0.930(0.898, 0.962)[†]	0.840(0.791, 0.893)[†]
CCI			1.060(0.962, 1.169)	1.133(0.937, 1.371)	1.059(0.961, 1.168)	1.134(0.937, 1.372)
25(OH)D(ng/ml)					1.005(0.989, 1.022)	0.976(0.940, 1.015)
i-PTH(pg/ml)					1.000(0.998, 1.003)	1.000(0.996, 1.004)

OR = odds ratio; WC = waist circumference; RASM = relative appendicular skeletal muscle; BMD = bone mineral density; SMAF = the Functional Autonomy Measurement System; MNA = Mini-nutrition assessment; MMSE = Mini–mental state examination; CCI = Charlson's Comorbidity Index; 25(OH)D = 25-hydroxyvitamin D; i-PTH = intact-parathyroid hormone.

[a] Includes age, gender, bone and muscle quality

[b] Includes age, gender, bone and muscle quality, and functional parameters

[c] Includes age, gender, bone and muscle quality, functional parameters, serum 25(OH)D and i-PTH levels

[†] Significant association.

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Despite all the effort that went into the research, there were some limitations in this study. First, the cross-sectional study design may have limited the possibilities of exploring the causal relationship of frailty and poorer musculoskeletal health of the elderly. However, since ILAS is a longitudinal cohort study, we believe that the follow-up data will facilitate in building the causal relationship between frailty and its adverse health impacts. Second, the determination of cut-offs for individual items of the frailty definition, including low physical activity, low hand-grip strength and low walking speed were obtained from the study sample from the original frailty definition. Since ILAS excluded subjects with disabilities, determination of the diagnostic cutoffs may not be applied to the general population. As a result, the study may underestimate the actual prevalence of pre-frailty and frailty. Third, participants were only included when they were able to complete their physical tests. Hence, those who were unable to complete the

physical function assessments were excluded, which may underestimate the true condition in the general population.

In conclusion, frailty is closely associated with lower bone mineral density, lower skeletal muscle mass, recent falls and history of hip fractures, which denotes a strong risk of further fragility fractures and associated adverse clinical outcomes. Therefore, a frailty intervention programs should take an integrated approach to strengthen both bone and muscle mass, as well as fall prevention.

Supporting Information

S1 File. ILAS frailty data.
(PDF)

Acknowledgments

Author Contributions

Conceived and designed the experiments: LKC MHL. Performed the experiments: LKL WJL. Analyzed the data: LKL LYC. Contributed reagents/materials/analysis tools: ACH LNP. Wrote the paper: LKL LKC.

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