REDUCING THE BURDEN OF AGE-RELATED DISEASE IN RELATION TO OSTEOPOROSIS, SARCOPENIA AND OSTEOSARCOPENIA

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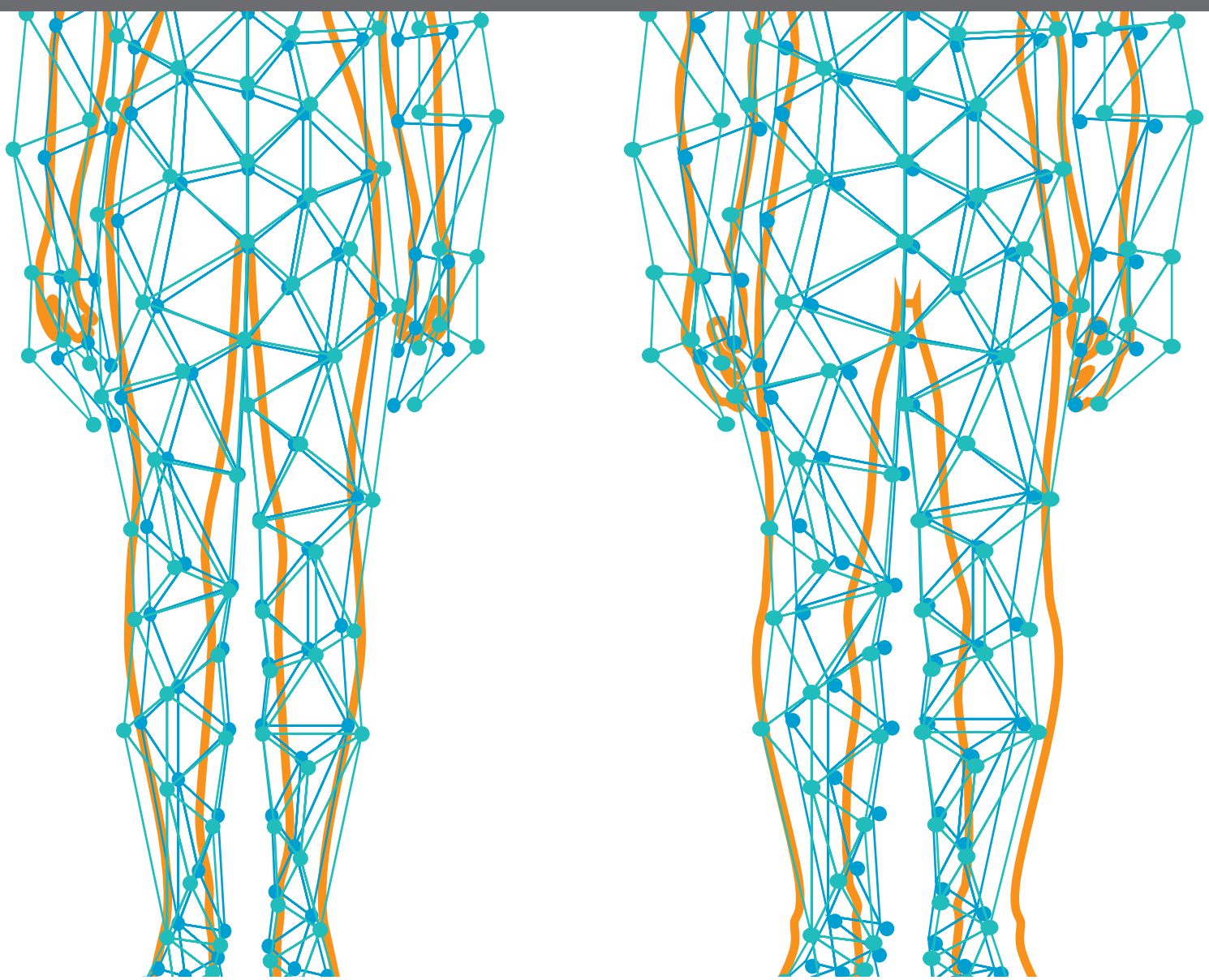

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REDUCING THE BURDEN OF AGE-RELATED DISEASE IN RELATION TO OSTEOPOROSIS, SARCOPENIA AND OSTEOSARCOPENIA

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Table of Contents

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EDITORIAL
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Editorial: Reducing the Burden of Age-Related Disease in Relation to Osteoporosis, Sarcopenia and Osteosarcopenia

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Keywords: osteoporosis, sarcopenia, osteosarcopenia, aging, physical frailty, bonehealth, muscle, burden

Editorial on the Research Topic

Reducing the Burden of Age-Related Disease in Relation to Osteoporosis, Sarcopenia and Osteosarcopenia

This Research Topic collection entitled "*Reducing the Burden of Age-Related Disease in Relation to Osteoporosis, Sarcopenia and Osteosarcopenia*," developed by authors from various countries, aims to investigate different strategies for screening, diagnosis, and management of sarcopenia and osteoporosis as major public health threats to aging populations. The articles published in this Research Topic introduce novel imaging and laboratory approaches for screening and early detection of osteoporosis and sarcopenia, and propose effective prevention and treatment strategies. They also provide evidence as to how newly emerged nutrition, physical activity, and medication approaches can effectively prevent devastating complications and consequences of sarcopenia and osteoporosis.

Sarcopenia is associated with a high risk for joint pain, functional dependence, institutionalization, high health costs, and mortality. Considering that a high prevalence of sarcopenia in elderly populations often remains undiagnosed, development of novel screening techniques for its detection is of crucial importance. Although, there exist various screening tools in the clinical setting, most of them have disadvantages such as cost, length of the procedure, and low diagnostic accuracy. One of the most widely used techniques for screening sarcopenia is bioelectrical impedance analysis (BIA) which is a relatively simple, inexpensive, fast, non-invasive, and reliable technique. In the first article of this Research Topic, the authors propose a phase angle (PA) cut-off point for screening sarcopenia in a population of elderly Mexican people, and conclude that PA can be an effective indicator for timely detecting sarcopenia and frailty (Rosas-Carrasco et al.). In the second article, Shafiee et al. report development of a simple, non-invasive, cost-effective, and practical tool called SarSA-Mod for screening sarcopenia in both genders. They propose that considering the fact that SarSA-Mod is an easy-to-calculate diagnostic procedure with simple

variables, it can be considered as an effective screening model for early detection of sarcopenia in a primary care setting.

Sarcopenia is associated with discomfort, disability, and pain in articular areas such as the shoulders. The third article investigates the possible relationship between sarcopenia and rotator cuff tendon diseases (Han et al.). The authors observe that although sarcopenia is associated with shoulder pain, it does not lead to serious rotator cuff injuries such as tendon tears. Exercise improves muscle strength, physical performance, and mental states such as cognition and mood. In the fourth article, the authors conduct a systematic review to examine the effects of exercise on muscle strength, body composition, and physical performance in older adults (Zhang et al.). In their meta-analysis, they report that exercise has positive effects on muscle strength, physical performance, and skeletal muscle mass in sarcopenia. Nonetheless, they contend that exercise does not alter body composition (e.g., fat mass, lean mass, and fat-free mass) in elderly people with sarcopenia.

In the fifth article, Azzolino et al. highlight nutrition and physical exercise as two important environmental factors which can effectively promote musculoskeletal health. In their review article, they briefly describe body composition changes across the lifespan and propose several nutrition and exercise strategies aiming at promotion of musculoskeletal health and delaying the aging process. This is in agreement with the sixth article which evaluates the impact of community-based dual-task exercise on muscle strength and physical function in sarcopenia. They analyze the effects of dual-task exercise on cognition, frailty, falls, social isolation, and perceived health in the elderly (Merchant et al.). Their results demonstrates that a dual-task exercise program is significantly effective in improving gait, speed, physical performance, handgrip strength, perceived health, and cognition, and reduces frailty and falls.

The authors of the seventh article contend that hitherto the link between sarcopenia and food-based inflammatory potential of the diet (FIPD), which demonstrates pro-inflammatory quality of the diet, has remained unexplored, and claim that their study has shed light on this topic (Bagheri et al.). Closely examining the association between FIPD and sarcopenia (and its components), they maintain that a greater FIPD score is positively linked with sarcopenia components, and propose that lower consumption of foods with a greater pro-inflammatory capacity, and higher intake of foods with anti-inflammatory features, may have a protective effect against sarcopenia.

The author of the eighth article describes HEPAS (healthy eating, physical activity, and sleep hygiene) as a multidisciplinary approach which can promote physical and mental health and wellbeing of individuals with neuropsychiatric diseases (Briguglio). In this opinion article, the author elaborates, in details, how HEPAS can be exploited to prevent sarcopenia, and comments that HEPAS can improve grip, muscle strength, and skeletal muscle mass in the elderly. The author ultimately concludes that this lifestyle modification strategy can be of great value for the promotion of the health of both community-dwelling and institutionalized elderly people.

Sarcopenia is associated with several extra-muscular complications such as mental disorders, cardiovascular diseases, and hypertension. Cardiovascular (CVD) complications of sarcopenia can be quite devastating, and can be detected by electrocardiography (ECG). In the ninth article, the authors report that in their elderly population with sarcopenia, ECG abnormality and the risk of cardiovascular involvement was significantly increased (Heshmat et al.). In the tenth article, the authors point out that although obesity is documented to be associated with hypertension, the link between sarcopenia (and sarcopenic obesity) and hypertension remains mostly obscure (Pasdar et al.). In a cross-sectional study conducted on 4,021 cases from Ravansar, Iran, they report that obesity was associated with hypertension, whereas sarcopenia and sarcopenic obesity had no such relationship with hypertension.

In the eleventh article, the authors comment that although cadmium (Cd) is linked to osteoporosis and osteopenia, there have found conflicting reports about this relationship (Li et al.). In their meta-analysis, they assert that while urine Cd concentration may be related to increased risk of osteoporosis and osteopenia, blood Cd concentrations have no such relationship. In the end, they propose that measurement of urine Cd concentration can provide a reliable assessment tool for screening and diagnosis of osteoporosis and osteopenia, whereas blood Cd concentrations are of no such diagnostic value.

The twelfth article reports the findings of a prospective multi-institutional randomized controlled study which aims to investigate whether zoledronate prevents loss of bone mineral density (BMD) after discontinuation of denosumab (Lee et al.). They conclude that although a single dose of zoledronate may be helpful, individuals' response to sequential therapy can widely vary based on the baseline fracture risk, bone turnover rate, and duration of denosumab treatment amongst several other factors.

To conclude, appreciating the high health burden of sarcopenia and osteoporosis, all articles of this Research Topic collection propose novel techniques and strategies for screening, diagnosis, prevention, and management of these two silent and devastating adverse health conditions of the elderly. This topic Research Topic can be considered as a great contribution to the body of scientific evidence in the field and the articles illuminate different obscure aspects of screening, diagnosis, and management of osteosarcopenia. Moreover, they highlight current research gaps and elucidate the path for future research on the topic, and put forward practical strategies to address scientific shortcomings and insufficiencies.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Phase Angle Cut-Off Points and Their Association With Sarcopenia and Frailty in Adults of 50–64 Years Old and Older Adults in Mexico City

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Background: In recent studies, the usefulness of the phase angle (PA) to assess geriatric conditions such as sarcopenia and frailty has been evaluated. However, there are no useful cut-off points for clinical research and/or practice.

Objective: To analyze PA cut-off points associated with sarcopenia and frailty in adults of 50-64 years old and older adults in Mexico City.

Design: Cross-sectional analysis of the FraDySMex cohort study (Frailty, Dynapenia, and Sarcopenia in Mexican Adults).

Setting and Participants: 498 people were included, 78.7% women, aged 71.1 ± 9.5 years. Methods: The sarcopenia measurements were made according to the European Working Group on Sarcopenia in Older People (EWGSOP) (2019) (by dynamometer to evaluate hand grip strength and dual energy X-ray absorptiometry (DXA) for appendicular muscle mass), and the frailty through the physical frailty phenotype with cut-off points adjusted to the Mexican population. The PA was evaluated by bioelectrical impedance analysis (BIA), tetrapolar to 50 Hz, other variables such as socio-demographic, comorbidity, cognitive status, and functional dependence were evaluated.

Results: The prevalence of frailty was 10.6% and sarcopenia 10.0%. The mean of the PA was 4.6° ± 0.70°. The PA cut-off point for frailty in adults 50 to 64 years was ≤4.3° [sensitivity (S) = 91.95%, specificity (Sp) 66.77%, AUROC (Area Under the Receiver Operating Characteristic) curve = 0.9273 95% CI (0.8720-0.9825)]; the PA cut-off point for sarcopenia was ≤4.3 [S = 91.95%, Sp = 66.77%, AUROC = 0.9306 95% CI (0.8508-1.000)]. The PA cut-off for frailty in adults ≥ 65 years was ≤4.1° [S = 72.37%, Sp 71.43%, AUROC = 0.7925 95%, CI (0.7280-0.8568)] for sarcopenia was ≤4.1° [S = 72.76%, Sp 73.81%, AUROC = 0.7930 95% CI (0.7272-0.8587)]. These cut-off points showed a significant association between PA with frailty (OR 4.84; 95% CI 2.61-8.99) and sarcopenia (OR 8.44; 95% CI 3.85-18.4) after adjusted by age, sex, BMI, comorbidity index and cognitive impairment.

Conclusions and Implications: These cut-off points of PA could be useful for the screening of sarcopenia and frailty in Mexican adults of 50 years and older in centers that have BIA.

Keywords: phase angle, cut-off point, sarcopenia, frailty, older adults, sensitivity, specificity, validity

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INTRODUCTION

The bioelectrical impedance analysis (BIA) is a relatively simple, inexpensive, fast, non-invasive, and reliable technique to assess body composition (1, 2). The BIA technique is based on the measurement of impedance made up of resistance (R) and reactance (Xc) through one or more electrical frequencies. The tangent area between resistance and reactance in a series or parallel circuit is called the phase angle (PA). The R and Xc values allow us to obtain, through various prediction equations, fat free mass (FFM), total body water (TBW), and fat mass (FM). The phase angle has its advantages, since it allows us to directly assess the permeability of the membrane by measuring intra and extracellular electrical flows, which makes it independent of the state of hydration, body weight, and does not require calculation using predictive models (3).

The PA represents an effective marker to preventively detect health conditions, as well as mortality, morbidity and lower survival with an established disease (4, 5). Due to its usefulness and simplicity, recent studies have explored PA cut-off points which can be effective in timely detecting conditions related to the functionality of the older adults, such as sarcopenia and frailty. Sarcopenia is the progressive and generalized loss of muscle mass and strength with the risk of adverse effects such as physical disability, poor quality of life and higher mortality (6). Frailty is the decrease in physiological reserve that would result in an increased risk of disability, loss of resistance and increased vulnerability to adverse events in individuals, which manifests itself in increased morbidity and mortality (7). According to a systematic review and meta-analysis, the prevalence of sarcopenia has been reported to be 10% for men (95% CI: 8-12%) and women (95% CI: 8-13%) respectively (8). According to a sample of adults over 60 years from Mexico City, the prevalence of sarcopenia was 9.7% and frailty was 15.7% (9, 10). Both conditions have serious clinical implications and, if detected in time, can be reversed with the support of an adequate treatment (11).

Recently the phase angle has been suggested as a possible effective biomarker for the prediction of both clinical conditions (5, 12). For example, Marini et al. (13) correlated a lower PA 5.2° in women and 5.0° in men with pre-sarcopenia defined by their muscle mass in their lower and upper extremities muscle mass <7.26 kg/m2 for men and 5.45 kg/m^2 for women (14). Likewise, in a Japanese population of older adults who were hospitalized, Yamada et al. (15). found a PA of 4.05° and 3.55° in men and women, respectively, being effective indicators for muscle function (measured by ultrasonography for the quality of muscle mass, muscle strength, and physical performance). Other authors have reported different cut-off points of PA for sarcopenia: 4.55°, 5.6° for men and 5.8° for women (16, 17). The PA has also been correlated with muscular arm strength in people with cirrhosis ($r = 0.53$) and cancer (men $r = 0.59$, women $r = 0.48$) as well as with a knee extension ($r = 0.4$) (12, 18, 19). Similarly, a lower PA has been correlated with a greater degree of physical frailty, according to the Fried scale ($r = -0.31$) and ETF (Essential Frailty Toolset) ($r = -0.31$) (5).

Although it is true that low PA values have proven to be predictive of negative outcomes, there is currently a wide variability in reported cut-off points. This variability may depend on determinants of PA such as sex, age, BMI and the type of clinical condition or disease (18, 19). In addition, it is important to consider other parameters such as the type of population studied (hospital, community, homes for the elderly), among others. To our knowledge, there are no PA cut-off points for adults between 50 and 64 years old and older adults, adjusted by sex and BMI, related to health conditions that allow its use in different clinical and research settings. Therefore, the objective was to report the cut-off points associated with sarcopenia and frailty in adults of 50-64 years and Mexican older adults.

MATERIALS AND METHODS

Design and Study Population

This study, a secondary analysis of the FraDySMex study (Frailty, Dynapenia and Sarcopenia in Mexican Adults), is a cohort of adults living in the community of two municipalities of Mexico City consisting of men and women over 50 years of age, all of whom are able to move with or without assistive devices and able to answer the questions of the study questionnaire by themselves or with the help of a caregiver if the score of the mini-mental state examination (MMSE) with 10 points or less. People with a total functional dependence, presence of edema in their extremities, current intake of diuretics, presence of fever, diarrhea, pacemaker carriers, cancer diagnosis of 5 years or less, were excluded. The study consisted of objective evaluations by the multidisciplinary team of the Research Laboratory in Functional Evaluation of the National Institute of Geriatrics in Mexico City. More details of the design, recruitment and selection of the FraDySMex study of participants can be found in another study (20). The study was approved by the Ethics Committee of the Mocel de Angeles General Hospital and enrolled in the National Institute of Geriatrics with the number DI-PI-002/2014. Informed signed consent was obtained by all individuals before the study.

TABLE 1 | Components and cut-off points used for the diagnosis of sarcopenia.

Sex	ASM[a]	Gait speed[b]	Hand-grip strength[c]
Males	ASM≤ 6.68 kg/m^2	Height ≤1.65m ≥ 5.7 s Height >1.65m ≥4.5 s	BMI ≤24.3 kg/m^2 ≤22 Kg BMI 24.4-26.6 kg/m^2 ≤22 Kg BMI 26.7-28.5 kg/m^2 ≤24 Kg BMI >28.5 kg/m^2 ≤22 Kg
Females	ASM ≤ 5.35 kg/m^2	Height ≤ 1.51m ≥ 6.8 s Height > 1.51m ≥5.4 s	BMI ≤24.7 kg/m^2 ≤12 Kg BMI 24.8-27.6 kg/m^2 ≤12 Kg BMI 27.7-30.5 kg/m^2 ≤12 Kg BMI >30.5 kg/m^2 ≤13 Kg

ASM, Appendicular muscle mass.
[a]*Cut-off points according to the lowest quintile of ASM.*
[b]*Cut-off points by height according to the lowest quintile of gait speed.*
[c]*Cut-off points by BMI quartile.*

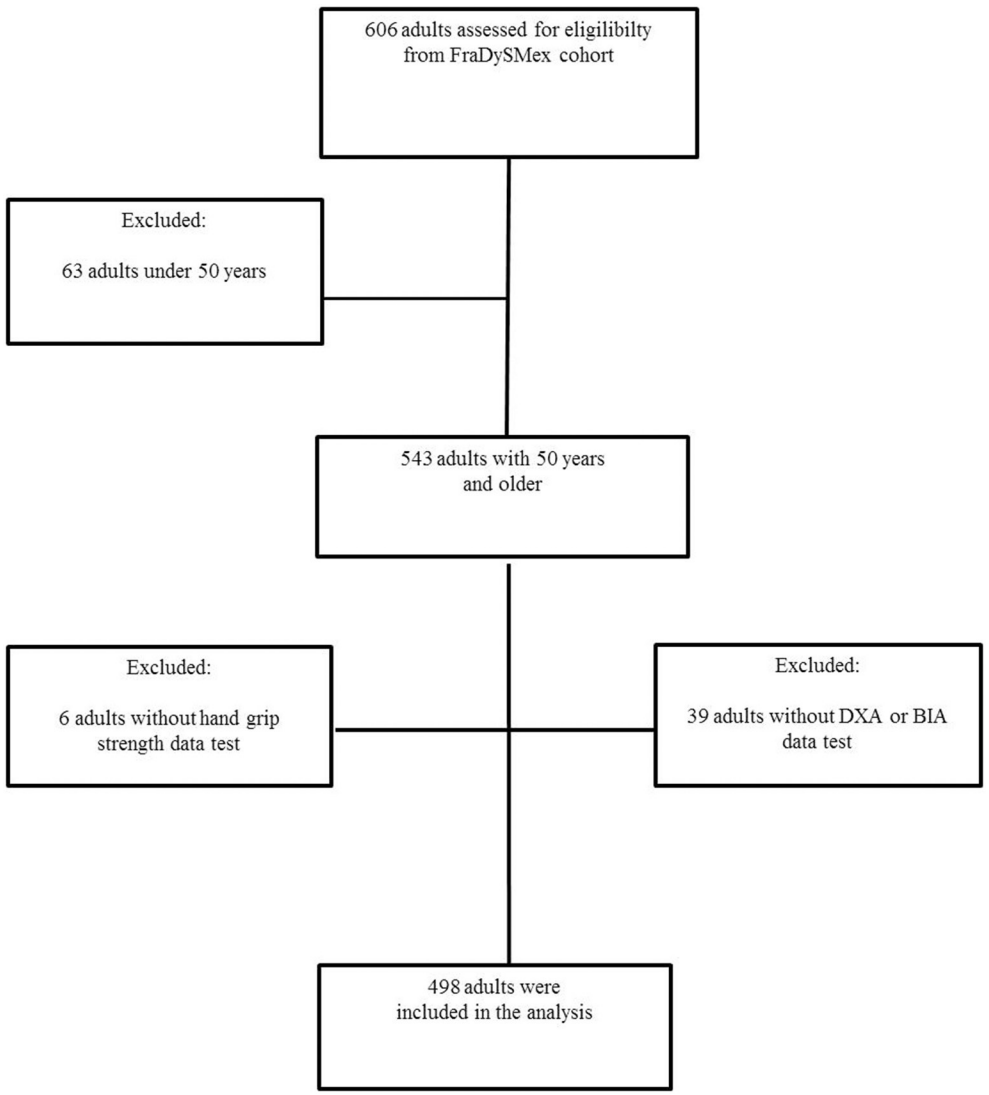

FIGURE 1 | Flowchart of the FraDySMex study (Frailty, Dynapenia and Sarcopenia in Mexican Adults). BIA (bioelectrical impedance) and DXA (dual energy X-ray absorptiometry).

Measurements

Phase angle. It was evaluated by the 50 Hz frequency bioelectrical impedance tetrapolar, brand SECA® model mBCA 514.

Diagnosis of Sarcopenia and Frailty

Sarcopenia was defined according to the criteria of the EWGSOP 2019 (6) adjusted to our population considering the low muscle strength (criterion 1), low muscle quantity (criterion 2) and the low physical performance (criterion 3). Probable sarcopenia is identified by criterion 1, diagnosis is confirmed by additional documentation of criterion 1 and 2 and criteria 1, 2, and 3 are all met, sarcopenia is considered severe. For this analysis, it was classified as sarcopenic when had sarcopenia confirmed and sarcopenia severe and as non-sarcopenic when had sarcopenia probable or don't present any criterion.

Muscle strength was evaluated with manual hand grip strength using the hydraulic JAMAR dynamometer, Lafayette, IN. Three measures of the dominant hand were taken and the highest was considered for the analysis. For low muscle strength, the lowest quartile for grip strength (kg) was considered adjusted for BMI (kg / mts^2) and sex (**Table 1**). Gait speed (GS) was recorded at a habitual gait of 6 meters on a Gait Rite instrumented mat (platinum 20) (204 x 35.5 x 0.25 inches, 100 Hz sampling rate). The GS cut-off points for our population were adjusted for height (m) and sex based on the lowest quintile (**Table 1**). Muscle quantity was evaluated with appendicular muscle mass (ASM) through the dual energy X-ray absorptiometry (DXA), (Hologic Discovery-WI; Hologic Inc., Bedford-MA; to define low muscle mass based on the lowest quintile for sex (**Table 1**).

TABLE 2 | General characteristics ($n = 498$).

Characteristics	Total	50-65, years ($n = 152$)	> 65 years ($n = 346$)	*P*
	Mean ± SD or *n* (%)			
Age, years	71.1 ± 9.5	59.7 ± 4.5	76.1 ± 6.4	0.0000
Sex;				0.2132
Women	392 (78.7)	123 (31.4)	269 (68.6)	
Men	106 (21.2)	29 (27.4)	77 (72.6)	
Schooling ≤ 9 years	250 (50.3)	55 (22.0)	195 (78.0)	0.0000
Cognitive impairment (MMSE adjusted for schooling)	56 (11.2)	10 (17.9)	46 (82.1)	0.0289
Depressive symptoms (CESD-7 ≥5 points)	231 (41.8)	48 (28.24)	122 (71.8)	0.4260
Comorbidity Index (Charlson scale ≥ 3 points)	124 (24.9)	32 (25.8)	92 (74.2)	0.4260
Falls (≥1 fall in the last year)	204 (40.9)	60 (29-4)	144 (70.6)	0.2070
Malnutrition (MNA scale ≤23 points)	136(24.6)	37 (27.2)	99 (72.8)	0.1489
BADL (Barthel index ≤90 total score)	40 (8.0)	5 (12.5)	35 (87.5)	0.0098
IADL (Lawton ≥1 activities)	82 (16.4)	7 (8.5)	75 (91.5)	0.0000
Low physical performance (SPPB scale ≤ 8 points	169 (34)	22 (13.0)	147 (86.9)	0.0000
Frailty (Fried Phenotype≥ 3 total score)	53 (10.6)	16 (30.1)	37 (69.8)	0.0003
Sarcopenia (EWGSOP, 2019)	50 (10.0)	4 (8.0)	46 (9.0)	0.0001
Phase angle (°)	4.6 ± 0.70	5.0 ± 0.61	4.3 ± 0.70	0.0000
Calf circumference, (cm)	34.7 ± 4.8	35.7 ± 5.2	34.3 ± 4.7	0.0050
Mild arm circumference, (cm)	29.9 ± 3.9	31.1 ± 3.8	39-5 ± 3.9	0.0000
Weight (kg)	65.8 ± 12.6	68.2 ± 12.8	65.2 ± 12.2	0.0138
Height (m)	1.53 ± 0.09	1.54 ± 0.09	1.52 ± 0.09	0.0014
BMI (kg/m^2)	27.9 ± 4.7	28.5 ± 4.9	28.3 ± 4.6	0.5226
Total lean mass (kg)	36.5 ± 7.7	37.6 ± 7.8	36.0 ± 7.7	0.0376
ASM/ht2 (kg/m^2)	6.4 ± 1.1	6.4 ± 1.1	6.3 ± 1.1	0.2737
Obesity, %	378 (70.1)	124 (32.8)	254 (67.2)	0.4098
Osteopenia/osteoporosis	252 (47.0)	52 (20.6)	200 (79.4)	0.0005
Hand-grip strength, (kg)	16.7 ± 7.2	19.1 ± 7.3	15.6 ± 7.1	0.0000
Gait speed, (seconds)	5.3 ± 2.8	4.3 ± 0.95	5.7 ± 3.2	0.0000

Data presented as mean (standard deviation) or number (%). ADL, activities of daily living; ASM/ht2, appendicular skeletal muscle mass adjusted by height square; BMI, body mass index; EWGSOP, European Working Group on Sarcopenia in Older People; IADL, instrumental activities of daily living; MMSE, the Mini-Mental State Examination, MNA (mini nutritional assessment), CES-D (Center for Epidemiologic Studies, Depression Scale), SPPB (short physical performance battery).
This table presents the general characteristics that describe the study population.

Physical Frailty

Using the Fried's criteria a score ≥ 3 was consider as frailty (21). The grip strength and gait velocity were defined as described in the sarcopenia variable. Low physical activity was defined using the lowest quintile of kilocalories per week obtained through the physical activity questionnaire for older adults (CHAMPS), <545.7 for men and <481.2 kcal/week for women (22). The following question was used for the variables of involuntary weight loss: In the last year, have you unintentionally lost 5 kg (or 5% of your weight) or more? For the low energy or exhaustion variable, 2 questions of the CES D-7 scale Mexican version were used (does it feel like everything you do is an effort? and the one that questioned if the person felt like doing nothing. These questions were answered as never or almost never, sometimes (1 to 2 times a week), frequently (3 to 4 days a week) and 1 (always or almost always (5 to 7 days a week) (23).

Other Variables

Other measures obtained were the following: depressive symptoms using the CES scale item D-7 (Center for Epidemiologic Studies, Depression Scale, Mexican version) (depression was considered if it scored ≥5) (23). Cognitive state was assessed using the MMSE (cognitive impairment was considered when it scored ≤ 23 points with ≤ 5 of school education, ≤ 19 points he/she was in school between 1 and 4 years, ≤ 16 without schooling or <1 year of schooling) (24, 25). Comorbidity was assessed using the comorbidity index adapted to Mexican Spanish (26, 27). Information about schooling in years (<10 y vs. ≥ 10 y), history of falls (one or more falls in the last year), low physical performance was assessed by the short physical performance battery (SPPB) using ≤ 8 points as the cut-off point (28). Functional dependence was also assessed using the Lawton scale for instrumental activities of daily life (IADL) (≥ 1 activities) and the Barthel scale for basic activities of daily living (BADL) (≤95 points) (29, 30). Malnutrition was evaluated with Mini Nutritional Assessment (MNA) scale and cutoff ≤ 23 points was used to define the risk of malnutrition. Other measures of body composition were also obtained through DXA, such as the percent total body fat considering obesity when calculated as > 30% in men and > 40% in women, bone

TABLE 3 | Criterion validity of phase angle vs. frailty and sarcopenia stratified by age.

PA values	Sensitivity	Specificity	LHR+	LHR-
50–65 years				
Frailty				
≤ 3.9	97.32%	0.00%	0.9732	−−
≤ 4	96.64%	0.00%	0.9664	−−
≤ 4.1	95.97%	33.33%	1.4396	0.1218
≤ 4.2	93.96%	33.33%	1.4094	0.1812
≤ 4.3	**91.95%**	**66.67%**	**2.7584**	**0.1208**
≤ 4.4	89.26%	66.67%	2.6779	0.1611
≤ 4.5	88.59%	100.0%	−−	0.1141
≤ 4.6	85.23%	100.0%	−−	0.1467
> 65 years				
Frailty				
≤ 3.9	83.55%	52.38%	1.7546	0.3140
≤ 4.0	78.95%	59.52%	1.9505	0.3537
≤ 4.1	**72.37%**	**71.43%**	**2.5329**	**0.3868**
≤ 4.2	66.12%	76.19%	2.7770	0.4447
≤ 4.3	59.21%	83.33%	3.5526	0.4895
≤ 4.4	53.95%	88.10%	4.5316	0.5228
≤ 4.5	44.08%	92.86%	6.1710	0.6022
≤ 4.6	36.51%	97.62%	15.3355	0.6504
50-65 years				
Sarcopenia				
≤ 3.9	97.99%	33.33%	1.4698	0.0604
≤ 4	97.32%	33.33%	1.4597	0.0805
≤ 4.1	95.97%	33.33%	1.4396	0.1208
≤ 4.2	93.96%	33.33%	1.4094	0.1812
≤ 4.3	**91.95%**	**66.67%**	**2.7584**	**0.1208**
≤ 4.4	89.26%	66.67%	2.6779	0.1611
≤ 4.5	87.92%	66.67%	2.6376	0.1812
≤ 4.6	85.23%	100.00%	−−	0.1477
>65 years				
Sarcopenia				
≤ 3.9	84.39%	59.52%	2.0848	0.2663
≤ 4	79.40%	61.90%	2.0843	0.3327
≤ 4.1	**72.76%**	**73.81%**	**2.7788**	**0.3691**
≤ 4.2	66.45%	78.57%	3.1008	0.4721
≤ 4.3	59.47%	85.71%	4.1628	0.4729
≤ 4.4	53.49%	85.71%	3.7442	0.5426
≤ 4.5	43.85%	90.48%	4.6047	0.6206
≤ 4.6	36.54%	95.24%	7.6744	0.6666

LHR, likelihood ratio; PA, phase angle. This table showed the PA cut-off points (in bold) and their association with sarcopenia and frailty, as well as their sensitivity, specificity and LHR.

mineral density of the hip and spine using the WHO cut-off points to define osteopenia and osteoporosis (31). Similarly, anthropometric measurements were obtained such as weight (kg), height (mts), calf and mild arm circumference (cm), and BMI (kg / mts^2).

Statistical Analysis

The data were analyzed using the Stata 12.0 statistical package. Descriptive statistics are reported as means ± SD for continuous variables and as frequencies for categorical variables. Some continuous variables were dichotomized for its analysis according to cut-off points previously established in the literature as exposed in the variable section. Determination of the cut-off points of the PA. The cut-off points were explored by sarcopenia and frailty in both aged groups) using sensitivity (S), specificity (Sp), and AUROC curve analysis.

To show the association of these cut-off points of PA with sarcopenia and frailty, were included in a simple and adjusted logistical regression. The results are shown as odds ratio (OR) with the respective 95% confidence intervals (CI); the final model was adjusted by sex and other variables reported in the literature that are associated with phase angle, sarcopenia, and frailty. To evaluate the goodness of fit of the models, we use Hosmer-Lemeshow goodness of fit test and AUCROC curve. The interaction and collinearity between the independent variables of the model were also evaluated.

RESULTS

The analytical sample consisted of 606 after excluding 63 participants younger than 50 years, 39 participants not submitted to DXA or BIA evaluation and 6 participants not submitted to hand-grip test (**Figure 1**). 498 adults over 50 years old were included, with 78.7% females ($n = 392$); the mean age was 71.1 ± 9.5 (SD) years and 50.3% had low schooling. The following prevalence's were observed in the total sample: depressive symptoms (41.8%), cognitive impairment (11.2%), higher comorbidity (24.9%), falls (40.9%), low physical performance (34%), functional dependence by IADL (16.4%) and BADL (8.0%), risk of malnutrition (24.6%), osteopenia/osteoporosis (47.0%), and obesity (70.1%). A prevalence of frailty of 10.6% and sarcopenia of 10.0% were found in the total sample (**Table 2**). The average of the PA in the total adults was 4.6° ± 0.70° (SD) and 5.0 ± 0.61 in the younger adults (50 to 65 years) and 4.3 ± 0.70 in the older adults (over 65 years), $p = 0.0000$. The PA cut-off points were generated for the two conditions (frailty and sarcopenia) stratified by age (adults with 50 to 65 years and adults over 65 years) reported (**Table 2**); the PA cut-off for frailty in adults 50 to 65 years was ≤4.3°, S = 91.95%, Sp 66.77% LHR (likelihood ratio) (+) 2.7584, LHR (-) 0.1208; AUROC = 0.9273 95% CI (0.8720-0.9825) (**Table 3**). PA cut-off for sarcopenia in the adults 50 to 65 years was ≤4.3°, S = 91.95%, Sp 66.77% LHR (+) 2.7589, LHR (-) 0.1208; AUROC = 0.9306 95% CI (0.8508-1.000) (**Table 3**). The PA cut off for frailty in adults over 65 years was ≤4.1°, S = 72.37%, Sp71.43% LHR (+) 2.5329, LHR (-) 0.3868; AUROC = 0.7925 95% CI (0.7280-0.8568). PA cut-off for sarcopenia in adults over 65 years was ≤4.1°, S = 72.76%, Sp= 73.81% LHR (+) 2.7788, LHR (-) 0.3691; AUROC = 0.7930 95% CI (0.7272-0.8587) (**Table 3**).

The **Table 4** included two models, the first adjusted model show a significant association between the low phase angle cut-off point ≤ 4.3 in the adults between 50 to 65 years old and ≤4.1 in the adults over 65 years) and frailty (OR 4.84; 95% CI 2.61-8.99); in the second model show a significant association with sarcopenia (OR 8.44; 95% CI 3.85-18.4); both models were adjusted by sex, BMI, comorbidity index and cognitive impairment.

TABLE 4 | Association between phase angle and sarcopenia and frailty.

	Model with frailty phenotype		Model with sarcopenia	
	OR (95% CI), *p* crude	**OR (95% CI), *p* adjusted**	**OR (95% CI), *p* crude**	**OR (95% CI), *p* adjusted**
Sex (women)	3.42 (1.20–9.70),0.020	4.51 (1.14–16.63), 0.023	1.16 (0.53–2.54), 0.694	1.24 (0.47–3.26), 0.649
Comorbidity index	1.32 (0.710–2.45), 0.380	1.18 (0.57–2.47), 0.651	1.46(0.698–3.07), 0.312	1.31 (0.50–3.45), 0.571
Cognitive impairment	4.69 (2.47–8.904), 0.000	2.68 (1.14–6.29), 0.023	3.72 (1.71–8.09), 0.001	2.35 (0.87–6.32), 0.088
BMI	0.88 (0.63–1.22), 0.454	1.08 (0.76–1.54), 0.655	0.21 (0.12–0.34), 0.000	0.27 (0.17–0.46), 0.000
Low phase angle	5.51 (3.05–9.95), 0.000	4.84 (2.61–8.99) 0.000	12.79 (6.36–25.69), 0.000	8.44 (3.85–18.4), 0.021
Hosmer-Lemeshow Goodness of fit	———	0.9945	———	0.7877
AUROC of model	———	0.7852	———	0.8887

AUROC area under the receiver operating characteristics; BMI body mass index; CI, confidence interval; OR, odds ratio. BMI was categorized in men as "0" <24.9, ¨1¨ 24.9-27.19, ¨2¨ >27.19, women "0" 25.19, ¨1¨25.19-28.11, ¨2¨>28.11. Low phase angle was considered as ≤4.3 in the adults with 50–65 years and ≤4.1 in the adults ≥65 years.

DISCUSSION

Our results show two new PA cut-off points for sarcopenia, in the adults 50 to 65 years was ≤4.3° with a high S (91.95%) and AUROC = 0.9306 95% CI (0.8508-1.000) both low Sp (66.77%). In adults over 65 years was ≤4.1° with acceptable S = 72.76% and Sp 73.81% and AUROC = 0.7930 95% CI (0.7272-0.8587) both cut-off points can be used for the screening of sarcopenia; in this regard a few studies have been conducted on the relationship between PA and sarcopenia. In the study of Basile et al. (12), with 207 people (mean age 76.2 ± 6.7 years) it was shown that there is an inverse correlation between the muscle mass (y = 3.16 + 0.08x; $r = 0.49$; $P < 0.001$) and muscular strength (y = 3.04 + 0.25x; $r = 0.60$; $P < 0001$) with the PA without specifying cut-off points. Previously Kilic et al. (16), showed that a cut-off point of <4.55° with an AUROC of 0.703 ($P < 0.0001$), with a sensitivity of 70% and specificity of 64.9% were acceptable for screening sarcopenia. However, in other study by Santana et al. (17), with 146 hospitalized people (age 71.6 ± 7.6 years) did not find an association between PA values and sarcopenia components. The most recent study to date on this association by Pessoa et al. (32) with 94 women, did not find an association with sarcopenia OR = 1.50 (0.520–4.319), low muscle mass index OR = 1.50 (0.520–4.319), low HGS OR = 3.15 0.954–10.401). This study mentions that the small sample size could impact the lack of association in PA and sarcopenia.

Our study proposes these cut-off points (≤4.3° for adults 50 to 65 years and ≤4.1° for adults over 65 years) based on their criterion validity through the following properties: sensitivity, specificity, AUROC and LHR +, LHR-. However, to strengthen this criterion validity, the low PA variable was included as independent variable in a model adjusted to sarcopenia and its was associated with a OR = 8.44 (95% CI 3.85-18.4), $P = 0.021$, which demonstrates that these cut-off points remains associated after the adjustment with variables such as age, sex, cognitive impairment and comorbidity. Indeed, there are conflicting results on the association between PA and sarcopenia which can be explained by the diversity of the criteria used to define sarcopenia and the diversity of the population studied (older adults in the community, such as the population we used in this work, hospitalized elders, adults with some advanced disease such as kidney failure, liver cirrhosis, heart failure, among others).

The gait speed and muscle strength are two dimensions of physical frailty suggested by Fried et al. (6), which are closely related to sarcopenia. Our results show that cut-off points of ≤4.3° for adults 50 to 65 years and ≤4.1° for adults over 65 years are associated with frailty with an S = 91.95%, specificity 66.77%; AUROC = 0.9273 95% CI (0.8720-0.9825) and sensitivity = 72.37%, Sp= 71.43%; AUROC = 0.7925 95% CI (0.7280-0.8568), respectively by age group. In the model adjusted for age, sex, BMI, cognitive status and comorbidity, these cut-off points remained associated with an OR = 4.84 (2.61-8.99) $P = 0.000$, which shows that low PA is also associated with physical frailty and could be used for screening frailty when a BIA is available and a dynamometer is not. In this regard, the study by Mullie et al. (5) found a low PA (<4.5°, based on the first tertile of the population), has a high predictive capacity for postoperative mortality at one month, with an OR = 3.57 (1.35-9.47 95% CI) for each decrease of a PA degree. In another study of 4,667 people aged 60 years and over (4), in a low PA (first quintile) in women, the range of the first quintile was 2,655 to 5,419°, with a significant association, with an OR = 4.4 (95% CI 2.6−7-7), and in men the range of the first quintile of the PA was 3,070 to 5,646° with a significant association with an OR = 3.1 (95% CI 1.2-7-9). In this same study at 12 years of follow-up, low PA was associated with an HR = 2.4 (95% CI [95% CI] 1.8–3.1) in women and an HR = 2.2 (95% CI 1.7–2.9) in men, demonstrating the predictive capacity for frailty and mortality. The issue that makes it difficult to take the first quintile by sex is that different cut-off points must be taken into account for sex, age, among other variables, unlike in our article that proposes a single cut-off point adjusted by these same variables, which in the adjusted model remains significantly associated.

Some limitations were considered for this study; it is a cross-sectional study that does not allow assessing the temporality of the presentation of the variables, as well as limiting their predictive capacity. However, this study incorporates the new European criteria for sarcopenia adjusted to the Mexican population that could not be very comparable with previous studies because they included criteria

of physical frailty of Fried et al. (6). However, an strength was to use the objective measures such as appendicular mass by DXA, gait speed by gait Rite® and hand grip strength by manual dynamometer (JAMAR®) to evaluate the main variables.

The cut-off points shown are not representative of the national context; however, since we do not have previous studies in this population, we believe that reporting a cut-off point of PA associated with sarcopenia and frailty contributes to establishing a criterion that can be used when the bioelectrical impedance is accessible (hospitals, nutricionist, medical and geriatrician offices).

CONCLUSION AND IMPLICATIONS

A PA with a cut-off point of $\leq$4.3 in the adults 50 to 65 years and $\leq$4.1° in adults over 65 years, showed association and acceptable sensitivity for the screening for sarcopenia and frailty in men and women. The PA can be indicator effective in timely detecting conditions related to the functionality of the older adults, such as sarcopenia and frailty. It is important to evaluate these geriatric conditions because are they associated with a greater functional dependence, institutionalization, higher health costs, and mortality.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the National Institute of Geriatrics with the number DI-PI-002/2014. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ML-T and OR-C contributed to the data collection, original idea, data analysis, manuscript writing and revision. RR-V manuscript writing and revision. All authors contributed to the article and approved the submitted version.

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Development of a Simple and Practical Screening Tool for Detection of Sarcopenia in Older People: The Bushehr Elderly Health Program

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Background: Sarcopenia is defined by the loss of muscle mass and function with a considerable prevalence which increases morbidity and mortality. We aimed to develop and validate a simple tool for screening of sarcopenia in Iranian older population.

Methods: In this study, we included 2,211 adults aged 60 years or older that participated in the stage II of Bushehr Elderly Health (BEH) program, a population-based prospective cohort study. We defined sarcopenia as reduced skeletal muscle strength plus low muscle mass. The study sample was divided into two parts; development set which were allocated to the development of the model ($n = 1,499$) and validation set ($n = 712$) were allocated to validation of the model.

Results: There were 22.9% of men and 23.2% women classified as having sarcopenia based on EWGSOP-2.After selection of variables, the final models named SarSA-Mod (Sarcopenia Scoring Assessment Models) were developed with area to under curves (AUC) of 0.82 (0.79–0.86) and 0.87 (0.84–0.90) in men and women, respectively. The final model included "age," "weight," and "calf circumference" in both sexes. The sensitivity and specificity and positive and negative predictive values for sarcopenia were 84.3, 76.0, 49.8, and 94.5% for women, 85.4, 64.8, 40.2, and 94.2% for men, respectively. The model performance was tested in the validation set with accuracy 91 and 84% among women and men, respectively.

Conclusions: Sarcopenia could be detected using SarSA-Mod, as a simple screening test with high accuracy among both sexes. Also, this screening test is valid, feasible, reliable and cost-effective compared to other tools.

Keywords: sarcopenia, screening tool, sensitivity, accuracy, iranian older population

INTRODUCTION

Sarcopenia is a geriatric disease, characterized by loss of skeletal muscle mass and muscle function, leading to adverse effects such as physical disability, poor quality of life and increased mortality (1, 2). The range of the prevalence of sarcopenia is 5–13% among older people (3–5). In addition, with the increasing number of the aged people in the world, its prevalence will increase and it is often regarded as a global public health problem (6, 7).

Moreover, individuals with sarcopenia are not aware of the disease in the earlier stage but gradually, critical events in physical and functional disability occur (8). Therefore, early detection of individuals at risk of sarcopenia forms the basis for primary prevention in order to reduce the progress of sarcopenia and prevent its severe outcomes (8, 9).

European Working Group on Sarcopenia in Older People (EWGSOP) and Asian Working Group for Sarcopenia (AWGS) commonly recommended the use of diagnostic algorithms for sarcopenia and also, they recommended to use of dual-energy X-ray absorptiometry (DXA) and/or bioelectrical impedance analysis (BIA) (3) for diagnosing low muscle mass (1, 10). However, these tools and other methods such as magnetic resonance imaging (MRI) and computed tomography (CT) are not recommended as screening tools for the entire population. Besides, they are not available everywhere and need special training. Therefore, screening of all individuals according to EWGSOP or AWGS algorithms with DXA, CT and/or MRI are very costly, time-consuming, and impractical approaches for clinical practice in poor clinical settings (11).

Other screening tools were recently developed to identify older adults at higher risk for sarcopenia. The SARC-F questionnaire is a simple and easy for screening of sarcopenia in older adults (12). However, it has been validated in different population in the world, but the low sensitivity is a problem for a good screening tool. Therefore, for increasing of sensitivity some researchers added simple anthropometric parameters such as calf circumference to the SARC-F. Some studies showed that combination of calf circumference with this questionnaire can improve diagnostic accuracy of SARC-F (13). Another tool for screening of sarcopenia is known as the Mini Sarcopenia Risk Assessment (MSRA) (14) with high sensitivity and specificity compared to SARC-F (15).

Although, there are various screening tools for sarcopenia, there is no consensus on the best tool for all older people in the world and most of these methods have not tested with other ethnic populations. Therefore, in the present study, the aim was to develop a simple, cost-effective, non-invasive model of parameters to identify sarcopenia in order to facilitate sarcopenia screening in clinical setting of Iranian older population. Finally, the accuracy and diagnostic value of this model compared with other screening tools in a community-dwelling older adult population.

MATERIALS AND METHODS

Study Design and Participants

The methodology of Bushehr Elderly Health (BEH) program has been previously described elsewhere (16). In summary, the BEH program is a prospective population-based cohort study aimed at determining the prevalence and risk factors of non-communicable diseases (NCD) among a representative sample of urban older population in Bushehr, South Iran. The target population of study was all people aged 60 years and over residing in the city of Bushehr. This population was about 10,000 persons according to District Health Center of Bushehr. We selected participants through a multi-stage, stratified cluster for BEH study. A total 3,000 people participated in the first Phase of this cohort. After 2.5 years, all participants were invited as the second stage of the BEH program for assessing of musculoskeletal disorders and cognitive impairment in these people (**Supplementary Figure 1**) (17). Until the time of the current study, 2,211 subject entered stage II. All participants signed a written informed consent and the Research Ethics Committee of Bushehr University of Medical Sciences approved the study.

Measurement of Sarcopenic Parameters and Anthropometric Measurements

Body composition was measured using dual x-ray absorptiometry (DXA, Discovery WI, HologicInc, USA). Appendicular skeletal muscle mass (ASM) for each participant was derived as the sum of upper and lower limb muscle mass and the skeletal muscle mass index (SMI) as ASM/height^2 (kg/m^2).

Muscle strength was measured by handgrip strength, using a digital dynamometer. The participant seated, elbow at side and 90^0 and the hand in a neutral position. The measurement was carried out three times for each hand and maximum grip strength was calculated by taking the highest measurement from both hands (18). Usual walking speed (m/s) on a 15 feet (4.57-meter) course was used as an objective measure of physical performance (1, 19). Heights and weights of participants were measured with a fixed stadiometer and a digital scale according to the standard protocol with shoes removed and the participants wearing light clothing. Body mass index (BMI) was calculated as weight (kg) divided by squared height (m^2). Waist circumference (WC) was measured at a point midway between the iliac crest and the lowest rib in standing position and hip circumference was measured at the most part of the hip, using a flexible tape,. Upper arm circumference was measured at the midpoint between the olecranon process and the acromion of right arm, as well as, forearm circumference was measured from the widest level with the arm hanging freely at the side. Mid-thigh circumference was measured at a midpoint between trochanterion (top of the thigh bone, femur) and tibialelaterale (top of the tibia bone) of right thigh. Calf circumference was measured at the widest level while the participant was standing upright. All measurements were read to the nearest 0.1 cm.

Blood pressure (BP) was measured twice in a seated position after 15 min rest using a standard mercury sphygmomanometer. The average of the two measurements was considered as the participant's blood pressure.

Definition of Sarcopenia

Sarcopenia was defined as low muscle strength plus reduced skeletal muscle mass based on the criteria set by EWGSOP-2 (2)

which recommends the use of reference data to determine cut-off points for muscle mass, along with AWGS (10). In a recent study, reference data from a normative Iranian population are available for detecting sarcopenia. Based on these data, the cut-off values for low SMIs were 7.0 kg/m2 and 5.4 kg/m2 among men and women, respectively (20). The muscle strength were handgrip strength <26 kg for men and <18 kg for women; while the cut-off value for low physical performance was a usual walking speed <0.8 m/s for both genders (10, 21). Using these cut-off points, sarcopenic individuals were identified.

Screening Tools

The SARC-F questionnaire and SARC-F with calf circumference were used to compare the new tool obtained from the current study. Strength, ambulation, rising from a chair, stair climbing and history of falling are five domains that are assessed. A score of four or more indicates a risk of sarcopenia (12). Another screening tool is SARCF-Calf that comprises five domains of the SARC-F and calf circumference. We used two cut-off points for calf circumference (CC) according to previous studies: (a) CC $\leq$31 cm for both genders and (b) CC $\leq$33 cm for women and CC $\leq$34 cm for men. The CC item is scored 0 points when it is above of the cut off and as 10 points if it is below or equals the cut points. A total score $\geq$11 indicates positive screening for sarcopenia (2, 21).

Sarcopenia Scoring Assessment Models (SarSA-Mod)

In the current study, we developed a statistical model for screening sarcopenia. Proposed model: "Sarcopenia Scoring Assessment Model (SarSA-Mod)" is based on a prediction equation for screening sarcopenia regarding factors effect on this disease in our study population. SarSA-Mod has been built of three variables including age, weight and calf circumference in both genders.

Details on the methods of developing and validation of SarSA-Mod are explained in the statistical section.

Statistical Analysis

Differences in between-group characteristics were examined by student's *t*-tests on the whole dataset.

To develop a statistical screening model to identify patients with sarcopenia, "True validation" or "holdout validation" method was used (22). Using random sampling, the study sample was divided into two parts; 67% of the cases ($n = 1{,}499$), called "development set," which were allocated to the development of the model as in true validation, and 33%; one third of the dataset ($n = 712$), named "validation set" were allocated to validation of the model. This method is a cross validation as named the holdout model. After dividing the dataset into two sets as earlier mentioned, analysis for developing the model in the development set begun and all analysis were stratified by sex.

Candidate variables including age, waist circumference, hip circumference, thigh, upper arm circumference, calf circumference and also weight and BMI were selected based on previous studies, cost-effectiveness, feasibility and availability of variables to be measured, and the results of bivariate analysis.

Chi-square test was used to estimate the effect of each variable with the outcome (sarcopenia) as the dependent variable.

Logistic regression analysis was applied in the development of the final model. To choose the best model, we considered the goodness of fit of the models in both genders.

After selecting final model, ß coefficient of each variable was used to calculate its index weight. To discriminate the effect of each variable, the values were rounded to the nearest integer and multiplied by 10, and the final values were used to develop a suitable scoring model.

The ability of the model to separate those with sarcopenia from those without sarcopenia was evaluated using receiver operating characteristic (ROC) curves and the area under the ROC curve. A suitable cut-off point was selected the maximum value of Youden's index with regards to sensitivity and specificity for the model SarSA-Mod (23, 24).

Then, sensitivity, specificity, positive and negative predictive values (PPV & NPV) and the accuracy of the scores were evaluated using the "validation set," which was left aside so far and not engaged in the model development process. In order to select and validate the final criteria for our scoring model, the model was applied to the validation set, using ROC analyses.

All analysis was performed using SPSS (version 16; SPSS Inc., Chicago, IL, USA) and STATA (Release 12. Statistical software. College Station, Texas: STATA Corp LP). *P*-value < 0.05 was defined as being statistically significant.

RESULTS

There were 22.9% of men and 23.2% women classified as having sarcopenia based on EWGSOP-2. The characteristics of the participants by sex and sarcopenia status are shown in **Table 1**. Participants with sarcopenia had significantly lower height, weight, BMI, waist and hip circumferences, calf and thigh circumferences, upper arm and forearm circumferences than those with non-sarcopenia in both sexes. Also, those with sarcopenia were older and had smaller handgrip strength, ASM, SMI and usual gait speed compared to those without sarcopenia in both sexes (all $P < 0.001$). There were no differences in DBP in men and SBP in both sexes irrespective of the presence of sarcopenia.

Table 2 shows the discriminatory performances of the models based on the number of variables. The following predictors were considered including: age, weight, and calf circumference for both sexes. This table presents ß coefficient, standard error and index weight of each variable in the final model in both genders. ß coefficients were rounded and multiplied by 10 to develop the final models. The formulas of final models were [(0.2 $*$ age(years)) $-$ (1.7 $*$ calf circumference(cm)) $-$ (weight(Kg) $+$ 92.56)] in women and [(1.4 $*$ age(years)) $-$ (1.2 $*$ calf circumference(cm)) $-$ (0.5 $*$ weight(Kg)) $-$ 37.42] in men.

The ROC (receiver operating characteristic) curves analyses were performed on the final scoring models for both genders. The

TABLE 1 | Characteristics of study population.

	Men			Women		
	No Sarcopenia (*n* = 831)	**Sarcopenia (*n* = 247)**	***P*-value**	**No Sarcopenia (*n* = 852)**	**Sarcopenia (*n* = 258)**	***P*-value**
Age (years)	68.13 ± 5.13	74.32 ± 7.38	<0.001	68.17 ± 5.66	71.85 ± 6.95	<0.001
Height (cm)	166.81 ± 6.03	162.85 ± 6.36	<0.001	152.86 ± 5.98	150.67 ± 6.36	<0.001
Weight (Kg)	74.74 ± 11.90	64.00 ± 9.96	<0.001	70.19 ± 11.45	54.15 ± 8.65	<0.001
BMI (Kg/m^2)	26.85 ± 3.95	24.11 ± 3.36	<0.001	30.05 ± 4.76	23.79 ± 3.13	<0.001
Grip Strength (Kg)	33.55 ± 7.00	20.74 ± 3.72	<0.001	18.75 ± 5.05	13.54 ± 3.11	<0.001
Waist Circumference (cm)	98.56 ± 10.88	92.40 ± 10.89	<0.001	103.48 ± 11.23	90.26 ± 10.36	<0.001
Hip circumference (cm)	100.55 ± 7.21	95.60 ± 7.25	<0.001	108.23 ± 10.18	96.11 ± 7.83	<0.001
Thigh circumference (cm)	50.76 ± 5.80	47.05 ± 5.09	<0.001	53.82 ± 6.74	46.75 ± 6.17	<0.001
Calf circumference (cm)	36.05 ± 3.43	33.20 ± 2.83	<0.001	36.67 ± 3.97	31.63 ± 2.92	<0.001
Upper arm circumference(cm)	30.13 ± 3.18	27.53 ± 2.77	<0.001	31.33 ± 3.51	26.95 ± 2.99	<0.001
Forearm circumference (cm)	26.85 ± 2.26	24.62 ± 1.96	<0.001	25.46 ± 2.13	22.67 ± 2.19	<0.001
SBP (mmHg)	140.06 ± 18.95	140.32 ± 21.09	0.851	139.87 ± 18.96	138.09 ± 19.58	0.190
DBP (mmHg)	82.74 ± 8.42	81.60 ± 9.09	0.067	81.52 ± 8.32	79.82 ± 7.89	0.004
Appendicular muscle mass(Kg)	19.36 ± 2.57	16.24 ± 1.88	<0.001	14.07 ± 1.91	11.14 ± 1.23	<0.001
SMI (Kg/m^2)	6.96 ± 0.80	6.12 ± 0.57	<0.001	6.03 ± 0.77	4.90 ± 0.37	<0.001
Usual gait speed (m/s)	1.00 ± 0.29	0.81 ± 0.29	<0.001	0.77 ± 0.30	0.72 ± 0.37	<0.001

Data are shown as mean ± standard deviation. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; SMI, skeletal muscle mass index.

TABLE 2 | The results of the multivariate analysis and the development scoring system in development set.

Variable	B coefficient (95% CI)	Standard error	*P*-value	Score
Men				
Age	0.14 (0.11 to 0.17)	0.0167	<0.001	1.4
Weight	−0.05 (−0.08 to −0.02)	0.0155	0.002	−0.5
Calf circumference	−0.12 (−0.22 to −0.006)	0.0552	0.040	−1.2
Constant	−3.742 (−7.09 to −0.39)	1.7105	0.029	
Pseudo R^2	0.34			
Women				
Age	0.02 (−0.01 to 0.06)	0.017	0.10	0.2
Weight	−0.10 (−0.14 to −0.07)	0.018	0.000	−1
Calf circumference	−0.17 (−0.27 to −0.08)	0.049	0.000	−1.7
Constant	9.256 (5.620 to 12.862)	1.840	0.000	
Pseudo R^2	0.31			

CI, confidence interval.

full models had values of area under curve (AUC) as 0.82 (95%CI: 0.79–0.86) for men and 0.87 (95% CI: 0.84–0.90) for women. Based on the ROC curves analyses, cut-off points of −19.07 and −14.19 were selected for men and women, respectively; as appropriate for the models.

The score of −19.07 correctly classified 69.4% of men with sarcopenia with a sensitivity of 85.4% and a specificity of 64.8% and also, among women the score of −14.19 correctly classified 77.8% of women with a sensitivity of 84.3% and specificity of 76.0%.

Next, the models were internally validated using the validation set. The performance of the models did not differ significantly in the development and validation datasets. In the validation sample, the model for men had a sensitivity of 87.6% and specificity of 62.8%, and correctly classified 69.2% of cases; and the model for women had sensitivity of 89.1% and specificity of 77.7%, and correctly classified 80.7% of patients (**Table 3**).

Table 4 shows the comparison between the screening methods; SarSA-Mod, SARC-F, SARCF-Calf (31 cm) and SARCF-Calf (33/34 cm) in the total population. The current tool could identify 86% of men or women with sarcopenia, but the SARC-F questionnaire classified only 42% of men and 45% women as screening targets. However, when calf circumference added to SARC-F with both cut-off points, the tools can identify

TABLE 3 | Performance of the SarSA-Mod in the development and validation samples.

Samples	Area under Curve	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Correctly classified (%)
Development set						
Men	0.82 (0.79–0.86)	85.4 (79.0–90.5)	64.8 (60.7–68.7)	40.2 (34.9–45.6)	94.2 (91.4–96.3)	69.4
Women	0.87 (0.84–0.90)	84.3 (77.9–89.5)	76.0 (72.3–79.4)	49.8 (43.8–55.8)	94.5 (92.0–96.4)	77.8
Validation set						
Men	0.84 (0.80–0.89)	87.6 (79.0–93.7)	62.8 (56.6–68.7)	44.8 (37.3–52.5)	93.6 (88.9–96.8)	69.2
Women	0.91 (0.88–0.94)	89.1 (80.9–94.7)	77.7 (72.2–82.6)	58.2 (49.6–66.4)	95.4 (91.7–97.8)	80.7

SarSA-Mod, Sarcopenia Scoring Assessment Model.

TABLE 4 | Comparison between the screening methods; SarSA-Mod, SARC-F, SARCF-Calf (31 cm), and SARCF-Calf (33/34 cm).

	Area under Curve	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
SARC-F					
Men	0.42 (0.37–0.47)	13.8 (9.8–18.8)	95.9 (94.3–97.1)	50.0 (37.6–62.4)	78.9 (76.2–81.4)
Women	0.45 (0.41–0.49)	29.6 (24.1–35.6)	73.4 (70.3–76.4)	25.3 (20.4–30.6)	77.6 (74.4–80.3)
Total	0.57 (0.54–0.60)	21.9 (18.3–25.7)	84.5 (82.7–86.2)	29.0 (25.2–34.8)	78.2 (76.3–80.1)
SARCF-Calf (31 cm)					
Men	0.49 (0.43–0.54)	9.4 (6.0–13.7)	98.7 (97.6–99.3)	67.7 (49.5–82.6)	78.5 (75.9–81.0)
Women	0.62 (0.57–0.66)	28.4 (23.0–34.3)	96.1 (94.6–97.3)	68.7 (59.1–77.5)	81.6 (79.0–83.9)
Total	0.64 (0.62–0.67)	19.1 (15.7–22.8)	97.4 (96.5–98.1)	68.6 (60.2–76.1)	80.0 (78.2–81.7)
SARCF-Calf (33/34 cm)					
Men	0.61 (0.56–0.66)	27.2 (21.8–33.3)	92.9 (90.9–94.5)	53.2 (44.1–62.1)	81.1 (78.4–83.5)
Women	0.73 (0.69–0.77)	48.6 (42.4–54.9)	89.6 (87.4–91.6)	58.7 (51.8–65.4)	85.2 (82.7–87.5)
Total	0.73 (0.70–0.76)	38.2 (33.9–42.6)	91.2 (89.8–92.5)	56.6 (51.2–62.0)	83.1 (81.3–84.8)
SarSA-Mod					
Men	0.83 (0.80–0.86)	86.2 (81.3–90.3)	64.3 (60.9–67.5)	41.8 (37.5–46.2)	94.0 (91.7–95.8)
Women	0.88 (0.86–0.90)	86.1 (81.2–90.0)	76.5 (73.5–79.3)	52.6 (47.7–57.5)	94.8 (92.8–96.3)
Total	0.86 (0.84–0.88)	86.1 (82.8–89.0)	70.5 (68.2–72.6)	46.7 (43.4–49.9)	94.4 (93.0–95.6)

SarSA-Mod, Sarcopenia Scoring Assessment Model.

sarcopenic patients better than SARC-F alone. SarSA-Mod was superior to SARC-F and SARCF-Calf in terms of AUC, sensitivity and NPV.

The AUC of SarSA-Mod, SARC-F, SARCF-Calf (31 cm) and SARCF-Calf (33/34 cm) in both sexes of total population are given in **Figure 1**. The AUCs of SarSA-Mod, SARC-F, SARCF-Calf (31 cm) and SARCF-Calf (33/34 cm) were 0.88, 0.53, 0.67 and 0.76 for women, 0.83, 0.61, 0.64 and 0.70 among men, respectively ($P < 0.001$).

Also we compared our models with calf circumference alone. The AUCs of calf circumference were 0.20, 0.15, and 0.25 for total population, women and men, respectively (**Supplementary Table 1**).

DISCUSSION

In the present study, the sarcopenia screening models for men and women were developed and validated in an Iranian population. Multivariate models were created based on selected variables and good discrimination ability of the models was found with the AUC of 0.82 and 0.87 for men and women, respectively. Based on the ROC curves analyses, the cut-off points of −19.07 and −14.19 were selected for men and women, respectively, and these scores could correctly classify sarcopenic patients with excellent discriminatory power.

To develop SarSA-Mod, important variables associated with sarcopenia or low muscle mass clinically or statistically significant, were examined. Of these factors, the best variables were selected as potential independent parameters of the models in both genders. First, a baseline model was identified according to age and weight which were important factors to develop the model in the previous studies (25, 26). Then, the incremental effect of anthropometric parameters to predict sarcopenia was investigated.

Among the anthropometric factors, measurement of calf circumference was simple and feasible and remained in our

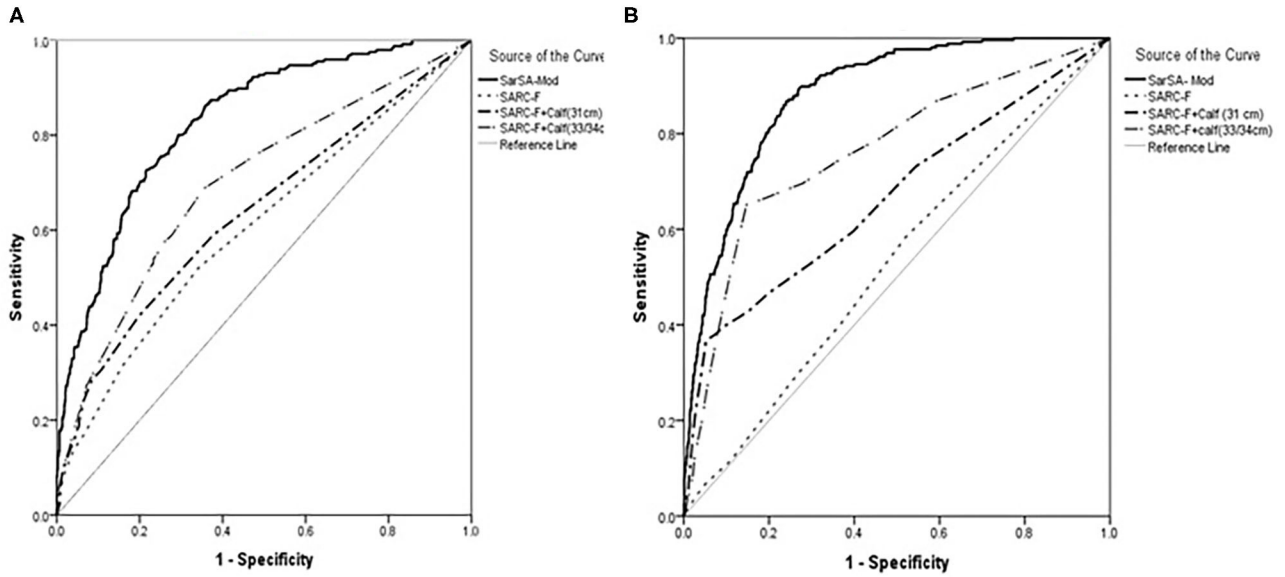

FIGURE 1 | The receiver operating characteristic (ROC) curve for SarSA-Mod (Sarcopenia Scoring Assessment Model), SARC-F, SARCF-Calf (31 cm) and SARCF-Calf (33/34 cm) in the total population in **(A)** men and **(B)** women.

multivariate models in both genders. Studies have reported that calf circumference was highly correlated with muscle mass in both genders (27, 28). Also, generally, the extremities have a lower fat mass than other body sites (29). So, calf circumference can be used as a replacement indicator of muscle mass for diagnosing sarcopenia.

Therefore, SarSA-Mods were developed based on simple variables including age, weight, and calf circumference to the final model in both sexes. It seems that SarSA-Mods can be easily used in a primary care setting for a screening of sarcopenia in the general population.

In the present study, a scoring system was developed for screening sarcopenia using an index weight of each variable from linear regression analyses. However, several studies attempted for estimation of muscle mass by a variety of variables especially anthropometric parameters (30–32), but few studies developed models with varying degrees of accuracy for sarcopenia which was defined based on muscle mass with muscle function (12, 33).

The most common screening tool for sarcopenia is a five-domain questionnaire, called SARC-F (12). This tool is a simple and quick method and does not require complex measurements. Previous studies showed that the SARC-F could predict adverse outcomes such as hospitalization, poor quality of life, and death (34, 35). However, a major weakness of this tool is its low sensitivity which is confirmed by our results and other studies (13, 36). The low sensitivity of the SARC-F questionnaire limits its use as a screening tool for sarcopenia because it may miss diagnosing subjects who have sarcopenia (9). For this reason, a research group added calf circumference to the SARC-F to improve diagnostic accuracy and sensitivity of the original SARC-F (37). The findings of this study showed that SARCF-Calf had higher sensitivity and accuracy than SARC-F alone. Similar results from other studies were reported that the addition of calf circumference could increase sensitivity (13, 38). In contrast, a study reported that SARCF-Calf had no superiority for sensitivity but improved diagnostic accuracy and specificity (39). In our study, two different cut-off points (40, 41) used in the screening of sarcopenia; 31 cm for both genders, and 33 cm for women, and 34 cm for men. Our results indicate that although both SARCF-calf (31 cm) and SARCF-calf (33/34 cm) improve sensitivity and diagnostic accuracy of SARC-F, there are sensitivity levels of 19.1% −38.2% and accuracy levels of 0.64–0.73. In line with previous reports (13, 40), our findings showed that however, SARCF-Calf has better overall accuracy and sensitivity than SARC-F, but as a screening tool is not perfect.

Some studies exist that have developed the models incorporating the use of the anthropometric equation for muscle mass (30, 31). Although, this score has high accuracy for detecting of sarcopenia, these studies attempted to diagnose sarcopenia, according to the recent definitions of sarcopenia, they require the presence of low muscle mass as well as muscle function. So, the present study developed statistical models in both genders for the screening of sarcopenia, which was defined based on muscle mass and muscle function. Also, Ishii and et al. developed a rapid screening test including age, grip strength, and calf circumference for detecting sarcopenia in an Asian population (33). Although this model is very accurate for sarcopenia, the measurement of muscle strength in many medical centers is not feasible due to the lack of dynamometer. We used the variables in our equation can be measured easily and economically in the most clinics even with poor resource.

The discriminative performance of SarSA-Mod was significantly superior to that of SARC-F (AUC = 0.86 and

0.57, respectively, $P < 0.001$). Additionally, SarSA-Mod showed higher sensitivity and NPV than the SARC-F and SARCF-Calf in both genders and total subjects. Therefore, SarSA-Mod as a simple, non-invasive, and feasible tool, with high sensitivity and accuracy is better than SARC-F and SARCF-Calf for the detection of sarcopenia.

The present results have to be interpreted within the context of strengths and potential limitations. First, the studied population was sampled from an urban population; as a result, the study's findings might not be generalizable to the rural population. Second, our models were developed in a cross-sectional cohort and similarly validated in a study set on the same population. There is a need for establishing the external validity of the models in other study populations.

To the best of our knowledge, the current study is the first to develop and validate a sarcopenia screening model for Middle-East older people. Since SarSA-Mod is easy to calculate with simple variables, it is a useful screening model for sarcopenia in a primary care setting. The scores of SarSA-Mod can be used as an effective screening tool and help in identifying people with sarcopenia for interventions to prevent further adverse events.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Research Ethics Committee of Bushehr University of Medical Sciences. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.655759/full#supplementary-material

Supplementary Figure 1 | The flowchart Bushehr Elderly Health (BEH) Program, phase I.

Supplementary Figure 2 | The distributions and histograms of variables of SarSA-Mod in both genders.

Supplementary Table 1 | The area under curve and other characteristics of calf circumference as screening tool for sarcopenia in the whole study population.

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Urine Cadmium as a Risk Factor for Osteoporosis and Osteopenia: A Meta-Analysis

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Background: As society ages, the incidence of osteoporosis increases. In several studies, cadmium (Cd) is thought to be related to osteoporosis. However, there are conflicting reports about the relationship between Cd and the risk of osteoporosis and osteopenia. Therefore, the purpose of this meta-analysis was to explore the relationship between Cd and osteoporosis and osteopenia.

Methods: Through a review of the literature, articles published in PubMed as of December 2020 were identified and the references of related publications and reviews were reviewed. Ultimately, 17 eligible articles were selected to determine the relationship between blood and urine Cd concentrations for the risk of osteoporosis or osteopenia. In this study, we performed a classification analysis, heterogeneity test, subgroup analysis, and evaluated publication bias.

Results: A total of 17 studies were included, including seven on blood Cd and 10 on urine Cd. By combining the odds ratio (OR) and 95% confidence interval (CI) for the lowest and highest categories, the odds ratio of blood Cd concentration that increased the risk of osteoporosis or osteopenia was OR 1.21 (95% CI: 0.84–1.58) and that of urine Cd concentration that increased the risk of osteoporosis or osteopenia was OR 1.80 (95% CI: 1.42–2.18), and the results of the subgroup analysis were also consistent.

Conclusions: Our research indicates that while urine cadmium (Cd) concentration may be related to increased risk of osteoporosis and osteopenia, blood Cd concentration may not. Therefore, compared to blood Cd concentration, urine Cd concentration may be more reliable as a risk factor for osteoporosis and osteopenia. This result should be interpreted with caution. Currently. research on the relationship between Cd concentration and osteoporosis and osteopenia is limited, thus, further large, high-quality prospective studies are required to elucidate the relationship between Cd concentration and osteoporosis and osteopenia.

Keywords: cadmium, osteoporosis, osteopenia, meta-analysis, risk factor

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INTRODUCTION

Osteoporosis is a systemic bone disease characterized by decreased bone mineral density, bone microstructure destruction, and increased risk of fragility fractures. Due to the high morbidity and mortality of diseases such as osteoporosis, fragility fractures, and other diseases, it has become a public health problem that needs to be solved urgently (1, 2). Some metals such as zinc, iron, and copper are closely related to human bones and are necessary to maintain normal physiological functions. However, heavy metals have been reported as risk factors for degenerative diseases such as osteoporosis and associated fractures (3, 4).

Cadmium (Cd) is a toxic non-essential transition metal. With the acceleration of global industrialization, Cd and its inorganic compounds are widely used in the manufacturing process of electroplating, batteries, pigments, plastics, and alloys. A large amount of Cd will enter the soil and, ultimately, the human body through contaminated food and water (5). Cd accumulates in plants and animals, and its half-life is ∼10–30 years. Epidemiological data indicate that occupational and environmental Cd exposure may be related to various types of cancer, and Cd may be a risk factor for osteoporosis (6). A number of animal studies have shown that Cd can directly affect bone density by stimulating osteoclast differentiation and activity (7) and can indirectly affect bone health by affecting other organ systems, such as the gastrointestinal tract, thyroid, and especially, the kidneys (8, 9). However, the results of investigations on the relationship among human Cd intake, body Cd concentration, and osteoporosis are not consistent. Songprasert et al. reported that excessive exposure and intake of Cd will cause bone density reduction and osteoporosis (10). Li X et al. also reached the same conclusion (11). However, Trzcinka-Ochocka suggested that Cd has no correlation with osteoporosis and bone density (12). Therefore, clarifying the relationship between Cd concentration and osteoporosis or osteopenia is helpful in the formulation of clinical policies and guidelines. However, there is currently no relevant meta-analysis to explain the relationship between blood and urine Cd concentrations and the risk of osteoporosis and osteopenia.

Therefore, the purpose of this meta-analysis was to explore the relationship between blood and urine Cd concentrations and the risk of osteoporosis or osteopenia.

METHODS

Ethical approval and written informed consent from patients were not necessary because our study was based on summaries and analyses of results of existing studies.

Search Strategy and Data Sources

Free keywords were used to search for articles published in PubMed till December 2020. The search words used were "cadmium," "osteoporosis," "osteopenia," and "bone density." In addition, in order to obtain further relevant literature, we manually searched the references for related articles.

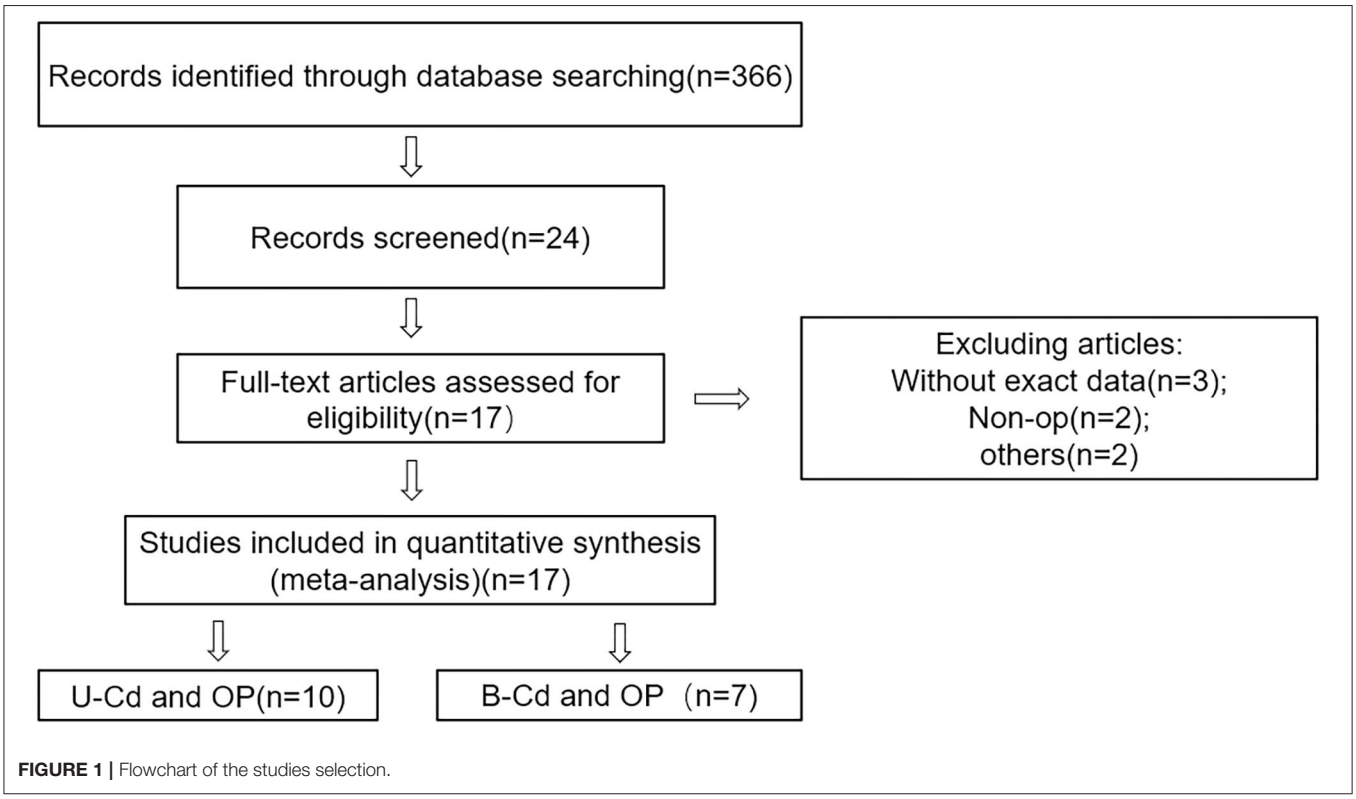

FIGURE 1 | Flowchart of the studies selection.

TABLE 1 | Summary characteristics of studies and participants.

References	Measured	Study type	Age (years)	Male-female ratio	Number	Country	BMD measured
Lim et al. (24)	B-Cd	Cross-sectional	>18	1,229/1,200	2,429	Korea	
Burm et al. (23)	B-Cd	Cross-sectional	40.3	1,275/–	1,275	Korea	Dual-energy X-ray
Choi and Han (22)	B-Cd	Cross-sectional	58.81	1,089/–	1,089	Korea	Dual-energy X-ray
Chen et al. (21)	B-Cd	Cross-sectional	Women Control area 51.9	119/202	321	China	Dual energy X-ray
			Women Polluted area 58.7				
			Men Control area 57.2				
			Men Polluted area 64.2				
Pollack et al. (20)	B-Cd	Cross-sectional	27.4	–/248	248	America	Dual energy X-ray
Cho et al. (19)	B-Cd	Cross-sectional	62.1 ± 8.2	–/481	481	Korea	Dual energy X-ray
Alfvén et al. (18)	B-Cd	Cross-sectional	Men 54	479/542	1,021	Sweden	Dual energy X-ray
			Women 52				
Lv et al. (32)	U-Cd	Cross-sectional	Non-Cd-polluted area 56.9	511/605	1,116	China	Dual energy X-ray
			Cd-polluted area 55.8				
Van Larebekea et al. (34)	U-Cd	Cross-sectional	50–65	–/808	808	Belgium	Dual energy X-ray
Kim et al. (31)	U-Cd	Cross-sectional	Male 63.8	456/630	1,086	Korea	Ultrasound bone densitometer
			Female 65.2				
Engström et al. (30)	U-Cd	Cross-sectional	<70	–/2,688	2,688	Sweden	Dual-energy X-ray
Shin et al. (29)	U-Cd	Prospective cohort		357/447	804	Korea	Dual-energy X-ray
Wu et al. (33)	U-Cd	Cross-sectional	30–90		10,978	America	
Nawrot et al. (28)	U-Cd	Cross-sectional	45	83/–	83	Belgium	Dual-energy X-ray
Gallagher et al. (27)	U-Cd	Cross-sectional	67	–/3,207	3,207	America	Dual-energy X-ray
Wang et al. (26)	U-Cd	Cross-sectional	Male control 54.3	302/488	790	China	SPA-4 single-photon absorptiometry
			Male moderate 51.1				
			Male heavy 55.4				
			Female control 50.0				
			Female moderate 51.3				
			Female heavy 52.4				
Alfvén et al. (25)	U-Cd	Cross-sectional	Environmentally exposed	520/544	1,064	Sweden	Dual-energy X-ray
			Male 52.0				
			Female 51.4				
			Occupationally exposed				
			Male 58.4				
			Female 56.5				

Selection Criteria

The articles were independently selected and commented on by two authors. First, the title and abstract were filtered based on the relevance of the topic. After reading the abstract, the full text was screened and articles that will eventually be included in the meta-analysis were selected. Articles that met the inclusion criteria were independently selected by two authors. When it was unclear whether an article should be included, a discussion was conducted with the third author to reach a consensus.

The inclusion criteria were as follows: (1) studies including human subjects; (2) observational studies; (3) studies that reported the relationship between blood or urine Cd concentration and osteoporosis or bone mass loss, and (4) studies that calculated and reported relative risk (RR), odds ratio (OR), or hazard ratio (HR) and 95% confidence interval (CI) values.

The exclusion criteria were as follows: (1) Animal experiments; (2) *in vitro* or laboratory studies; and (3) comments or case reports.

Data Extraction and Quality Assessment

Two examiners used standardized data collection forms to extract data independently. These differences were resolved through discussions with other investigators and referenced to the original article. The data extracted from each study included the first author's last name, publication year, study type, average age, male to female ratio, sample size, study country, bone density measurement method, blood or urine Cd concentration, adjusted variables, and the corresponding 95% CIs-OR estimate. If the OR value of different potential confounding factors was high, the OR value extracted reflected the maximum control of the

TABLE 2 | Summary characteristics of studies.

B-Cd							
References	**Measured**	**Type**		**B-Cd(μg/g)**	**or**	**95% CI**	**Adjustment**
Lim et al. (24)	Graphite furnace atomic absorption spectrometry		Q1	0.66	1		Age, sex, lifestyle behaviors (smoking status, alcohol drinking, and living region). sociodemographic factors (educational level, occupation and family income).
			Q2	0.825	0.99	(0.77–1.26)	
			Q3	1.2145	1.01	(0.79–1.31)	
			Q4	1.439	1.8	(1.35–2.4)	
Burm et al. (23)	Atomic absorption spectrophotometry	Total femur		0.83	1.81	(1.07–3.07)	Age, body mass index, height, household income, alcohol consumption, hypertention, diabetes mellitus, exercise and urinary cotinine.
		Lumbar spine		0.83	1.17	(0.87–1.57)	
		Femoral neck		0.83	1.49	(1.1–2.03)	
Choi and Han (22)	Graphite furnace atomic absorption spectrometry	Non-Obese	Q1	1	1		Age, BMI (as a continuous variable), serum creatinine (as a continuous variable), vitamin D deficiency [serum 25(OH)D < 20 ng/mL], smoking (current smoker vs. non-smoker), alcohol drinking (>7 drinks of alcoholic beverage per time, twice or more in a week: yes or no) and physical activity (vigorous physical activity for more than 20 min per time, three times or more in a week: yes or no).
		Non-Obese	Q2	1.25	0.83	(0.51–1.36)	
		Non-Obese	Q3	1.5	0.72	(0.42–1.23)	
		Obese	Q1	1	1		
		Obese	Q2	1.25	2.36	(0.92–6.08)	
		Obese	Q3	1.5	5.71	(1.99–16.38)	
Chen et al. (21)	Graphite furnace atomic absorption spectrometry	Male		2	0.93	(0.3–2.74)	Age, weight, height, smoking, alcohol and menopause status (women)
		Female		2	2.5	(1.11–5.43)	
Pollack et al. (20)	Inductively coupled plasma mass spectrometry	Whole body		0.36	0.76	(0.36–1.61)	Age (continuous), race (white, black, Asian, other), parity, average caloric intake (continuous), age at menarche (continuous)
		Total hip		0.36	0.98	(0.89–1.07)	
		Lumbar spine		0.36	1.17	(0.56–2.46)	
		Wrist		0.36	0.91	(0.43–1.94)	
Cho et al. (19)	Atomic absorption spectrophotometry		Q1	1	1		Intake of caloric energy and calcium, fish consumption, and vitamin D level in addition to the corrections included in model 1. Pb, lead; Hg, mercury; Cd, cadmium; As, arsenic.
			Q2	1.19	1.22	(0.65–2.29)	
			Q3	1.58	1.27	(0.68–2.39)	
			Q4	1.78	0.96	(0.51–1.81)	
Alfvén et al. (18)	Inductively coupled plasma mass spectrometry		Q1	0.56	1		Weight, smoking,
			Q2	0.84	2	(1.1–3.9)	
			Q3	1.12	2.9	(1.4–5.8)	

U-Cd							
References	**Measured**	**Type**		**U-Cd (μg/g)**	**OR**	**95% CI**	**Adjustment**
Lv et al. (32)	Inductively coupled plasma mass spectrometry	Total	Q1	2.05	1	1	Age, gender, BMI, serum albumin, urinary Ca, and urinary U-Alb.
		Total	Q2	3.01	3.07	(1.77–5.33)	
		Total	Q3	6.43	4.63	(2.68–7.98)	
		Total	Q4	8.89	9.15	(5.26–15.94)	
		Nonsmokers	Q1	2.05	1		
		Nonsmokers	Q2	3.01	1.85	(0.89–3.86)	
		Nonsmokers	Q3	6.43	3.27	(1.6–6.68)	
		Nonsmokers	Q4	8.89	9.29	(4.56–18.93)	
Van Larebekea et al. (34)	Inductively coupled plasma mass spectrometry	Female		0.625	1.26	(0.97–1.63)	BMI, education status, and exercise level
Kim et al. (31)	Atomic absorption spectrophotometer	Male	Q1	≤5	1		Age, smoking status, alcohol intake, BMI, diabetes, hypertension, and menopause (only females).
		Male	Q2	>5	3.12	(1.36–7.14)	
		Female	Q1	≤5	1		
		Female	Q2	>5	2.8	(1.6–4.9)	
		Total	Q1	≤5	1		Age, sex (only total subjects), smoking status, alcohol, intake, BMI, diabetes, hypertension, and menopause (only females).
		Total	Q2	>5	1.54	(1.05–2.25)	

(Continued)

TABLE 2 | Continued

References	Measured	Type		U-Cd(μg/g)	or	95% CI	Adjustment
Engström et al. (30)	Inductively coupled plasma mass spectrometry	Femoral neck	Q1	0.5	1		Age (years), education (≤9 and >9 years; yes/no), height (cm), total fat mass (kg), lean body mass (kg), parity (0–6), use of postmenopausal hormones (yes/no), ever use of corticosteroids (yes/no), total physical activity (MET-hours/day), smoking status (never/ever), alcohol intake (g ethanol/day), inflammatory joint diseases (yes/no), kidney diseases (yes/no), liver diseases (yes/no), malabsorption (yes/no).
		Femoral neck	Q2	0.625	2.17	(1.51–3.11)	
		Femoral neck	Q3	0.75	2.45	(1.51–3.97)	
		Total hip	Q1	0.5	1		
		Total hip	Q2	0.625	1.49	(0.75–2.97)	
		Total hip	Q	0.75	3.01	(1.41–6.43)	
		Lumbar spine	Q1	0.5	1		
		Lumbar spine	Q2	0.625	1.3	(0.91–1.86)	
		Lumbar spine	Q3	0.75	1.97	(1.24–3.14)	
		Hip or spine	Q1	0.5	1		
		Hip or spine	Q2	0.625	1.61	(1.2–2.16)	
		Hip or spine	Q3	0.75	1.95	(1.3–2.93)	
Shin et al. (29)	Atomic absorption spectroscopy	Male		0.5	1		
		Male		0.75	1.18	(0.57–2.44)	
		Male		1	2.92	(1.51–5.64)	
		Female		0.5	1		
		Female		0.75	1.29	(0.49–3.36)	
		Female		1	3.37	(1.09–10.38)	
Nawrot et al. (28)	Inductively coupled plasma mass spectrometry		Q1	0.51	1		Age, age squared, and current smoking
			Q2	1.195	4.8	(0.88–29.1)	
			Q3	1.88	9.9	(1.8–55.2)	
Wu et al. (33)	Atomic absorption spectrometry	Opo-total	Q1	1	1		Age (continuous), sex (men vs. women, not for sex subgroup analysis), ethnicity or race (non-Hispanic black and Mexican American compared with non-Hispanic white, not for race subgroup analysis), BMI (continuous), calcium intake (continuous), and physical activity
		Opo-total	Q2	1.5	1.78	(1.26-2.52)	
		Opo-total	Q3	2	3.8	(2.36-6.14)	
		Opo-male	Q1	1	1		
		Opo-male	Q2	1.5	2.11	(1.05–4.22)	
		Opo-male	Q3	2	5.36	(2.31–12.64)	
		Opo-female	Q1	1	1		
		Opo-female	Q2	1.5	1.6	(1.12–2.29)	
		Opo-female	Q3	2	3.36	(1.86–6.04)	
		Ope-total	Q1	1	1		
		Ope-total	Q2	1.5	1.49	(1.24–1.8)	
		Ope-total	Q3	2	2.05	(1.52–2.78)	
		Ope-male	Q1	1	1		
		Ope-male	Q2	1.5	1.46	(1.03–2.07)	
		Ope-male	Q3	2	2.52	(1.24–5.11)	
		Ope-female	Q1	1	1		
		Ope-female	Q2	1.5	1.41	(1.13–1.75)	
		Ope-female	Q3	2	1.81	(1.21–2.71)	
Gallagher et al. (27)	Atomic absorption spectrometry	Hip BMD	Q1	0.5	1		Age, race, income, ever-smoker, underweight, and survey-respondent–reported physician diag- nosis of renal impairment.
		Hip BMD	Q2	0.75	1.43	(1.02–2)	
		Hip BMD	Q3	1	1.4	(0.97–2.03	
		Physician diagnosed	Q1	0.5	1		
		Physician diagnosed	Q2	0.75	1.46	(0.84–2.55)	
		Physician diagnosed	Q3	1	1.47	(0.81–2.66)	

(Continued)

TABLE 2 | Continued

References	Measured	Type		U-Cd(μg/g)	or	95% CI	Adjustment
Wang et al. (26)	Atomic absorption spectrophotometry	Male	Q1	1.58	1		
		Male	Q2	2.27	0.75	(0.1–4.5)	
		Male	Q3	9.2	1.72	(0.5–5.9)	
		Females	Q1	1.79	1		
		Females	Q2	4.45	1.38	(0.7–2.8)	
		Females	Q3	12.86	2.09	(1.1–4)	
Alfvén et al. (25)	Inductively coupled plasma mass spectrometry		Q1	0.5	1		
			Q2	1.75	1.2	(0.82–1.8	
			Q3	3	2.5	(1.2–5.2)	

potential confounding factors. When required, the authors of the preliminary study were contacted for more information.

Statistical Analyses

Research data consisting of the OR of blood or urine Cd concentration and the risk of osteoporosis or osteopenia were included for analysis, and the size of the impact was expressed as 95% CI; a random-effects model was implemented (13). Cochran Q statistics and I^2 statistics were used to assess the heterogeneity between studies (14). I^2 values of 25%, 50, and 75% were considered low, medium, and high heterogeneity, respectively (15). Subgroup analysis separately assessed the relationship between blood and urine Cd concentrations and related research characteristics (sex and degree of osteoporosis) of the risk of osteoporosis or osteopenia, as a possible source of heterogeneity. Funnel chart asymmetry was used to test publication bias, and Begg's and Egger's tests were employed to measure funnel chart asymmetry (16). A "cut and fill" assessment was conducted to further evaluate the possible impact of publication bias in our meta-analysis. This method reflects the empirical research that causes funnel graph asymmetry by conservatively attributing to hypothetical negative unpublished research (17). Osteoporosis was classified as normal (T-score > -1.0), osteopenia ($-2.5 \leq$ T-score ≤ -1.0), and osteoporosis (T-score < -2.5). All statistical analyses were performed using STATA 12 (StataCorp, College Station, TX, USA).

RESULTS

Search Results

Figure 1 shows the process of document screening, research selection, and exclusion. The initial database search included 336 articles. After reading the abstract and title, 342 articles were excluded. The quality of the remaining 24 articles was evaluated, and seven articles that did not meet the inclusion criteria were excluded. Finally, 17 articles were selected for the meta-analysis, of which seven were focused on blood Cd concentrations (18–24) and 10 on urine Cd concentrations (25–34).

Research Characteristics

A total of 29,488 people from 17 studies were included in the analysis. Seven studies measured blood Cd concentration, involving a total of 6,864 subjects, with 4,191 men and 2,673 women. Only two articles were related to osteoporosis and the remaining five articles were related to osteoporosis and osteopenia. Meanwhile, 10 studies measured urine Cd concentration, involving 22,624 people, with 2,229 males and 9,417 females. Six articles involved osteoporosis, two involved osteopenia, and two involved osteoporosis and osteopenia. The risk estimates provided by most studies were adjusted for age, sex, smoking, body mass index, physical activity, and weight.

Tables 1, **2** summarize the characteristics of the study and participants.

Blood Cadmium Concentration Level and the Risk of Osteoporosis or Osteopenia

Figure 2A shows the results of blood Cd meta-analysis. Blood Cd concentration increased the risk of osteoporosis or osteopenia (OR = 1.21, 95% CI: 0.84–1.58), and the heterogeneity between different studies was moderate ($I^2 = 57.9\%$, $P = 0.015$). The comprehensive estimate of the risk of blood Cd concentration events did not change substantially without any research conducted through sensitivity analysis (**Figure 3A**).

Urinary Cadmium Concentration Level and the Risk of Osteoporosis or Osteopenia

Figure 2B shows the results of the urine Cd meta-analysis. Urinary Cd concentration increased the risk of osteoporosis or osteopenia (OR = 1.80, 95% CI: 1.42–2.18). The heterogeneity between different studies was moderate ($I^2 = 45.7\%$, $P = 0.032$). The comprehensive estimate of the risk of urinary Cd concentration events did not change substantially after excluding any research conducted through sensitivity analysis (**Figure 3B**).

Publication Bias

For the relationship between blood Cd concentration and osteoporosis and osteopenia, the Begg's test ($P = 0.297$, $z = 1.04$) and Egger's test ($P = 0.396$) showed no publication bias, whereas for the relationship between urine Cd concentration and

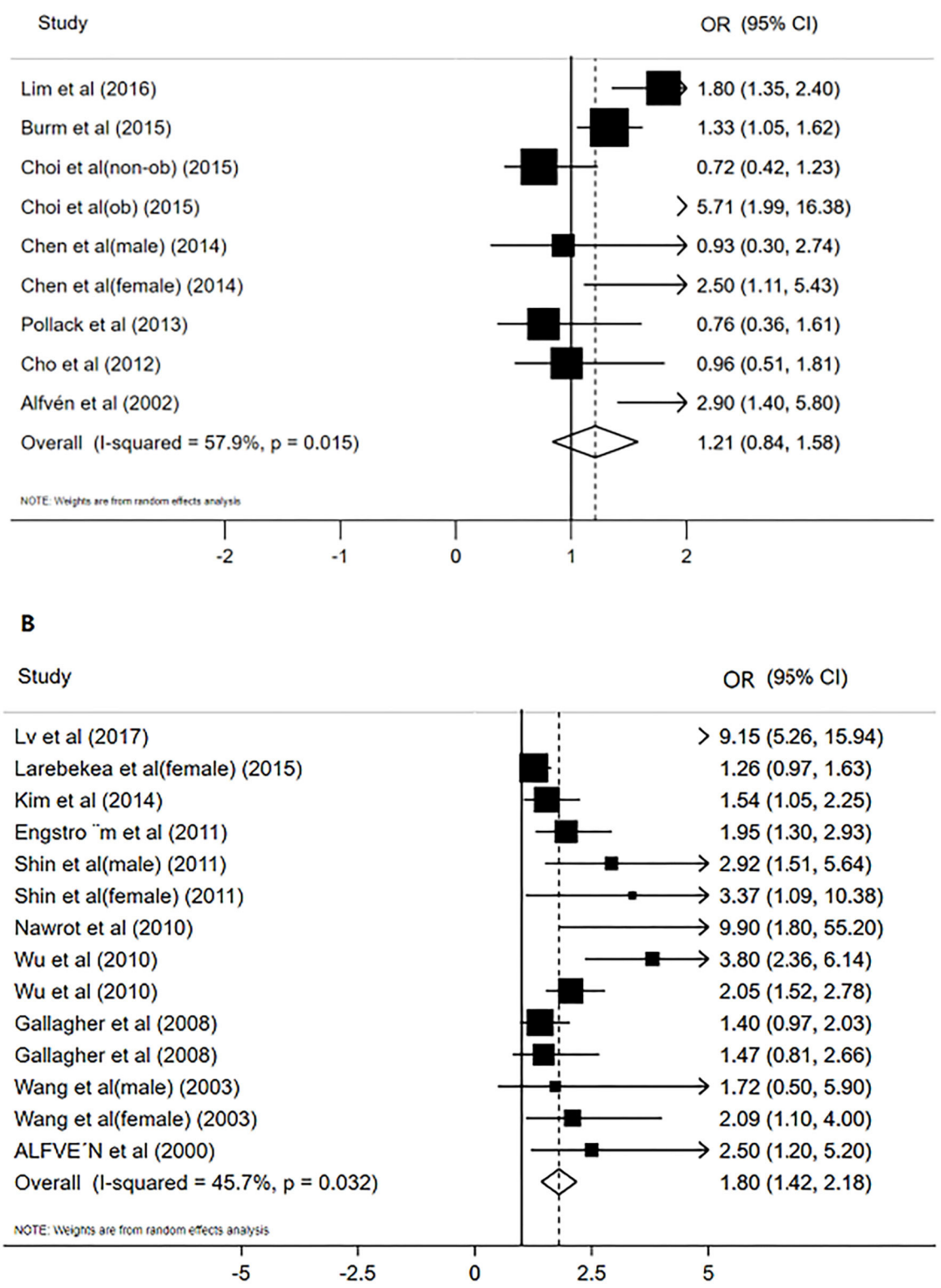

FIGURE 2 | The forest plot for studies on the concentration of blood Cd and osteoporosis or osteopenia **(A)**, Urinary Cd concentration and osteoporosis or osteopenia **(B)**.

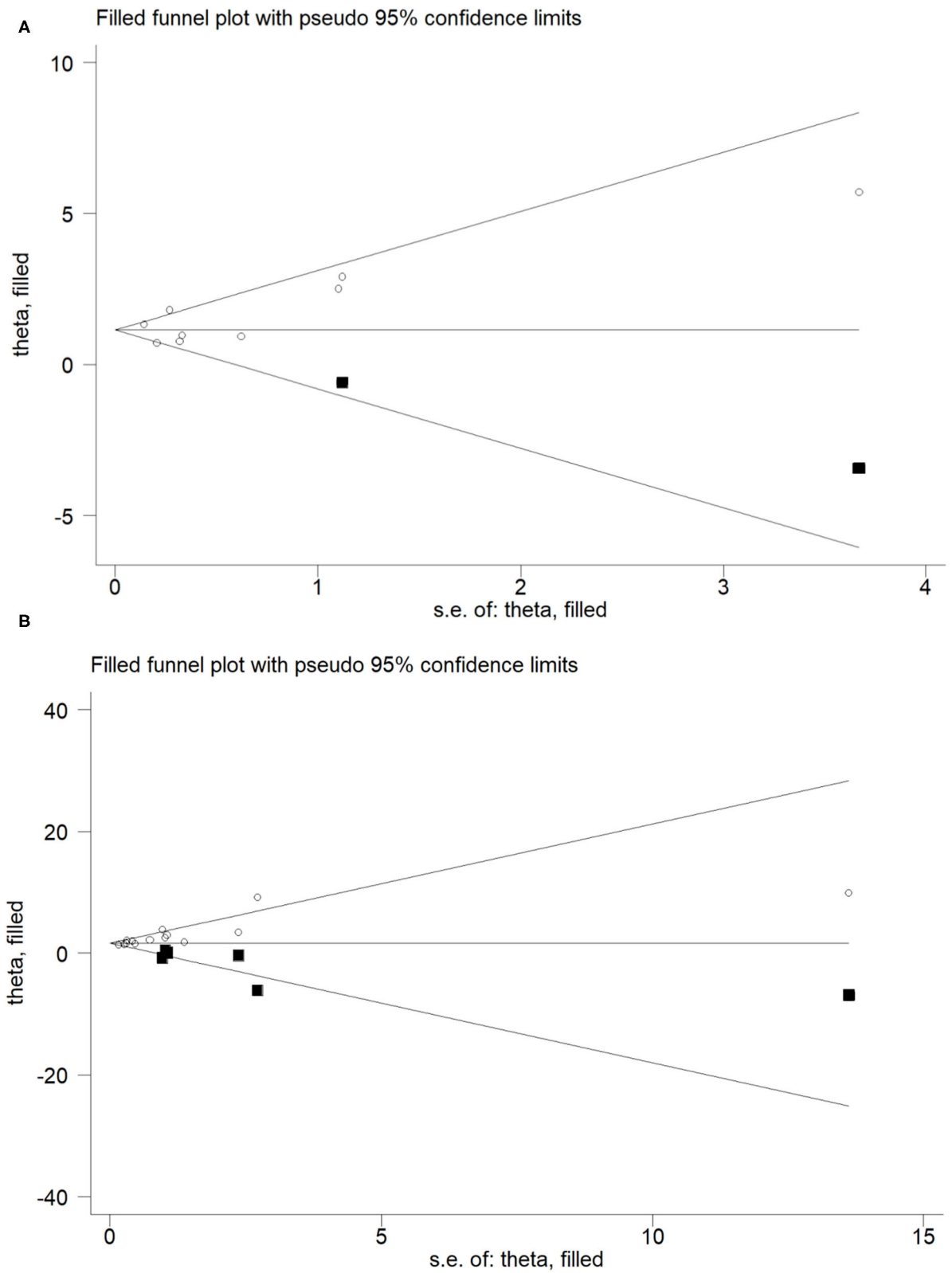

FIGURE 3 | Trim and fill funnel plot for meta-analysis of the association between Blood Cd concentration and osteoporosis or osteopenia **(A)**, Urinary Cd concentration and osteoporosis or osteopenia **(B)**.

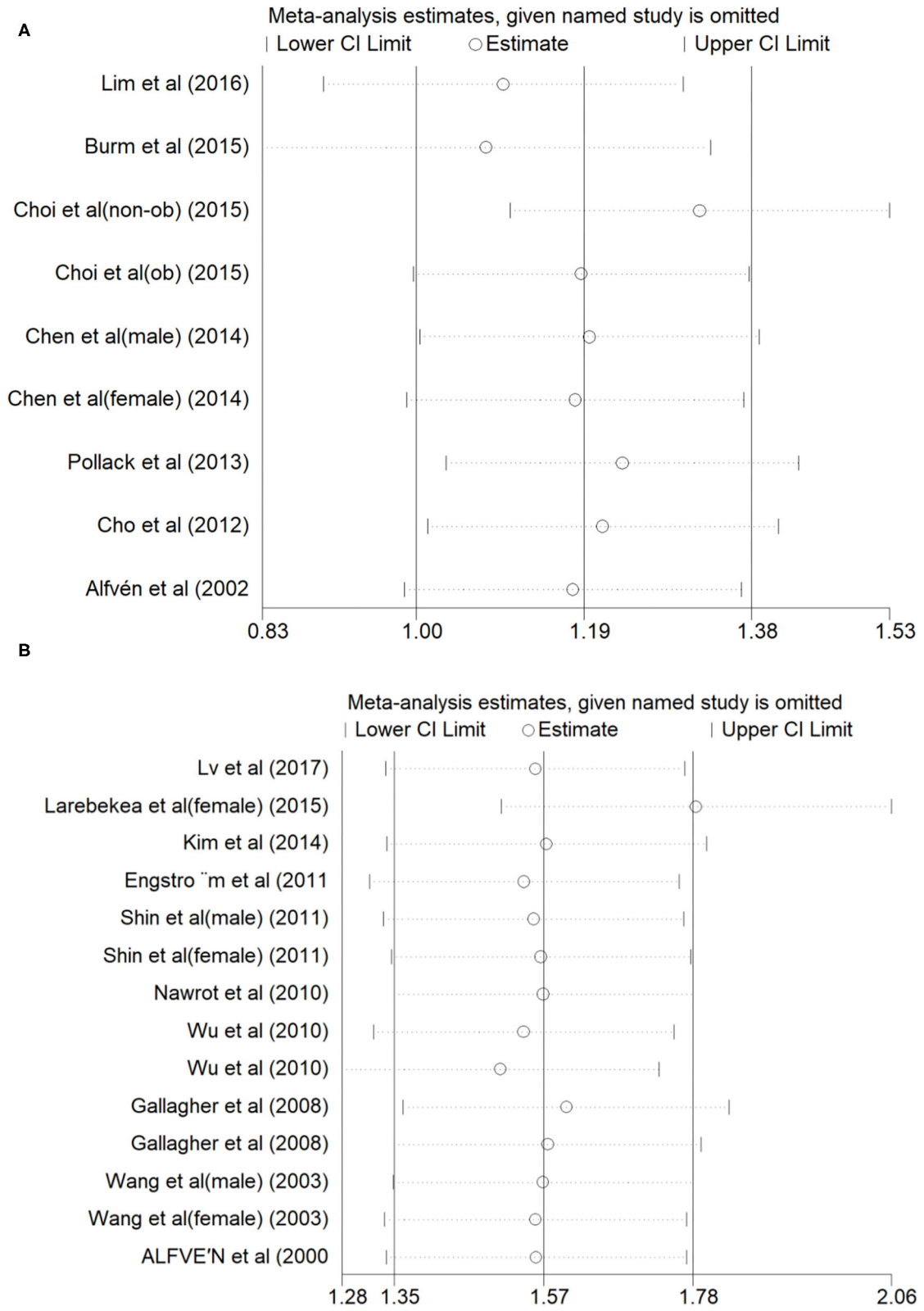

FIGURE 4 | Sensitivity analysis of Blood Cd concentration and osteoporosis or osteopenia **(A)**, Urinary Cd concentration and osteoporosis or osteopenia **(B)**.

osteoporosis and osteopenia, the Begg's test ($P = 0.021$, $z = 2.31$) and Egger's test ($P = 0.000$) showed publication bias. In order to further evaluate publication bias, we adopted the method of pruning and filling. Through computer filling, the results after correction for publication bias did not change (Estimate = 1.600; 95% CI: 1.166–2.034) (**Figure 4**).

Subgroup Analysis

The correlation between blood Cd concentration and osteoporosis and osteopenia was analyzed by subgroup analysis. The results are shown in **Table 3**. Sex was evaluated as a source of heterogeneity. Blood Cd concentration was associated with an increased risk of osteoporosis and osteopenia for both males and females (male OR = 1.05, 95% CI: 0.54–1.57, $I^2 = 59.9\%$, $P = 0.058$; female OR = 0.94, 95% CI: 0.44–1.44, I^2=13.8%, $P = 0.313$). In addition, a subgroup analysis of the degree of osteoporosis was conducted, with the following categories: normal (T-score > -1.0), osteopenia ($-2.5 \leq$ T-score ≤ -1.0), and osteoporosis (T-score < -2.5). Blood Cd concentration was associated with an increased risk of osteoporosis (T-score ≤ -1.0, OR = 1.38, 95% CI: 0.96–1.81, $I^2 = 48.5\%$, $P = 0.084$) and osteopenia (T-score < -2.5, OR = 0.81, 95% CI: 0.43–1.19, $I^2 = 7.9\%$, $P = 0.338$).

The correlation between urine Cd concentration and the risk of osteoporosis and osteopenia was analyzed using subgroup analysis. A subgroup analysis of sex revealed that urine Cd concentration was associated with an increased risk of osteoporosis and osteopenia for both males and females (male OR = 2.74, 95% CI: 1.62–3.86, $I^2 = 0.00\%$, $P = 0.855$; female OR = 1.62, 95% CI: 1.29–1.94, $I^2 = 25.1\%$, $P = 0.22$). For the analysis of the degree of osteoporosis, urine Cd concentration was associated with an increased risk of osteoporosis ($-2.5 \leq$ T-score ≤ -1.0, OR = 2.03, 95% CI: 1.38–2.69, $I^2 = 0.0\%$, $P = 0.657$) and osteopenia (T-score < -2.5, OR = 1.86, 95% CI: 1.36–2.36, $I^2 = 47.7\%$, $P = 0.033$).

TABLE 3 | Subgroup analysis to investigate differences between studies included in meta-analysis.

Type	studies	OR (95% CI)	I^2	*P*-value
B-Cd				
Osteoporosis and Osteopenia	5	1.38 (0.96–1.81)	48.5%	0.084
Osteoporosis	2	0.81 (0.43–1.19)	7.9%	0.338
B-Cd				
Male	3	1.05 (0.54–1.57)	59.9%	0.058
Female	3	0.94 (0.44–1.44)	13.8%	0.313
U-cd				
Osteoporosis	8	1.86 (1.36–2.36)	47.7%	0.033
Osteopenia	2	2.03 (1.38–2.69)	0.0%	0.657
U-Cd				
Male	5	2.74 (1.62–3.86)	0.0%	0.855
Female	7	1.62 (1.29–1.94)	25.1%	0.22

DISCUSSION

The results of our meta-analysis showed that blood Cd concentration was not associated with the risk of osteoporosis and osteopenia. However, urine Cd concentration was associated with an increased risk of osteoporosis and osteopenia.

In the 1840s, a "Itai-itai" characterized by multiple fractures and bone pain caused by Cd pollution was discovered in Japan. The patient's radiograph showed signs of false fractures of osteomalacia and severe decalcification during osteoporosis, as well as signs of proteinuria and other renal damage (35). After Cd enters the body, the kidneys and bones are the main target organs. About 50–80% of Cd accumulate in the bones and kidneys, leading to osteoporosis and also causing severe glomerular and tubular dysfunction (36). The effect on bones is considered to be the late manifestation of Cd toxicity. Regarding the mechanism of Cd specifically causing osteoporosis, Liu W et al. found that Cd can increase osteoblast apoptosis through autophagy (37). Arbon's study and other studies have also shown that Cd can directly inhibit osteoblasts and cause osteoporosis (38). Ma et al. and other studies have shown that Cd exposure significantly inhibits the differentiation of bone marrow mesenchymal stem cells, osteoblasts, and osteoclasts and promotes the occurrence of osteoporosis by promoting osteoblast apoptosis (39). In general, the pathophysiology of Cd-induced osteoporosis involves the inhibition of the accumulation of peak bone mass during growth. This adversely affects the maintenance of bone mass during bone maturation and enhances age-related osteopenia.

In an investigation of Cd-induced osteoporosis and osteopenia, Chen et al. found that high concentrations of cumulative Cd intake were associated with an increased incidence of osteoporosis and fractures in women. In men, similar trends were observed, but no statistical significance was found (40). In a study involving Japanese women, Horiguchi et al. concluded that the environmental level of Cd exposure was not enough to induce renal tubular dysfunction and would not affect bone mineral density (41). In addition to studies on adults, Sughis et al. found a consistent association between urine Cd concentration and children's bone resorption and bone demineralization in a study of children aged 8–12 years (42). In a Swedish study, Wallin et al. evaluated the effect of Cd concentration in 109 living kidneys on osteoporosis and concluded a negative correlation between kidney Cd and bone mineral density (43); however, there are very few studies on this measurement method. The current measurement method of Cd in the human body still uses blood and urine Cd concentrations as the most common biomarkers of Cd exposure. Urinary Cd mainly reflects Cd accumulation in the kidney and is also a manifestation of renal damage and osteoporosis in the later stage, whereas blood Cd shows acute and chronic exposure. The concentration of the two is essential for bone density.

There is no clear conclusion on the relationship between Cd concentration and osteoporosis and osteopenia, and there are few meta-analyses on Cd and bone health. Cheng et al. conducted a meta-analysis of Cd exposure and fracture risk and performed a subgroup analysis of urinary and blood Cd, and the results showed that Cd exposure may be a risk factor for any increased risk of fracture (44). In a meta-analysis on heavy

metal concentration and osteoporosis, Jalili et al. mentioned that blood Cd is a risk factor for osteoporosis, whereas urinary Cd is not associated with osteoporosis (45). After careful comparison of reference data, there is a misclassification of urine and blood Cd data in the article, with very few studies evaluating urinary Cd concentrations; thus the article's heterogeneity makes the results questionable.

Advantages and Limitations

To the best of our knowledge, this is the first meta-analysis to explore the relationship between blood and urine Cd concentration and osteoporosis and osteopenia. In our study, a total of 29,488 people were included, and the sample heterogeneity was small. At the same time, a subgroup analysis was conducted based on men and women and the degree of osteoporosis.

However, our research also has certain limitations. First, available research on Cd and osteoporosis is limited, which can imply that the relationship between Cd concentrations and osteoporosis and osteopenia is not sufficiently convincing. Second, observational studies have inherent limitations, such as selection bias and recall or memory bias. In addition, blood and urine Cd concentrations and the risk of osteoporosis will be affected by factors such as age. Finally, the studies included in this study may be affected by population, influence of statistical characteristics, limitations of the detection method, and other factors. For these reasons, we recommend our conclusions should be interpreted conservatively.

Conclusion

Our research indicates that while urine cadmium (Cd) concentration may be related to increased risk of osteoporosis and osteopenia, blood Cd concentration may not. Therefore, compared to blood Cd concentration, urine Cd concentration may be more reliable as a risk factor for osteoporosis and osteopenia. This result should be interpreted with caution. Currently. research on the relationship between Cd concentration and osteoporosis and osteopenia is limited, thus, further large, high-quality prospective studies are required to elucidate the relationship between Cd concentration and osteoporosis and osteopenia.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

AUTHOR CONTRIBUTIONS

BY and HL designed the meta-analysis. HL, MZ, and JM performed the literature retrieval and the data extraction. DL and LH contributed to writing the article. All authors read and approved the final manuscript.

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Possible Sarcopenia and Impact of Dual-Task Exercise on Gait Speed, Handgrip Strength, Falls, and Perceived Health

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Background: Sarcopenia is defined as a progressive age-related loss in muscle mass and strength affecting physical performance. It is associated with many negative outcomes including falls, disability, cognitive decline, and mortality. Protein enriched diet and resistance training have shown to improve muscle strength and function but there is limited evidence on impact of dual-task exercise in possible sarcopenia.

Objective: To evaluate impact of community-based dual-task exercise on muscle strength and physical function in possible sarcopenia defined by either slow gait (SG) or poor handgrip strength (HGS). The secondary aims include effect on cognition, frailty, falls, social isolation, and perceived health.

Methods: Community-dwelling older adults ≥60 years old were recruited from screening program intended to identify seniors at risk, and invited to participate in dual-task exercise program called HAPPY (Healthy Aging Promotion Program for You). One hundred and eleven participants with possible sarcopenia completed 3 months follow-up. Questionnaire was administered on demographics, frailty, sarcopenia, falls, perceived health, social network, functional, and cognitive status. Physical performance included assessment of HGS, gait speed, and Short Physical Performance Battery test (SPPB).

Results: The mean age of the Exercise group was 75.9 years old and 73.0% were women. The Exercise group had more female (73.0 vs. 47.5%), were older (75.9 vs. 72.5 years old), had higher prevalence of falls (32.4 vs. 15.0%), lower BMI (23.7 vs. 25.8), and education (4.0 vs. 7.2 years). The gait speed of the Exercise group increased significantly with significant reduction in the prevalence of SG and poor HGS. All components of SPPB as well as the total score increased significantly while the prevalence of pre-frailty and falls dropped by half. The risk of social isolation reduced by 25% with significant improvement in perceived health and cognition in the Exercise group. Significant impact on improvement gait speed and SPPB persisted after adjustment for baseline factors.

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Conclusion: Dual-task exercise program is effective in improving gait speed, SPPB score, and reducing the prevalence of poor HGS with significant improvement in perceived health, cognition, and reduction in falls and frailty. Future prospective randomized control trials are needed to evaluate the effectiveness of dual-task interventions in reversing sarcopenia.

Keywords: sarcopenia, grip strength, gait speed, dual-task exercise, frailty, perceived health, social isolation

INTRODUCTION

The world's older population ≥ 65 years old is projected to increase from 703 million in 2019 to 1.5 billion in 2050 causing an exponential increase in people with sarcopenia, frailty, cognitive impairment, and associated disability (1). Similarly, older persons ≥ 80 years old is projected to triple between 2019 and 2050 to 426 million (1). Sarcopenia is defined as a progressive age-related loss in muscle mass and strength affecting physical performance (2). It is classified as a disease under the World Health Organization (WHO)'s International Statistical Classification of Diseases and Related Health Problems (ICD) (3). The prevalence of sarcopenia ranges between 9 and 51%, and probable or possible sarcopenia between 26.3 and 73.3% depending on the case finding approach, population subgroup, and definitions used (4–8). Aging is a known risk factor for sarcopenia and the number of individuals with sarcopenia is projected to increase by 72.4% in Europe between 2016 and 2045 (9, 10).

Sarcopenia is associated with many negative health outcomes such as falls, fractures, functional decline, fear of falling, cognitive decline, depression, and mortality (2, 11). It is the precursor for physical frailty (9). While sarcopenia is a target for drug development, most drug therapeutic trials have been unsuccessful (12). The European Working Group on Sarcopenia in Older People recently updated the clinical definition and consensus diagnostic criteria for sarcopenia in 2018 incorporating low muscle mass, strength, and low physical performance (13). In recent years, there has been increasing emphasis on muscle quality where low muscle strength and poor performance rather than muscle mass are considered as principal determinants of adverse outcomes. The Sarcopenia Definition and Outcomes Consortium proposed for weakness defined by low handgrip strength (HGS) and slowness defined by low gait speed to be included in the definition of sarcopenia as both individually or in combination are associated with poor health outcomes (14).

Sarcopenia is often overlooked and undertreated in a busy clinical practice where a practical and effective screening tool like SARC-F can be used (15, 16). Slow gait (SG), prolonged chair-stand test, and/or poor HGS are included in many guidelines to diagnose possible sarcopenia to enable earlier case finding, assessment, and implement interventions to delay the decline or reverse the condition (13, 17).

Various studies have shown that muscle strength and function can be improved with protein enriched diet and resistance training exercise with variable impact on muscle mass (18). Gait and cognition share a common neural pathway, and dual-task exercise of varying intensity has shown to improve cognition and gait speed (19, 20). There is limited evidence on impact of dual task exercise on muscle strength and muscle function, and the type, intensity, and frequency of exercise in older adults with differing functional status is an emerging area of research (21). The aim of our study is to evaluate impact of community-based dual-task exercise on muscle strength and physical function in participants with possible sarcopenia. The secondary aims include effect on cognition, frailty, falls, social isolation, and overall perceived health.

METHODS

Community-dwelling older adults ≥ 60 years old in Singapore were recruited from population screening program intended to identify seniors at risk, e.g., pre-frail, frail, and those with cognitive impairment between August 2017 and December 2018. The publicity was through network of grassroots volunteers, senior activity centers, and words of peers. Phase 1 of the screening program was for general population, and those screened to be high risk were invited to participate in phase 2 screening and dual-task exercise program called HAPPY (Healthy Aging Promotion Program for You) conducted once or twice weekly within the neighborhood setting. The HAPPY program is adapted from "Cognicise," a multi-component program designed by the National Center for Geriatrics and Gerontology (NCGG) in Nagoya, Japan (20). There are more than 80 different dual-task exercises of increasing complexity and intensity. The 60 min exercise sessions led by trained health coaches comprise of 20 min of stretching, warming up, and cooling down with 40 min of personalized dual-task training incorporating resistance, balance, aerobic, and cognitive tasks (e.g., marching, clapping, with step-up/down movement on the step-board with simultaneous naming/recalling tasks, subtracting, adding, and remembering the steps on the numbered colorful ladder). The implementation and types of exercises are described in a recently published paper (20).

Exclusion criteria were diagnosis of dementia (Chinese Mini-Mental State Examination <18 or known diagnosis of dementia), wheelchair or bedbound, and living in a nursing home. A total of 569 seniors attended phase 1 screening, 296 participants were enrolled in phase 2 and complete follow up data was available for 197 participants at 3 months where 111 participants had either poor HGS or SG (**Figure 1**).

An interview questionnaire was administered by trained staff and included questions on demographics, frailty (FRAIL - Fatigue, Resistance, Ambulation, Illness, and Loss of Weight)

(22), sarcopenia (SARC-F - lifting and carrying 10 pounds, walking across a room, transferring from bed/chair, climbing a flight of 10 stairs, and frequency of falls in the past 1 year) (16), falls, perceived health (EuroQol vertical visual analog scale) (23), social network (6-item Lubben Social Network Scale) (24), activities of daily living (ADL), and instrumental activities of daily living (IADL) using the KATZ ADL scale, and Lawton IADL scale, respectively (25, 26). Cognitive status was assessed using the modified Chinese Mini-Mental State Examination (cMMSE) which has been validated in the multi-ethnic groups locally and the Montreal Cognitive Assessment (MoCA) (27–29). The FRAIL questionnaire has been validated in Asian countries including locally, easy to administer and comparable with multidimensional deficit accumulation frailty index in predicting disability and mortality (22–31). The scores range from 0 to 5, where scores of 1–2 represent prefrail and 3–5 frail. Multi-morbidity was defined as presence of 2 or more of the following comorbidities: hypertension, hyperlipidemia, diabetes mellitus, heart disease, cancer, stroke, and lung disease.

Physical performance test comprised assessment of HGS, gait speed, and Short Physical Performance Battery test (SPPB). HGS was measured on the dominant arm using Jamar hand dynamometer in the seated position with elbow flexed at 90°. Maximum HGS was taken from two trials. Cut-offs of 28 kg for males and 18 kg for females were used to define poor HGS according to the Asian Working Group for Sarcopenia criteria (17). The SPPB was scored out of a total of 12 points and included components on balance, gait speed over 4 m, and five continuous chair-stand with a maximum of 4 points awarded for each component.

The controls aged $\geq$ 65 years old were recruited from a primary care practice in Singapore between October 2019 and December 2020. This group of participants did not participate in any intervention except being treated for their chronic diseases by their primary care physician and led their usual lifestyle.

Possible sarcopenia was defined as either having poor HGS or SG (<1 m/s) according to the Asian Working Group

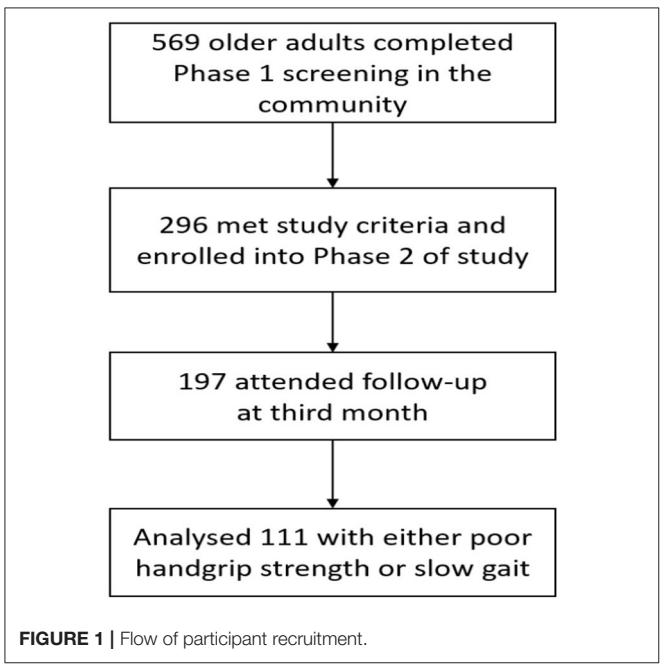

FIGURE 1 | Flow of participant recruitment.

TABLE 1 | Baseline characteristics of participants in exercise and control groups.

	Exercise (n = 111)	Control (n = 40)	P-value
Gender			**<0.01**
Male	30 (27.0)	21 (52.5)	
Female	81 (73.0)	19 (47.5)	
Age, years	75.9 ± 7.3	72.5 ± 5.5	**<0.01**
Ethnicity			**<0.01**
Chinese	105 (62.1)	30 (71.4)	
Malay	3 (42.9)	6 (85.7)	
Indian	3 (75.0)	4 (80.0)	
BMI, kg/m^2	23.7 ± 4.2	25.8 ± 4.3	**<0.01**
Education, years	4.0 ± 3.7	7.2 ± 3.8	**<0.01**
Exercise sessions attended, number	13 ± 6	-	
At least 1 fall in past year	36 (32.4)	6 (15.0)	**0.035**
Fear of fall	83 (74.8)	31 (86.1)	0.073
Multi-morbidities, (At least two chronic conditions)	54 (48.6)	29 (74.4)	**<0.01**
Hypertension	65 (58.6)	27 (69.2)	0.239
Hyperlipidemia	57 (51.4)	33 (84.6)	**<0.01**
Diabetes mellitus	28 (25.2)	18 (46.2)	**0.015**
Heart disease	15 (13.5)	7 (17.9)	0.501
cMMSE score	25.0 ± 3.5	26.5 ± 2.8	**0.019**
Frail status			**<0.01**
Robust	31 (27.9)	0 (0.0)	
Prefrail	72 (64.9)	38 (97.4)	
Frail	8 (7.2)	1 (2.6)	
Sarcopenic	10 (9.0)	5 (14.3)	0.130
Pain (At least moderate)	57 (51.4)	17 (42.5)	0.337
Anxiety (At least moderately anxious/depressed)	7 (6.4)	5 (13.9)	0.159
EQ-5D VAS score	70.5 ± 15.1	70.2 ± 14.0	0.893
SPPB Total score	8.9 ± 2.4	9.6 ± 1.7	0.134
SPPB Balance score	3.1 ± 1.1	3.7 ± 0.6	**<0.01**
SPPB Gait score	3.4 ± 0.9	3.5 ± 0.6	0.334
SPPB Chair-stand score	2.5 ± 1.2	2.3 ± 1.2	0.391
Maximum grip strength, kg	19.6 ± 5.2	22.2 ± 5.7	**<0.01**
Poor handgrip strength	61 (62.9)	24 (61.5)	0.866
Maximum gait speed (4m), m/s	0.90 ± 0.28	0.87 ± 0.15	0.458
Slow gait	82 (75.2)	31 (86.1)	0.203
Takes part in moderate/vigorous intensity exercise weekly	30 (27.5)	24 (60.0)	**<0.01**
At risk of social isolation	59 (54.1)	14 (41.7)	0.195
At least one ADL impairment	10 (9.0)	6 (16.7)	0.200
At least one IADL impairment	27 (24.3)	9 (25.0)	0.935

BMI, Body mass index; cMMSE, Chinese Mini-mental state examination; EQ-5DVAS, EuroQol Visual analog scale; SPPB, Short physical performance battery; ADL, Activities of daily life; IADL, Instrumental activities of daily life.
Data are presented as n (%), otherwise as mean (standard deviation). Bold values indicates statistically significant.

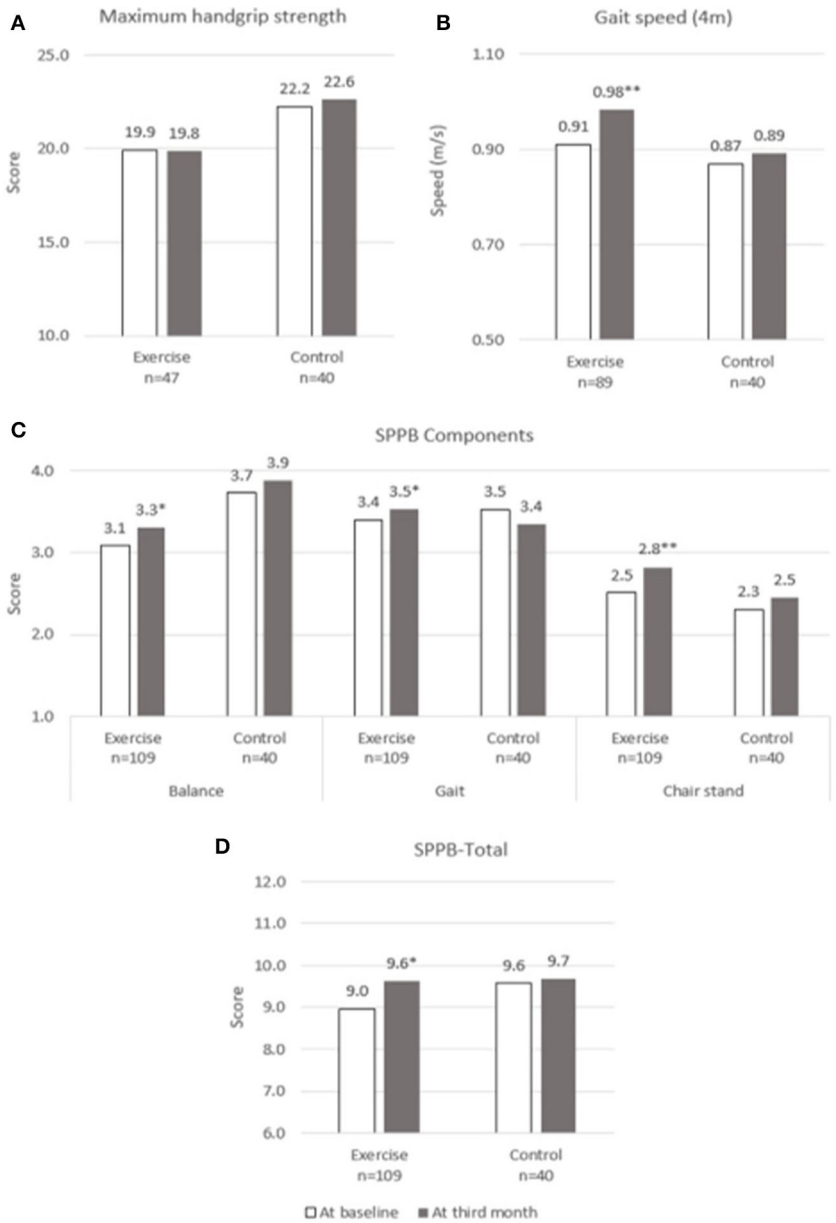

FIGURE 2 | Physical performance at baseline and third month. **(A)** Maximum Handgrip Strength, **(B)** Gait speed, **(C)** SPPB Components, **(D)** SPPB-Total. SPPB, short physical performance battery. * and **indicate significant difference at $p < 0.05$ and $p < 0.01$, respectively between baseline and third month using paired sample *t*-test.

for Sarcopenia recommendations (17). Both the Exercise and Control groups had baseline assessments at 0 and 3 months. Ethics approval was obtained from Domain-Specific Review Board of National Healthcare Group, Singapore. All participants provided written informed consent.

Statistical Analysis

Descriptive statistics were presented as mean values (standard deviation) for continuous variables and frequencies (percentages) for categorical variables. Differences in baseline characteristics between the Exercise and Control group were analyzed using Independent *T*-test on continuous variables and Chi-square on categorical variables. Change in outcome variables were calculated as difference between baseline and 3rd month time-point with positive values indicating improvement and negative values indicates decline. Paired sample *t*-test and McNemar were performed to determine statistical difference between baseline and 3rd month for continuous and categorical variables, respectively. To find out if changes were significantly different between the Exercise and Control group, linear regression was performed with change in individual outcomes variables as dependent variable and grouping (Exercise/Control), age,

education level, and number of exercise sessions attended as independent variables in Model 1 and further, adjusted for corresponding baseline values, level of physical activity and presence of multi-morbidities in Model 2. Significance level was set at $p < 0.05$ and all analyses were analyzed using SPSS Version 26.0.

RESULTS

A total of 111 participants with either poor HGS or SG, participated in the HAPPY Program and completed assessment at 3rd month (**Figure 1**). The mean age of the Exercise group was 75.9 years old and 73.0% were women. The participants attended an average of 13 sessions over 3 months. Data of 40 participants recruited from the primary care practices with either HGS or SG, and did not participate in any intervention was used as "Control". Comparison of baseline characteristics between the Exercise and Control groups are shown in **Table 1**. The Exercise group had more female (73.0 vs. 47.5%), were older (75.9 vs. 72.5years old), had higher prevalence of fall (32.4 vs. 15.0%), lower BMI (23.7 vs. 25.8), and education (4.0 vs. 7.2 years) than the Control group. Prevalence of chronic conditions was however higher in the Control group where almost 3 in 4 had multi-morbidities, 84.6% had hyperlipidemia, and 46.2% had diabetes mellitus. Majority of the participants in the Control group were pre-frail (97.4%), had higher cognitive score, better balance (3.7 vs. 3.1), and greater HGS (22.2 vs. 19.6kg).

Changes over the 3 months for both groups are shown in **Figures 2**–**5**. Several significant improvements were observed in the Exercise group. The maximum gait speed of the Exercise group increased significantly after 3 months from 0.91 (95% CI 0.86–0.96) to 0.98 (95% CI 0.92–1.04) m/s, and the prevalence of SG decreased from 75.2% (95% CI 66.2–82.4%) to 53.2% (95% CI 44.3–62.9%). There was no significant change in maximum HGS for both the groups but the prevalence of poor HGS decreased significantly in the Exercise group. All components of SPPB as well as the total score increased significantly in the Exercise group while the prevalence of pre-frailty dropped by half from 61.1% (95% CI 50.9–70.5%) to 31.1% and falls 31.1% (95% CI 22.3–41.2%) to 16.7% (95% CI 10.1–25.4%).

The risk of social isolation reduced from 52.8% (95% CI 42.5–63.0%) to 39.4% (95% CI 29.7–49.7%) in the Exercise group. There was significant within group improvement of self-perceived health rating from 70.6 (95% CI 67.7–73.5) to 73.5 (95% CI 70.6–76.5) for the Exercise group while rating for the Control group remained unchanged. Significant increase in cognitive score (cMMSE) was seen in the Exercise group from 25.0 (95% CI 24.3–25.6) to 26.1 (95% CI 25.4–26.8) while the score remained the same for the control group after 3 months.

When comparing differences between the Exercise and Control groups, the Exercise group showed significantly greater improvement in cMMSE (Unstandardized $\beta = 1.11$, 95% CI = 0.13–2.10, $p = 0.027$) before adjustment (**Table 2**). Model 1 was adjusted for age, education level, and number of sessions attended and model 2 was further adjusted for corresponding baseline scores/measurements, physical activity level and presence of multi-morbidities. Improvement in maximum gait speed and total SPPB score were significantly greater in the Exercise group both in Model 1 (Unstandardized $\beta = 0.15$, 95% CI = 0.03–0.26, $p = 0.017$ and Unstandardized $\beta = 1.31$, 95% CI = 0.35–2.26, $P < 0.01$) and Model 2 (Unstandardized $\beta = 0.17$, 95% CI = 0.05–0.30, $p < 0.01$ and Unstandardized $\beta = 1.13$, 95% CI = 0.23–2.03, $P = 0.014$).

DISCUSSION

With population aging, maintaining functional and cognitive ability, improving quality of life, and reducing social isolation should be every country's priority. The Decade of Healthy Aging Report has highlighted on the need to design national programs on age-friendly cities and community to add life to years (32). Many countries are focusing on multi-strategic cost-effective population programs to maintain functional and cognitive ability (21, 33, 34). Older adults are heterogenous and may not be able to participate in high intensity resistance exercise. Determining the threshold and optimal levels of physical activity that are necessary for healthy aging or disease management is crucial for older persons with declining intrinsic capacity. The Healthy Aging Promotion Program for You (HAPPY) is a community-based tailored dual-task exercise program for older adults led by health coaches (HC) to promote healthy aging has shown to improve function and cognition in at risk older adults (20). Three months of dual-task exercise program for older adults with possible sarcopenia defined by poor HGS or SG showed significant improvement in gait speed, balance, chair-stand, frailty status, cognition, perceived health, and reduction in falls compared with control. The significant improvement in gait speed and total SPPB scores persisted even after adjusting for confounding factors such as age, education, multimorbidity, and physical activity.

Various guidelines have defined possible or probable sarcopenia as the presence of weakness or slowness as a reflection of muscle quality to enable upstream interventions before the onset of sarcopenia or severe sarcopenia (13, 14, 17). SARC-F which has a very high specificity, fast, and practical has been used as a case-finding tool in the community and hospital setting (35, 36). HGS is a good surrogate for muscle strength and gait speed for physical performance where both are well-established markers of biological aging and intrinsic capacity (37). Various studies have found that higher gait speed, HGS, and shorter time to complete chair-stand test are associated with independent aging (38). HGS is reproducible, reliable, and can be measured easily using inexpensive portable device. Low HGS is a known predictor of poor health outcomes such as falls, mobility limitation, functional impairment, and mortality in community dwelling older adults. The various guidelines on diagnosis of sarcopenia have different cut-point for poor HGS depending on gender, age, ethnicity, and population. Poor HGS can also be affected by occupation, depression, motivation, pain, and arthritis of the hands which were not evaluated in our study (17, 39).

Sarcopenia and cognition are closely related, both associated with aging and still an area of ongoing research. Sarcopenia is a risk factor for metabolic syndrome as skeletal muscle plays a crucial role in body's glucose metabolism, and both

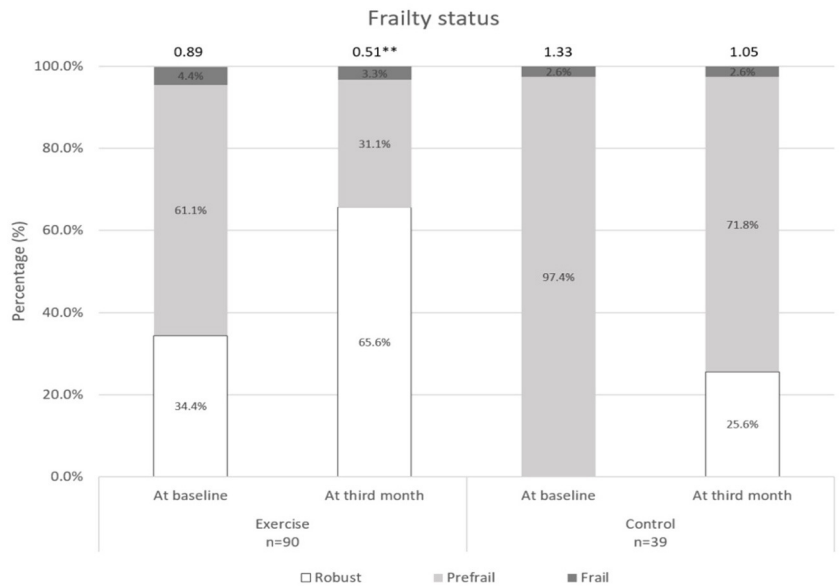

FIGURE 3 | Frailty status at baseline and third month. **indicates significant difference at $p < 0.01$ between baseline and third month.

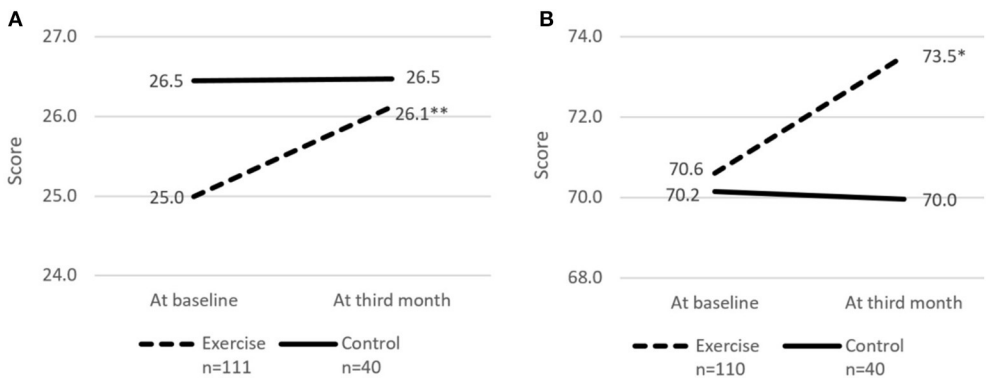

FIGURE 4 | Cognitive score and perceived health rating at baseline and third month. **(A)** cMMSE. **(B)** Perceived health rating. cMMSE, Chinese Mini-mental state examination. Perceived health rating derived from EuroQol - Visual Analog Scale. * and **indicates significant difference at $p < 0.05$ and $p < 0.01$, respectively between baseline and third month using paired sample *t*-test.

conditions either in isolation or together are associated with increased prevalence of cognitive impairment (40). Brain-derived neurotrophic factor released by contracting skeletal muscles is responsible for synapse and structural connectivity. The individual components of sarcopenia such as SG and muscle strength are known to be associated with cognitive impairment. In a study by Buchman et al. there was 9% increased risk of AD with each 1-lb annual decline in HGS (41). Gait speed is a well-recognized predictor of dementia especially in those with underlying cognitive impairment (42). Gait is a complex activity which involves planning and interplay between the central and peripheral nervous system, body systems e.g., cardiovascular, respiratory and musculoskeletal systems, fitness, and vision. Gait and cognition share similar neural pathway involving the corpus callosum, prefrontal, parietal, and temporal areas. SG is associated with impairment in many cognitive domains including attention, executive function, language, construction, abstraction, and orientation (43). More than one third male and one-half female $\geq$ 80 years old have SG (43). Strength training and aerobic exercises between 10 and 24 weeks have shown to improve cognition in prior studies (44). Dual-task exercise incorporating cognitive task and physical exercise showed increased activation in Broca's area, corresponding area on right hemisphere, widespread cortical activation across fronto-temporo-parietal areas and prefrontal cortex (45, 46). The participants in the dual-task exercise group in our study did improve in gait speed, cognition, balance, and chair-stand after 3 months. Previous studies have shown that dual-task exercises

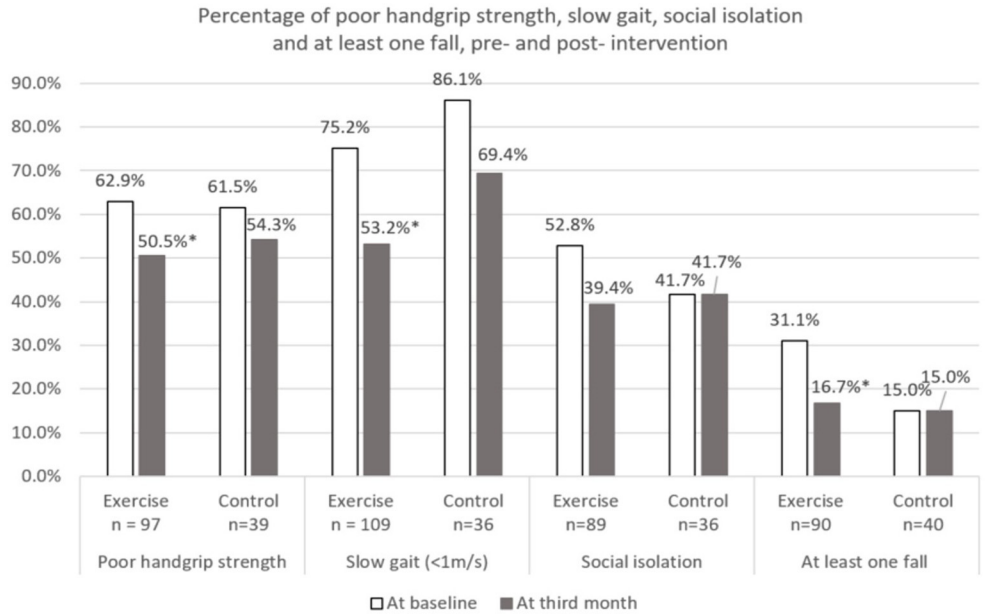

FIGURE 5 | Percentage of poor physical performance, social isolation, and at least one fall at baseline and third month. *Indicates significant difference at $p < 0.05$ between baseline and third month using McNemar test. Poor handgrip strength defined using Asian Working Group for Sarcopenia (2019) (Cut-off: Male < 28 kg and Female < 18 kg). Social isolation defined using 6-item Lubben social network scale (Cut-off: < Score of 12).

TABLE 2 | Intervention effect on change in cognition, physical performance, and overall health rating.

Factors	Unstandardized β-coefficient		
	Unadjusted	**Model 1**	**Model 2**
Maximum handgrip strength	−0.24 (−1.52–1.04) 0.709	0.16 (−0.14–0.09) 0.643	−0.79 (−2.93–1.35) 0.466
Maximum gait speed (4 m)	0.05 (−0.03–0.13) 0.189	**0.15 (0.03–0.26) 0.017**	**0.17 (0.05–0.30) <0.01**
EQ-5D VAS	3.12 (−2.40–8.64) 0.266	−0.53 (−0.92–8.35) 0.906	3.84 (−4.41–12.10) 0.359
cMMSE	**1.11 (0.13–2.10) 0.027**	0.57 (−1.01–2.15) 0.475	0.55 (−1.03–2.13) 0.492
SPPB total	0.56 (−0.06–1.16) 0.074	**1.31 (0.35–2.26) <0.01**	**1.13 (0.23–2.03) 0.014**
Frailty score	0.02 (−0.33–0.37) 0.896	−0.24 (−0.81–0.34) 0.416	0.09 (−0.39–0.56) 0.720
Lubben social network score	0.94 (−0.77–2.65) 0.280	2.65 (−0.13–5.42) 0.061	2.19 (−0.53–4.92) 0.114

Unstandardized β-coefficients (95% CIs) and p-values are shown from linear regression models with change in scores/readings as dependent variable. Model 1 is adjusted for age, education level, and number of sessions attended. Model 2 is further adjusted for corresponding baseline scores/measurements, physical activity level, and presence of multi-morbidities. Bold font indicates p-values <0.05.

are better than single-task in improving gait speed, cadence, and other cognitive variables (47).

There was significant reduction in falls in the Exercise group at 3 months. Older adults are at higher risk of falls during dual task activities such as talking while walking. Motor control and walking requires intact neural system, attention, and planning. Cognitive impairment affects the planning and multisensory integration processes for gait in turn causing falls. Participation in cognitive activities is effective in improving neuromotor performance and possibly reducing falls with shorter foot reactive time and faster gait speed (48). The Exercise group also had significantly better perceived health at 3 months and reduction of social isolation by 25%.

Decline in physical performance during hospitalization and up to 3 months post discharge has been attributable to loss of muscle mass and muscle strength, and exercise programs in the hospital and post discharge is crucial to reduce the impact of acute illness on physical performance and enhance recovery (21, 49, 50). Most studies have focused on high intensity resistance training. Based on findings from our study and a recent study by Martínez-Velilla et al. (50), exercises tailored to individual's functional status can also be introduced in the hospital and post discharge to reduce the impact of post-hospitalization functional decline.

Covid-19 pandemic and associated measures such as social distancing and lockdown has resulted in reduction of physical activity and alteration in dietary habit increasing sarcopenia prevalence (51). While previous studies have emphasized on the need of resistance exercise and protein supplement, our study is the first to document improvement in gait speed, with reduction

in the prevalence of SG and poor HGS after 3 months of dual-task exercise. While there are many studies evaluating web-based multi-domain interventions in the home setting, the inclusion of web-based dual-task exercises combined with resistance exercise, and protein enriched diet needs to studied to guide Public Health authorities on measures to prevent sarcopenia during future pandemics and lockdown (52).

There is a constant debate on how do we define outcomes which are meaningful for participants as statistically significant may not necessarily translate into being clinically meaningful and vice versa (53). Improvement in gait speed of 0.07 m/s and SPPB 0.5 points are considered clinically meaningful change based on ICFSR Task Force perspective and our study participants did show improvement of 0.07 m/s in gait speed and 0.6 points in SPPB which were also statistically significant. There was no significant change in HGS between the groups but greater significant reduction in the prevalence of poor HGS in the Exercise group. The possible explanation could be due to higher numbers of male in the Control group whom are known to have higher HGS and higher cut-off for poor HGS, and gender variation between the two groups. It is not known if 3 months is too short to notice any improvement in HGS as other multicomponent studies have shown similar findings (54).

The main strengths of our study are inclusion of community dwelling older adults with either poor HGS or SG, and the increasing complexity dual-task exercises conducted in neighborhood setting by trained health coaches suited to their functional performance. However, there are several limitations. The initial selection criteria to participate in the dual-task exercise were either prefrail, frail, or underlying cognitive impairment (cMMSE $\leq$ 26). SG and poor HGS is a subgroup analysis and were not the primary inclusion criteria. In addition, our interventions were not homogenous nor fully standardized, conducted twice weekly in slightly more than half of the participants, and the type and intensity of the dual-task exercises varied each week at health coaches discretion. Despite this, there were significant improvements and possibility of greater improvement if the exercises were conducted twice weekly in the Exercise group as shown in the entire group (20). Our study was not a randomized controlled trial but the recruitments were from different sites, and the final results were adjusted for differences between the 2 groups.

Despite the limitations, our study has generated a few interesting findings. Gait speed and cognition are closely associated, and 3 months dual-task exercise of varying intensity and complexity is effective in reducing the prevalence of SG, poor HGS, improving gait speed, frailty, perceived health, cognition, reducing falls, and social isolation. Population level screening with SARC-F with necessary targeted intervention may help reduce prevalence of sarcopenia and associated complications, reduce falls, and improve quality of life (33).

Future prospective randomized studies are needed to compare aerobic, high intensity strength training, and dual-task exercise with or without high protein diet in older people with differing functional status on the effect of muscle strength, performance, and muscle mass.

CONCLUSION

Possible sarcopenia defined by either SG or poor HGS are known to be associated with poor outcomes. High intensity resistance exercise and high protein diet are known to improve muscle strength and performance. Dual-task exercise program of varying type and increasing intensity is useful in improving gait speed, SPPB scores, and reducing the prevalence of poor HGS with significantly improved perceived health. Future prospective randomized control trials are needed to evaluate the effectiveness of dual-task interventions in reversing sarcopenia and associated complications.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Domain Specific Review Board of National Healthcare Group. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Conceptualization was performed by RM, JL, and JM. Funding acquisition and writing of original draft was performed by RM. Statistical analysis was performed by RM, YC, and JL. Methodology, project administration, review, and editing were performed by RM, JL, RH, SK, SS, LA, and JM. All authors contributed to the article and approved the final draft.

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OPINION
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The Burdens of Orthopedic Patients and the Value of the HEPAS Approach (Healthy Eating, Physical Activity, and Sleep Hygiene)

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"NO COUNTRY FOR OLD MEN" (JOEL AND ETHAN COEN, 2007)

Aging is accompanied by an inexorable decline in physiological reserves, with life-course determinants entangling with conditions that put a strain on both the body and mind. In the current research panorama, the concept of health restoration is often associated with the fast regaining of bodily abilities intended as physical and mental dynamisms (1, 2), echoing the movement Futurism of the early 1990's that despised the stasis of reality and exalted the beauty of speed (3). What slowly deteriorates has to be quickly corrected and there would be no room for old age nevertheless, slowing the body, the mind, and the society. Indeed, orthopedic care pathways are often referred to as accelerated pathways or "fast-tracks," symbolizing the firm surgery times, the shortened hospital stay, and the early rehabilitation (4). However, it is a fact that the world is populated by old people. On the one hand, there is high life expectancy while on the other hand there exists a technological society in which most of the elderly have no place. Their physical frailty, mainly associated with poor nutrition and immobility, is inevitably aggravated by psychological and social connotations (5). The HEPAS (Healthy Eating, Physical Activity, and Sleep hygiene) is a multidisciplinary approach to support the physical and mental health of individuals at risk of/with neuropsychiatric diseases that was first presented by Italian and American experts from IRCCS Orthopedic Institute Galeazzi and Stanford University (6). The cornerstones of this program include food and nutrition education, the promotion of an active lifestyle, and indications to aid restful sleep. In its conceptual model, HEPAS may not only be translated from Neuropsychiatry to Orthopedics, but it could also be feasible in the various stages of orthopedic disease progression, being implemented during the phase of health promotion and prevention of musculoskeletal disorders, the phase of reduction of disease burden, and the phase of adverse outcome prevention. The aim of this opinion article is to discuss how HEPAS can be exploited in the journey of orthopedic patients, showing its potential value in perfectly matching the burdens that grip the old person.

"GRAVITY" (ALFONSO CUARÓN, 2013)

Terrestrial gravity has designed the evolution of our musculoskeletal system under a constant force of 1 g, pointing to a finite bone mineral density. This is evident in the variance between those with heavy vs. light bodyweight (7) or between those who exercise vs. those who do not (8). Regardless of the gravitational force, nutrition plays a major role in sustaining musculoskeletal health and this has been clearly highlighted by studies on long stays in space (9). Regrettably, aging is commonly associated with weight loss and therefore reduced gravitational pressure on bones, malabsorption that couples with low nutrient intake, increased anabolic threshold that alters requirements, and

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monotonous dietary habits that reduce nutrient coverages. The resulting consequence is an aging individual dealing with a para-physiological musculoskeletal involution who embraces a bed-kitchen-sofa lifestyle and repeated naps/sleepless nights that expose to behavioral alterations and reduce the ability to cope with listlessness in meal preparation or everyday exercise (10). Targeted interventions favoring healthier dietary habits and a more active lifestyle have often been studied -albeit separately- in elderly individual at risk of/with osteosarcopenia or undergoing elective orthopedic surgery (11–13). However, the systematic integration of a comprehensive lifestyle approach like HEPAS has not yet been reported, and the prototypical community-dwelling old men is still being an individual of about 70 years of age suffering from nutritional deficiencies, sarcopenia, osteoporosis, and cardiovascular diseases (14, 15). Importantly, various syndromic or pathological combinations can give rise to more complex prototypes, such as the obese sarcopenic or the multi-frail (16). For these individuals, gravitational acceleration is a double-edged sword because, while keeping the bones dense, it pushes down the body of those who are unstable, fracturing the fragile bones.

"FRACTURE" (GREGORY HOBLIT, 2007)

Once in the hospital, the old patient with a fracture is exposed to many hazards if not carefully managed. Indeed, the hospital is a hostile environment for the oldest bodies (17), minds (18), and for the health of intestinal microbes (19), and it is known that the longer the exposures to these iatrogenic hazards the higher the risk of adverse outcomes. The hospital has different routines from the elderly's home, and in-patients have to adapt to meal hours, appointments for physiotherapy, and to an uncomfortable bed while feeling pain and sharing private space with dubious roommates. Furthermore, it is not uncommon that part of the ordered food is left on the plate (20), often due to the lack of appetite or to the unrequited patient's expectations of hospital meal. Irrespective to the hours of physiotherapy per day, the orthopedic patient remains for most of the time in bed, numb from drugs and with no stimuli. Similarly if not worse than at home, the lack of restful sleep causes mood changes and further reduces the desire to move or socially interact (21). If the old patient was malnourished, sarcopenic, osteoporotic, and with sleep debt even before accessing the surgical room, the hospital stay is likely to aggravate the clinical picture. Indeed, it makes sense to aim for accelerated paths. However, some cases require longer stays (e.g., in-hospital rehabilitation) and therefore it is necessary to take measures. In addition to the abovementioned preventive and pre-habilitation programs as far as it is concerned for elective orthopedic surgery, the feasibility of early supervised nutritional (22), motor (23), and sleep care (24) was already suggested for improving outcomes in hospitalized patients. Certainly, the more extended is the contact with the patient the more information, education, and therefore reassurance can be conveyed. However, many contextual barriers can frustrate the adherence to hospital-based educational programs, such as the not uncommon post-operative delirium that reduces the attention and increases the disorientation of the old patient (25) or the general resistant to change of clinicians. The adaptation to fit local settings (e.g., areas for motor activity), the redevelopment of hospital systems (e.g., meal ordering system, beds), and the presence of a full-time specialized staff are just some of the facilitating factors for efficacious integrations of innovative protocols nevertheless (26).

"HOME ALONE" (CHRIS COLUMBUS, 1990)

There is little use in feeding healthy food without teaching to cook, in exercising without giving autonomy to movements, and in providing rest without guaranteeing the same conditions at home. The home of the elderly can be considered, similarly but in some ways with less hazards than hospital, a hostile environment. The surgical procedure may have certainly improved the joint pain but the home-based routine is still scattered with risks of malnutrition, falls, insomnia, and solitude as soon as the patient is discharged. Frequent add-on broad-spectrum conditions like the geriatric anorexia (27), inflammaging (28), and immunosenescence (29) may be present, being frequently associated with a basal malnutrition and immunoincompentence (30). Readmissions figures from surgical/medical causes are not scarce (31) and only a small percentage may be potentially preventable (32). Intrinsic factors are numerous nevertheless, counting a history of fall, polypharmacotherapy, and age-related physical and mental decline (33). This unescapable phenomenon emphasizes the need for an effective integration between preventive, treatment, and rehabilitation paths, as it appears that one cannot discern from the other. Home-based nutritional (34), motor (35), and sleep programs (36) were already suggested to be worthy of being considered as effective other than safe. Certainly, attentive medical information and monitoring for increasing adherence is a critical success factor as the educational nature of HEPAS is the genuine backbone of the whole approach. Its principles must be taught and perceived not as temporary interventions but as definitive long-term changes. Life planning after Orthopedics is unique not only to those who have a whole life ahead (37) but also to those who have been on the other side of the path (38).

"UNBROKEN" (ANGELINA JOLIE, 2014)

The elderly are the most fragile segment of the population and are the first to pay when the health system is severely tested (10, 39). Indeed, older adults are the individuals who suffer the most from nutritional, motor, and sleep deficits nevertheless, easily stumbling upon the double-edged blade of gravity, emergency procedures, hospital hazards, inauspicious recovery, and risk of long-term disability (10). State-of-the-art orthopedic procedures fix what was previously broken. However, it is not only the joint that needs to be reconstituted but also the perception of society toward what is old and slow. Nourishment, movement, and rest are primary needs for an old person's quality of life and they are not least associated with the number of years nevertheless. The HEPAS could succeed in taking care of older people because its dimensions precisely fill the recurrent educational gaps that accelerate the para-physiological decline. Integrated with a self-government education that balances the doctor-patient

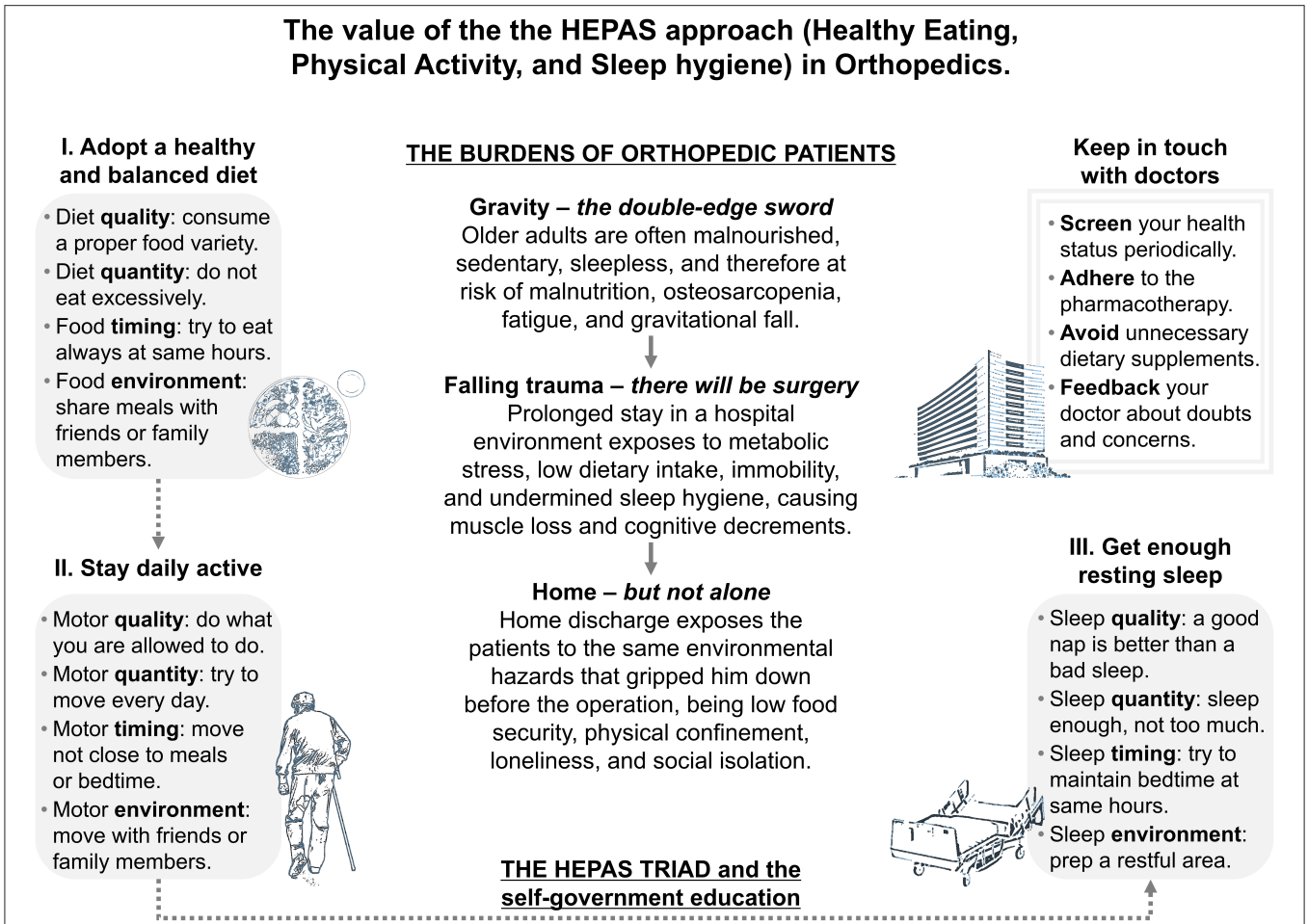

FIGURE 1 | The value of the HEPAS approach (Healthy Eating, Physical Activity, and Sleep hygiene) in Orthopedics. Each phase of musculoskeletal disease progression and care path is known to be stumbling upon deficits of nutritional, motor, and night-rest nature, eventually leading to falling traumas or orthopedic surgery. The HEPAS approach brings together indications on healthy eating, physical activity, and sleep hygiene. This triad, completed by an appropriate self-government education, may be the ideal candidate program to support individual health both in the home environment and institutionalized settings.

relationship, perhaps the HEPAS itself can be the valuable means to finally slow down (see **Figure 1**). It is also important to consider that older adults progressively lose the ability to clearly think, learn, and remember. A cognitive enhancement program *via* environmental enrichment (e.g., creation of reliable social networks and digital systems), in contrast to the electric (e.g., neural prostheses or non-invasive neuromodulation) and drug enhancement, may be useful in complementing the behavioral triad (40). In parallel, the health system could breathe a sigh of relief as it is constantly focused on treating the consequences while missing the causes, sooner or later being unable to qualitatively assist the growing number of incapacitated seniors (41, 42). Taking care of the deficits that affect muscles, bones, and the general physical and mental ability, the HEPAS could have value in musculoskeletal health promotion, prevention of osteosarcopenia and falling traumas, optimization before elective orthopedic surgery, post-operative rehabilitation, and home-base life sustenance. In the future, assuming that HEPAS can be applied for different musculoskeletal-related conditions, it will be necessary to detail the adaptation of each dimension to patient types (e.g., at risk of vs. with disease) and phase (e.g., prevention vs. rehabilitation). Confidently, telemedicine approaches will favor the inclusion of valid remote programs (43), managing home-based individuals through interactive platforms capable of reviving the "Eternal Sunshine of the Spotless Mind" (by Michel Gondry, 2004).

AUTHOR CONTRIBUTIONS

MB formulated the opinion, wrote the first draft, contributed to sections, and approved the submitted version of the manuscript.

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Sarcopenia Is Associated With Increased Risks of Rotator Cuff Tendon Diseases Among Community-Dwelling Elders: A Cross-Sectional Quantitative Ultrasound Study

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Backgrounds: Recently, the association between sarcopenia and various musculoskeletal disorders, such as lumbar spine stenosis and fibromyalgia, has been highlighted. However, the relationship between sarcopenia and rotator cuff tendon diseases has rarely been investigated. This study aimed to evaluate whether sarcopenia was associated with shoulder pain and to determine whether rotator cuff tendons differed in echotexture between the sarcopenic and non-sarcopenic populations.

Methods: The thickness and echogenicity ratio of the tendon vs. the overlying muscle (ER_{TM}) or subcutaneous tissue (ER_{TT}) were measured using high-resolution ultrasonography in 56 sarcopenic patients and 56 sex- and age- matched controls. The association between ultrasound measurements of the rotator cuff tendon complex and sarcopenia was investigated using the generalized estimating equation (GEE).

Results: The sarcopenic group had an increased prevalence of shoulder pain. Based on the GEE analysis, sarcopenia was significantly associated with an increase in supraspinatus tendon thickness (β coefficient $= 0.447$, $p < 0.001$) and a decrease in the ER_{TM} for the biceps long head and rotator cuff tendons. A negative trend of association was observed between sarcopenia and ER_{TT} in the supraspinatus tendons (β coefficient $= -0.097$, $p = 0.070$). Nevertheless, sarcopenia was not associated with an increased risk of rotator cuff tendon tears.

Conclusions: Patients with sarcopenia have a higher risk of shoulder pain. A consistent tendinopathic change develops in the supraspinatus tendons in sarcopenic patients.

However, sarcopenia is less likely to be associated with serious rotator cuff pathology, such as tendon tears. Prospective cohort studies are warranted to explore the causal relationship between sarcopenia and shoulder disorders.

Keywords: ultrasound, shoulder pain, aging, frailty, sarcopenia

INTRODUCTION

Sarcopenia, characterized by aging-related gradual loss of muscle performance and function, has a prevalence of ∼10% in the population aged > 60 years (1). The causes of sarcopenia are multifactorial, comprising physical inactivity, decline in nutritional intake, degeneration of neuromuscular junctions, and chronic systemic inflammation (2). Currently, an increasing number of potential health consequences of sarcopenia have been uncovered, such as cognitive impairment (3), depression (4), increased mortality (5), and a high risk of falls and mobility limitation (6). The association between sarcopenia and musculoskeletal disorders has been uncovered in the recent years. In patients with lumbar spinal stenosis, sarcopenia was associated with an increased degree of vertebral slippage, more intense lower back pain, and a higher incidence of dyslipidemia and cardiovascular disease (7, 8). A retrospective cohort study also pointed out that grip strength, a widely used parameter for the diagnosis of sarcopenia, was a predictor for the risk of falls in patients following decompression and fusion for lumbar spinal stenosis (9). To date, only a limited number of studies have investigated the relationship between sarcopenia and painful shoulder disorders.

Shoulder pain is a common musculoskeletal complaint, with an annual cumulative incidence of up to 2.4% in adults aged 45–64 years, based on a systematic review (10). Among various types of musculoskeletal pain, painful shoulder disorders have the highest negative impact on the quality of life of middle-aged and elderly people (11). In patients who visited a primary care institute for shoulder problems, the most prevalent pathology arose from the rotator cuff tendons and related structures, such as the subacromial bursa (12). Rotator cuff tendon tears are regarded as the most detrimental type of shoulder tendon disorders and frequently lead to severe disability. In recent years, high-resolution ultrasound has been widely used in the evaluation of rotator cuff tendon disorders (13–15), and its diagnostic accuracy is comparable to that of magnetic resonance imaging (16). In contrast to reports of descriptive findings, quantitative measurements of thickness, and echo intensity provide more objective assessments of tendon texture. Previous studies have demonstrated the capability of quantitative ultrasound in detecting acute echotexture changes in the biceps long head tendon after wheelchair sports (17) and differentiating symptomatic supraspinatus tendinopathy (18). Sarcopenia and painful shoulder syndrome both lead to adverse medical consequences; thus, knowing how they interplay would be helpful for early diagnosis and intervention. Therefore, the present study aimed to evaluate the association between sarcopenia and shoulder pain, and to determine whether the echotexture of rotator cuff tendons changed in sarcopenic patients.

Abbreviations: ER_{TM}, echogenicity ratio of the tendon vs. the overlying muscle; ER_{TT}, echogenicity ratio of the tendon vs. the subcutaneous tissue; GEE, generalized estimating equation; BMI, body mass index; SMI, skeletal muscle index; SPADI, shoulder pain and disability index; ROI, region of interest; ICC, intraclass correlation coefficient; SD, standard deviation.

METHODS

Participant Selection

The participants were community-dwelling elders (age ≥ 65 years) who attended the annual health examination in a community hospital in Taipei, Taiwan. They were excluded if they needed assistance during level walking, had impaired cognitive function, had difficulty complying with instructions and completing the questionnaire, were currently treated for malignancies, had injections/surgeries on either side of the shoulders within 6 months, and had uncontrolled medical conditions (such as severe infection and unstable angina). People with sarcopenia were first enrolled, followed by a sex- and age-matched (±1 year) control group without sarcopenia. The research project was approved by the Institutional Review Board of the National Taiwan University Hospital (IRB No. 201601091RIND). All participants were required to provide written informed consent prior to the commencement of the study.

Anthropometric Measurement

Body weights and heights of all participants were measured using a standard digital weight and height meter with a minimum scale of 100 g and 1 mm, respectively. Body mass index (BMI) was derived from the weight divided by the height squared (kg/m^2). Body composition was determined by whole-body dual-energy X-ray absorptiometry (DXA, Stratos dR, DMS Group, France) (19). All participants were required to fast overnight for at least 8 h and wear gowns during examination. The skeletal muscle index (SMI) was derived from the total of four limbs' lean soft tissue (bone-free and fat-free mass, kilogram) divided by the square of the height (m^2) (19).

Measurement of Muscle Strength

Grip strength of the participants' dominant hands was measured in the seated position with the elbow flexed at 90° and the forearm supinated. They were asked to forcefully squeeze the isometric dynamometer (Baseline® hydraulic hand dynamometer, Fabrication Enterprises Inc., Irvington, NY, USA) three times with an interval of at least 1 min between each trial. The maximal value was used as the grip strength.

Diagnosis of Sarcopenia

Sarcopenia was defined as loss of muscle strength and skeletal muscle mass in accordance with the consensus of the European Working Group on Sarcopenia in Older People (20). The cutoff value for low handgrip strength was 30 kg for men and 20 kg for women. An SMI <7.40 kg/m^2 for men or <5.14 kg/m^2 for women was considered as low skeletal muscle mass. All included sarcopenic participants were required to fulfill both criteria (21).

Clinical Evaluation

All participants were required to complete two copies of the Chinese version of the Shoulder Pain and Disability Index (SPADI) tool; one for each shoulder (22). There are 13 items in the tool used to assess shoulder pain and function impairment. Each item has a rating from 0 (no pain or no difficulty) to 10 (worst pain or extreme difficulty). The total score of the SPADI is converted from its pain and functional domains, with a highest value of 100 points. In our study, the presence of shoulder pain was defined as SPADI (total) > 0.

Ultrasound Scanning Protocol

The examination was performed in accordance with the EURO-MUSCULUS/USPRM shoulder scanning protocol (23). The participant was seated with the arm naturally positioned beside the trunk during the examination of the biceps long head tendon. The transducer was placed across the bicipital groove at the same level as the coracoid process to obtain the short-axis view of the tendon. The transducer was then pivoted 90° to visualize the tendon's long axis. The participant was then asked to externally rotate the arm and the transducer was moved cranially to the coracoid process in the horizontal plane to investigate the subscapularis tendon. Afterwards, the participant was invited to put the hand over the buttock with the elbow pointed backwards, which is the modified Crass position. The transducer was placed lateral to the acromial arch to obtain the long and short axes of the supraspinatus tendon. Finally, the transducer was positioned in the horizontal plane to examine the long axis of the infraspinatus tendon. All the imaging procedures were performed by a physician with 10 years of experience in musculoskeletal ultrasound using a multi-frequency (5–14 MHz) linear transducer (UP 200, BenQ Medical Technology Corporation, Taipei, Taiwan). The physician was unaware of the data of body compositions and physical performance during the ultrasound examination. The scanning depth was set at 40 mm, and the frame rate was set at 300 frames per second. The gain, focus, and dynamic range of the ultrasound machine were kept constant during the examination.

Ultrasound Diagnostic Protocol

The effusion surrounding the sheath of the long head of the biceps tendon was considered pathological if its thickness was more than 1 mm (24). Subluxation of the long head of the biceps tendon was diagnosed when more than 50% of the tendon's cross-section was outside the bicipital groove. The diagnosis of subdeltoid bursitis was made when the bursa was thicker than 2 mm (24). Intra-tendinous calcification was defined as the presence of hyperechoic plaques with acoustic shadows underneath. Rotator cuff tendon tears were indicated by the existence of visible gaps or total absence of tendon tissue in the subacromial space. As the supraspinatus tendon was large, we further categorized its lesions as full-thickness and partial-thickness tears. A full-thickness tear was identified by an intra-tendinous gap between the subdeltoid bursa and the articular surface of the humeral head (25). In a partial-thickness tear, the gap did not span the entire thickness of the supraspinatus tendon (24).

Quantitative Ultrasound Measurement

Thickness and echogenicity measurements were conducted on the long axis of the tendon using the straight-line tool and histogram function of the image processing software, Image J (**Supplementary Figure 1**) (15, 24). A line was drawn perpendicular to the most proximal end of the bicipital groove until it reached the superficial border of the tendon to measure the thickness of the biceps long head tendon (**Figure 1A**). A region of interest (ROI) encircling the cranial 1 cm length of the biceps tendon was selected for echogenicity measurement. Regarding the thickness measurements of the subscapularis (**Figure 1B**), supraspinatus (**Figure 1C**), and infraspinatus (**Figure 1D**) tendons, a vertical line was depicted from the periosteum next to the anatomical neck of the humerus until it reached the superficial edge of the tendon. An ROI encompassing the tendinous area distal to the anatomical neck was marked to obtain echogenicity. A squared ROI (5×10 mm) located in the middle of the deltoid muscle over the tendon was employed to calculate the echogenicity ratio of tendon-to-muscle (ER_{TM}), denoting the echo intensity of the tendon divided by that of the reference muscle. Likewise, an ROI of the same size was placed at the subcutaneous layer to obtain the echogenicity ratio of tendon-to-tissue (ER_{TT}), indicating echo intensity of the tendon divided by that of the subcutaneous tissue. A pilot test was conducted to evaluate the reliability of quantitative ultrasound measurements among five healthy individuals other than the study participants. The intra- and inter-rater reliabilities of the intraclass correlation coefficient (ICC) for measuring tendon thickness were 0.946 and 0.808, respectively. The intra- and inter-rater reliabilities of the ICC for measuring tendon echogenicity were 0.915 and 0.805, respectively. All measurements for the enrolled participants were performed offline by a research assistant who was blinded to their diagnosis.

Statistical Analysis

The sample size was estimated by identifying a between-group difference of 10 pixels in tendon echogenicity with a standard deviation (SD) of 25 pixels. The alpha level (α) and power (β) were set at 5 and 80%, respectively. The minimum required sample size was 100 shoulders per group.

The mean and SD values were used to report continuous variables, whereas numbers and percentages were used to report categorical variables. Comparisons between normally distributed continuous variables were made using analysis of variance, and the Mann–Whitney U-test was used in case the variables were not normally distributed. Categorical variables were compared using the Chi-square test or Fisher's exact test (for sparse data).

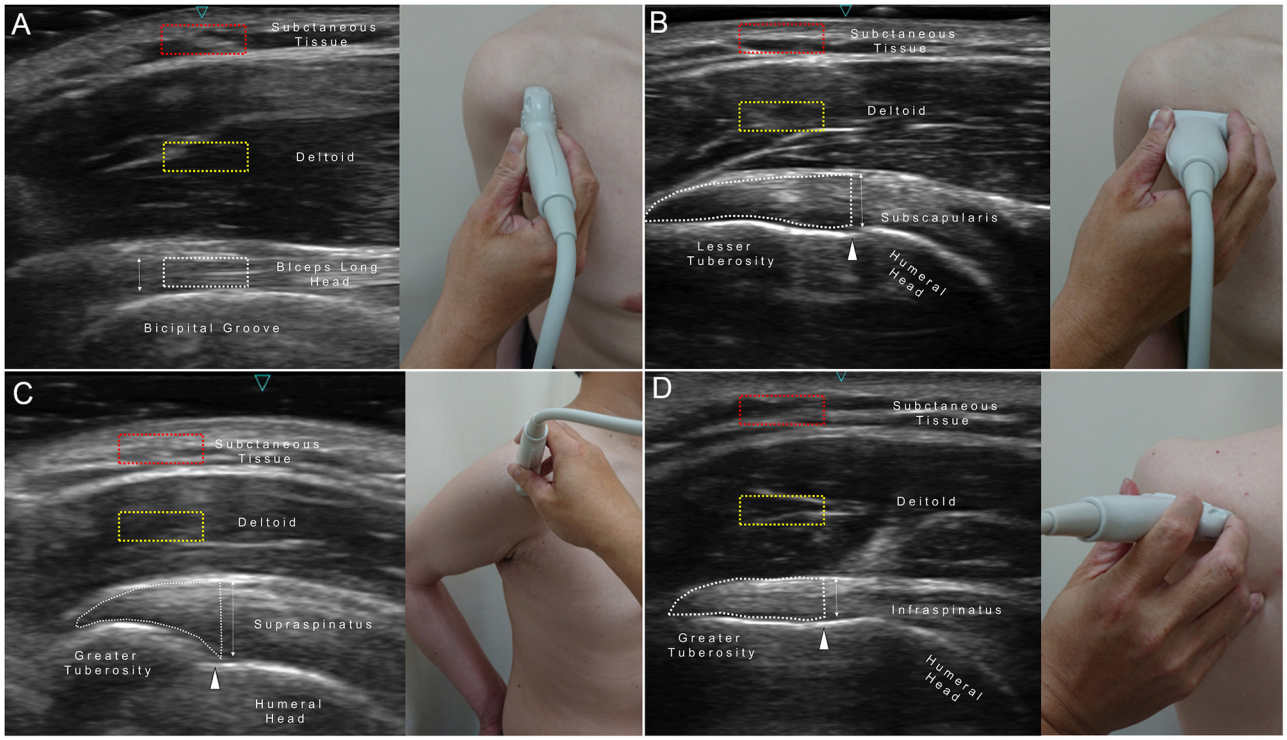

FIGURE 1 | Region of interest (ROI) and site for measuring the echogenicity and thickness of the biceps long head **(A)**, subscapularis **(B)**, supraspinatus **(C)**, and infraspinatus tendons **(D)**. Red dashed squares, ROI for the subcutaneous tissue; yellow dashed squares, ROI for the deltoid muscle; white dashed area, ROI for the target tendon; double arrowed line, tendon thickness; white arrowheads, anatomic neck of the humerus.

The association between quantitative ultrasound measurements of shoulder tendons and sarcopenia was investigated using the generalized estimating equation (GEE) (26). The GEE model is widely applied for analyzing longitudinal/clustered data, such as shoulder ultrasound measurements on the right and left sides of the same person. In this model, the participant's identification number served as the clustering variable, while the laterality (right/left side) was imputed as an exchangeable correlation item. Furthermore, Pearson's correlation coefficient (r) was applied to measure the correlation of quantitative ultrasound measurements with grip strength and SMI. The analyses were implemented using MedCalc 14.0 (MedCalc Software, Ostend, Belgium) and SPSS 21.0 (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp) statistical software, and a p-value < 0.05 was considered statistically significant.

RESULTS

Demographics and Clinical Assessment

A total of 56 participants with sarcopenia and 56 healthy controls were enrolled. No significant between-group differences were observed in age, sex ratio, height and the prevalence of comorbidities (**Supplementary Table 1**). Compared with controls, the sarcopenic group had lower body weight, BMI, handgrip strength and SMI. An increased prevalence of shoulder pain and a higher average total SPADI score were observed in the sarcopenic group as compared to the control group (**Table 1**).

Descriptive and Quantitative Ultrasound Findings

Regarding descriptive ultrasound findings, there were no significant differences in bicep peritendinous effusion, subdeltoid bursitis, calcification, and partial/full-thickness tears of the three rotator cuff tendons (**Table 1**). In terms of quantitative ultrasound measurements, the sarcopenic group presented with increased thickness and lower ER_{TM} and ER_{TT} of the supraspinatus tendons than those in the control group. Furthermore, the ER_{TM} of the biceps, subscapularis, and infraspinatus tendons was also lower in the sarcopenic group (**Table 2**). Based on the GEE analysis, sarcopenia was significantly associated with an increase in thickness of the supraspinatus tendon and a decrease in ER_{TM} of the long head of the biceps, subscapularis, and supraspinatus tendons. Sarcopenia was likely to be associated with a decrease in ER_{TT} of the supraspinatus tendon ($p = 0.07$) (**Table 3**).

Correlation of Ultrasound Measurements With Grip Strength and SMI

The correlation analyses indicated significant positive relationships between grip strength and ER_{TM} of the four tendons. Likewise, SMI was positively correlated with ER_{TT}

TABLE 1 | Descriptive ultrasound findings and clinical evaluation of the study participants.

	Sarcopenia (+) (shoulder = 112)	Sarcopenia (-) (shoulder = 112)	*p*-value
Positive ultrasound findings			
Biceps medial subluxation (number, %)	0 (0.00%) (0.00–0.00%)	2 (1.78%) (-0.70–4.27%)	0.156
Subscapularis tendon tear (number, %)	4 (3.57%) (0.08–7.06%)	2 (1.78%) (-0.70–4.27%)	0.408
Subscapularis tendon calcification (number, %)	17 (15.17%) (8.43–21.93%)	13 (11.60%) (5.58–17.63%)	0.433
Subdeltoid bursitis (number, %)	4 (3.57%) (0.08–7.06%)	5 (4.46%) (0.58–8.34%)	0.734
Supraspinatus tendon full thickness tear (number, %)	7 (6.25%) (1.69–10.80%)	5 (4.46%) (0.58–8.34%)	0.553
Supraspinatus tendon partial thickness tear (number, %)	2 (1.78%) (-0.70–4.27%)	0 (0.00%) (0.00–0.00%)	0.156
Supraspinatus tendon calcification (number, %)	18 (16.07%) (9.16–22.98%)	17 (15.17%) (8.43–21.93%)	0.854
Infraspinatus tendon tear (number, %)	2 (1.78%) (-0.70–4.27%)	1 (0.89%) (-0.87–2.66%)	0.561
Infraspinatus tendon calcification (number, %)	6 (5.35%) (1.12–9.59%)	6 (5.35%) (1.12–9.59%)	1.000
Clinical evaluation			
Presence of pain (number, %)	28 (25.00%) (16.86–33.14%)	12 (10.71%) (4.89–16.53%)	0.005*
Pain domain of SPADI (mean ± SD)	1.49 ± 3.15 (0.90–2.08)	0.49 ± 1.78 (0.15–0.82)	0.004*
Function domain of SPADI (mean ± SD)	0.34 ± 1.12 (0.13–0.55)	0.12 ± 0.61 (<0.01–0.24)	0.068
Total score of SPADI (mean ± SD)	0.78 ± 1.66 (0.47–1.10)	0.26 ± 1.02 (0.07–0.45)	0.005*

*Continuous variables are given as mean ± standard deviation and 95% confidence interval. Categorical variables are given as number (percentage) and 95% confidence interval. SPADI, Shoulder Pain and Disability Index. SPADI (total) = [SPADI (pain) *0.5+SPADI (function)*0.8] * (10/13). P-values pertain to between-group comparisons.*
**Indicates $p < 0.05$.*

of the supraspinatus tendons, and ER_{TM} measurements of the four tendons (**Figure 2**, **Supplementary Figures 2–4**). Nevertheless, SMI was negatively correlated with the thickness of the supraspinatus tendons. A trend of negative correlation ($p = 0.084$) was observed between grip strength and thickness of the supraspinatus tendon (**Figure 2**).

Echogenicity of Target Tendons, Overlying Muscles, and Subcutaneous Tissue

Furthermore, between-group comparisons were conducted for echogenicity of the four tendons as well as adjacent deltoid muscles and overlying subcutaneous tissues, used for calculating ER_{TM} and ER_{TT}. Although mean values of tendon echogenicity appeared lower in the sarcopenic group, none of the comparisons were statistically significant. However, the echogenicity of the deltoid muscles on top of the four tendons was significantly higher in the sarcopenic group. No between-group differences were observed in the echogenicity of the subcutaneous tissues (**Supplementary Table 2**).

DISCUSSION

In this study, based on data from community-dwelling elders, we discovered that those with sarcopenia had a higher prevalence of shoulder pain. Sarcopenia was significantly associated with an increase in supraspinatus tendon thickness and a decrease in ER_{TM} for the biceps long head and rotator cuff tendons. A negative trend of association between sarcopenia and ER_{TT} of supraspinatus tendons was observed. Nevertheless, sarcopenia was not associated with an increased risk of rotator cuff tendon tears.

The relationship between sarcopenia and musculoskeletal pain has been uncovered in recent years. In 2015, Koca et al. studied body composition and physical performance of patients with fibromyalgia syndrome and discovered that the fibromyalgia group had significantly lower grip strength than healthy controls (27). In 2019, Sit et al. conducted a survey among elderly patients (age $\geq$ 60 years) from primary care clinics and found that sarcopenia, defined by a score $\geq$ 4 on the SARC-F (Strength,

TABLE 2 | Quantitative measurement of rotator cuff tendon complex in participants with and those without sarcopenia.

	Sarcopenia (+) (shoulder = 112)	Sarcopenia (-) (shoulder = 112)	*p*-value
Biceps long head tendon			
Tendon thickness (mm)	2.34 ± 0.46	2.33 ± 0.42	0.907
	(2.25–2.43)	(2.25–2.41)	
ER_{TM}	1.37 ± 0.47	1.88 ± 0.58	<0.001*
	(1.29–1.46)	(1.77–1.99)	
ER_{TT}	1.83 ± 0.62	1.94 ± 0.65	0.207
	(1.71–1.95)	(1.82–2.06)	
Subscapularis tendon			
Tendon thickness (mm)	3.93 ± 0.84	3.74 ± 0.81	0.081
	(3.78–4.09)	(3.59–3.89)	
ER_{TM}	1.02 ± 0.46	1.42 ± 0.45	<0.001*
	(0.93–1.10)	(1.33–1.50)	
ER_{TT}	1.24 ± 0.45	1.30 ± 0.37	0.329
	(1.16–1.33)	(1.23–1.37)	
Supraspinatus tendon			
Tendon thickness (mm)	5.49 ± 1.15	4.83 ± 1.06	<0.001*
	(5.27–5.70)	(4.63–5.03)	
ERTM	0.87 ± 0.32	1.30 ± 0.52	<0.001*
	(0.81–0.93)	(1.20–1.40)	
ERTT	1.08 ± 0.31	1.18±0.38	0.042*
	(1.02–1.14)	(1.11–1.25)	
Infraspinatus tendon			
Tendon thickness (mm)	3.86 ± 1.24	3.65 ± 1.01	0.163
	(3.63–4.09)	(3.46–3.84)	
ERTM	0.90 ± 0.34	1.20 ± 0.35	<0.001*
	(0.84–0.97)	(1.13–1.27)	
ERTT	1.28 ± 0.42	1.40 ± 0.57	0.096
	(1.20–1.36)	(1.29–1.50)	

Values are given as mean ± standard deviation and 95% confidence interval. ER_{TM}, echogenicity ratio of the tendon vs. the overlying deltoid muscle; ER_{TT}, echogenicity ratio of the tendon vs. the overlying subcutaneous tissue. P-values pertain to between-group comparisons.
**Indicates $p < 0.05$.*

Assistance with walking, Rise from a chair, Climb stairs and Falls) questionnaire, was associated with chronic musculoskeletal pain (28). Their study also pointed out that patients with sarcopenia were more likely to present with pain in multiple sites. In 2020, Imagama et al. identified an independent association between sarcopenia and neuropathic pain among community-dwelling middle-aged and elderly volunteers. Several possible mechanisms have been proposed for interpreting the link between sarcopenia and musculoskeletal pain. First, pain limits the activities of the affected limbs, which further leads to disuse muscle atrophy (29). Second, weakened muscles in sarcopenic participants fail to provide adequate stability of the joints, which elicits repeated injury of juxta-articular structures (28). Third, sarcopenia is similar to a subclinical state of inflammation, wherein increased levels of circulating pro-inflammatory cytokines, such as IL-6 and TNFα, might potentiate pain sensitivity of the musculoskeletal system (30).

Our study found a higher prevalence of shoulder pain and increased impairment of shoulder function in the sarcopenic group than in healthy controls. However, the number of shoulders with discomfort only accounted for appropriately 25% of the sarcopenic group. Since there were no symptoms in a majority of our participants, pain was less likely to be the main cause of sarcopenia. In contrast, as sarcopenia is characterized by a decline in muscle mass and function (21), our study has identified its effect on muscles over the shoulder girdle. The echogenicity of the deltoid muscle over the four target tendons appeared higher in the sarcopenic group, implying fatty infiltration and atrophic changes (31). Therefore, we support the theory that sarcopenia resulted in weakness and incoordination of the shoulder girdle muscles, and subsequent tendon injury due to joint instability. Furthermore, in patients who already have shoulder pain, their symptoms might lead to physical inactivity and further worsen the status of sarcopenia. A vicious cycle of sarcopenia- pain-inactivity-sarcopenia is thus formed (**Figure 3**). However, as this is a cross-sectional study, the aforementioned speculation might be just a statistical correlation. Patients with sarcopenia are likely to be comorbid with many chronic diseases, like diabetes mellitus (32), which has been proven to affect the quality of rotator cuff tendons (33). We believed a longitudinal study would be needed for clarifying the biological correlation between sarcopenia and shoulder pathologies.

Increased thickness and decreased echogenicity are the hallmarks of tendinopathy in ultrasound imaging, reflecting myxoid degeneration and disorganization of the collagen bundles (34). Among all tendons in the rotator cuff complex, our findings revealed that the supraspinatus tendons in the sarcopenic group consistently presented with degenerative changes, comprising an increase in tendon thickness and a decline in ER_{TM} and ER_{TT}. Our correlation analyses also implied that worsening of the quantitative parameters of the supraspinatus tendons was mostly correlated with a decline in grip strength and SMI. The supraspinatus muscle plays an important role in shoulder abduction and external rotation, and its tendon has been shown to be more frequently affected than other rotator cuff tendons (35). It also helps to depress the humeral head during overhead activity to prevent subacromial impingement (35). In patients with sarcopenia, we speculated that supraspinatus muscles might be affected/weakened like deltoid muscles, which led to a narrower subacromial space upon arm elevation and subsequent tendon injury due to impingement.

The ER_{TM} is a common ultrasound parameter to evaluate tendon quality (18, 25). While isolating a deeper structure, the target appears more hypoechoic due to absorption of ultrasound energy (36). Using echogenicity of the overlying muscles as the reference, the ER_{TM} can partly counteract the influences of signal gain at various depths, which is considered better than using tendon echogenicity alone for comparisons among different subjects. Furthermore, compared with the subcutaneous tissue, the overlying muscle is less compressible and serves as a superior reference target for calculating the echogenicity ratio. However, when applying the ER_{TM} for shoulder tendons on participants with sarcopenia, the values could have been underestimated, as the echogenicity of the deltoid muscles was

TABLE 3 | Association of sarcopenia and demographics with quantitative ultrasound measurements of rotator cuff tendon complex.

	Biceps long head tendon			Subscapularis tendon			Supraspinatus tendon			Infraspinatus tendon		
	Thickness	**ER_{TM}**	**ER_{TT}**	**Thickness**	**ER_{TM}**	**ER_{TT}**	**Thickness**	**ER_{TM}**	**ER_{TT}**	**Thickness**	**ER_{TM}**	**ER_{TT}**
Sarcopenia	−0.022	−0.599	−0.065	0.173	−0.442	−0.051	0.703	−0.447	−0.097	0.144	−0.277	−0.050
	(−0.16 to 0.11)	(−0.76 to −0.43)	(−0.30 to 0.17)	(−0.10 to 0.45)	(−0.57 to −0.30)	(−0.18 to 0.08)	(0.32 to 1.08)	(−0.57 to −0.31)	(−0.20 to 0.008)	(−0.23 to 0.51)	(−0.38 to −0.17)	(−0.21 to 0.11)
	$p = 0.757$	$p < 0.001$*	$p = 0.587$	$p = 0.224$	$p < 0.001$*	$p = 0.469$	$p < 0.001$*	$p < 0.001$*	$p = 0.070$*	$p = 0.451$	$p < 0.001$*	$p = 0.548$
Age (years)	0.005	0.004	0.001	0.009	−0.005	0.002	−0.029	−0.003	−0.001	−0.013	0.005	0.011
	(−0.006 to 0.01)	(−0.01 to 0.02)	(−0.01 to 0.02)	(−0.01 to 0.03)	(−0.01 to 0.008)	(−0.009 to 0.01)	(−0.05 to 0.00)	(−0.01 to 0.009)	(−0.01 to 0.008)	(−0.03 to 0.01)	(−0.005 to 0.01)	(−0.004 to 0.02)
	$p = 0.350$	$p = 0.607$	$p = 0.875$	$p = 0.425$	$p = 0.490$	$p = 0.743$	$p = 0.052$	$p = 0.660$	$p = 0.780$	$p = 0.327$	$p = 0.305$	$p = 0.166$
Female gender	−0.182	−0.350	0.157	−0.092	−0.194	0.106	0.071	−0.341	−0.160	0.072	0.010	0.226
	(−0.37 to 0.07)	(−0.61 to −0.09)	(−0.16 to 0.48)	(−0.48 to 0.30)	(−0.43 to 0.04)	(−0.10 to 0.32)	(−0.42 to 0.57)	(−0.55 to −0.12)	(−0.30 to −0.01)	(−0.35 to 0.49)	(−0.12 to 0.14)	(−0.04 to 0.49)
	$p = 0.059$	$p = 0.008$	$p = 0.345$	$p = 0.649$	$p = 0.112$	$p = 0.334$	$p = 0.779$	$p = 0.002$*	$p = 0.027$*	$p = 0.740$	$p = 0.887$	$p = 0.105$
Height (cm)	−0.003	−0.007	0.002	−0.004	−0.003	0.000	0.001	0.001	0.002	−0.002	0.001	0.003
	(−0.008 to 0.003)	(−0.01 to 0.001)	(−0.009 to 0.01)	(−0.01 to 0.008)	(−0.009 to 0.004)	(−0.006 to 0.007)	(−0.01 to 0.01)	(−0.005 to 0.007)	(−0.002 to 0.006)	(−0.01 to 0.01)	(−0.003 to 0.005)	(−0.006 to 0.01)
	$p = 0.382$	$p = 0.090$	$p = 0.671$	$p = 0.478$	$p = 0.446$	$p = 0.934$	$p = 0.850$	$p = 0.760$	$p = 0.359$	$p = 0.691$	$p = 0.534$	$p = 0.558$
Weight (kg)	−0.003	−0.009	0.004	−0.001	−0.004	0.000	0.005	−0.001	0.000	−0.007	0.002	0.006
	(−0.007 to 0.002)	(−0.01 to −0.001)	(−0.006 to 0.01)	(−0.01 to 0.01)	(−0.01 to 0.003)	(−0.006 to 0.007)	(−0.01 to 0.02)	(−0.008 to 0.005)	(−0.005 to 0.004)	(−0.01 to 0.005)	(−0.002 to 0.005)	(−0.002 to 0.01)
	$p = 0.270$	$p = 0.026$*	$p = 0.411$	$p = 0.827$	$p = 0.233$	$p = 0.918$	$p = 0.498$	$p = 0.648$	$p = 0.812$	$p = 0.247$	$p = 0.420$	$p = 0.130$
Left side	0.002	0.142	0.055	0.162	0.020	0.085	0.022	−0.046	−0.059	−0.049	0.077	0.063
	(−0.10 to 0.10)	(0.03 to 0.25)	(−0.06 to 0.17)	(−0.003 to 0.32)	(−0.07 to 0.11)	(−0.004 to 0.17)	(−0.21 to 0.26)	(−0.13 to 0.04)	(−0.13 to 0.01)	(−0.29 to 0.19)	(−0.005 to 0.15)	(−0.02 to 0.15)
	$p = 0.966$	$p = 0.011$*	$p = 0.363$	$p = 0.054$	$p = 0.685$	$p = 0.062$	$p = 0.855$	$p = 0.307$	$p = 0.130$	$p = 0.696$	$p = 0.067$	$p = 0.180$

ER_{TM}, echogenicity ratio of the tendon vs. the overlying deltoid muscle; ER_{TT}, echogenicity ratio of the tendon vs. the overlying subcutaneous tissue.
**indicates $p < 0.05$.*

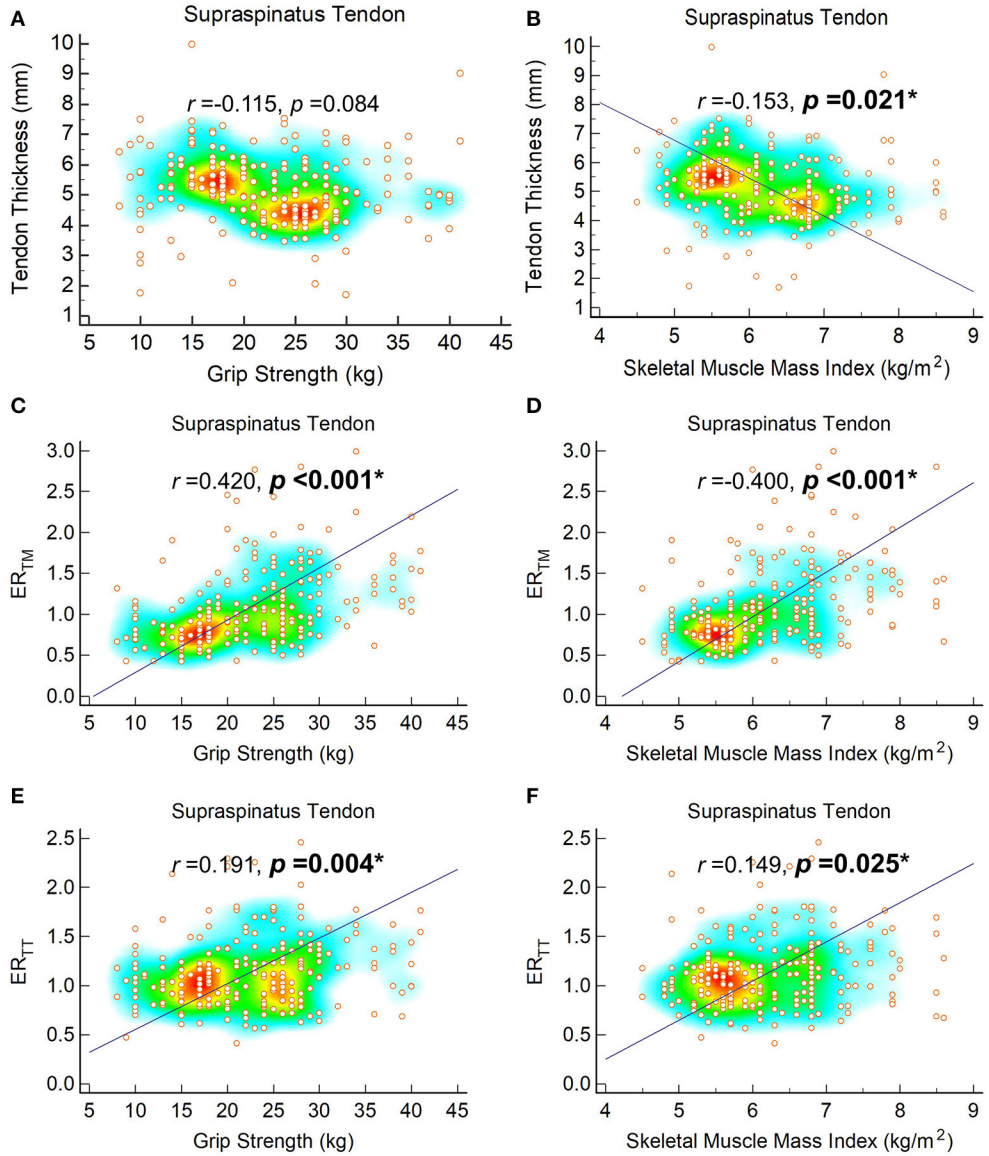

FIGURE 2 | Correlation of tendon thickness with grip strength **(A)** and skeletal muscle mass index **(B)**, ER_{TM} with grip strength **(C)** and skeletal muscle mass index **(D)** and ER_{TT} with grip strength **(E)** and skeletal muscle mass index **(F)** of the supraspinatus tendons. The regression line is plotted on when *p*-value is < 0.05. The heat map with background color coding suggests clusters of observations. ER_{TM}, echogenicity ratio of the tendon vs. the overlying deltoid muscle; ER_{TT}, echogenicity ratio of the tendon vs. the overlying subcutaneous tissue.

increased (**Supplementary Table 2**). Therefore, we also validated the tendon echotexture by employing ER_{TT} and found that the biceps long head, subscapularis, and supraspinatus tendons had decreased ER_{TM}, but not ER_{TT}. As the thickness of the biceps long head, subscapularis, and supraspinatus tendons did not differ among participants with and without sarcopenia, there was no robust evidence to prove the decline in their tendon echotexture.

Our results showed no significant differences in the prevalence of rotator cuff tendon tears between participants with and without sarcopenia. In 2016, Chung et al. compared the sarcopenia index between patients with surgically proven rotator cuff tendon tears and healthy participants (37). They found that the grip strength and SMI tended to be lower in the group with torn tendons than in the age- and sex-matched controls. In addition, patients with large tears had an inferior sarcopenia index compared to those with small tears. Rotator cuff syndrome is a spectrum of diseases, ranging from tendinopathy to tendon tears, and the latter pathology commonly causes severe pain and disability (38). Unlike Chung et al., who enrolled patients with rotator cuff tendon tears needing surgical intervention, our participants were mostly

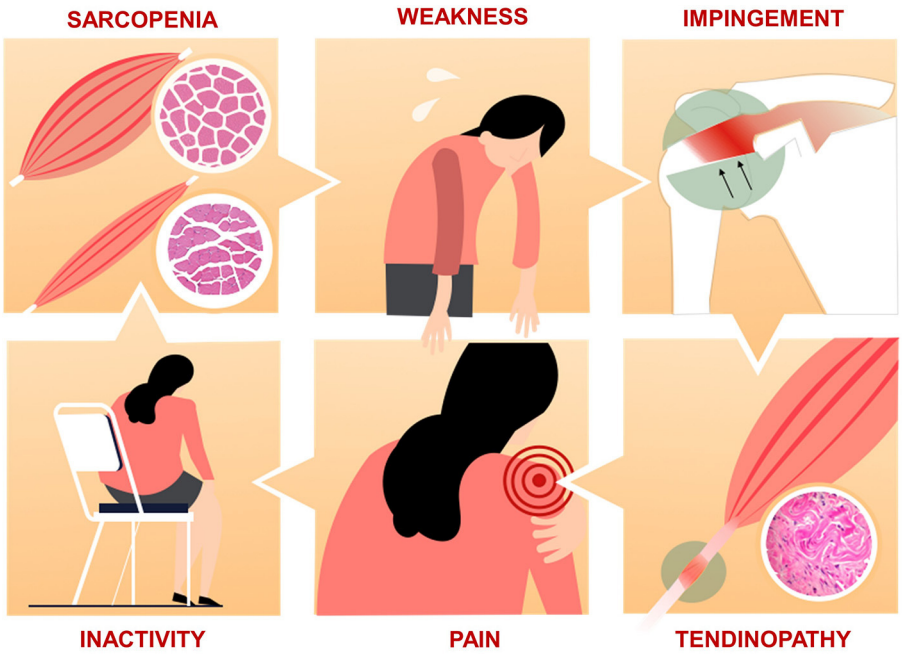

FIGURE 3 | A plausible diagram illustrating how sarcopenia interacts with rotator cuff tendon diseases.

asymptomatic. Therefore, although certain pathologic changes could be observed in the supraspinatus tendons in the sarcopenic group, the majority of their symptoms remained mild without progression to tendon ruptures.

Several limitations of our study should be noted. First, we used a cross-sectional design, and the causal relationship between sarcopenia and rotator cuff tendon disorders could not be clarified through our analysis. A cohort study with longitudinal follow up of body composition, physical performance and shoulder ultrasonography would be helpful in validation of the biological association between sarcopenia and shoulder pathologies. Second, we did not measure strength of the muscles in the shoulder girdle and we were not aware if weakness could be identified in rotator cuff muscles of participants with sarcopenia. Isokinetic testing of shoulder abductors/adductors, flexors/extensors, and external/internal rotators should be incorporated in future studies. Third, the case number in the present study was relatively small. The differences in echotexture of the rotator cuff tendons might not be limited to the supraspinatus tendons if the statistical power can be improved with an increase in the participant number. Therefore, a large-scale study is still needed for verifying our preliminary observation.

CONCLUSION

Patients with sarcopenia have a high risk of shoulder pain. A consistent pathological change develops in the supraspinatus tendons of sarcopenic patients. Nevertheless, sarcopenia is less likely to be associated with serious rotator cuff pathology, such as tendon tears. Prospective cohort studies are warranted to assess the relationship between sarcopenia and various shoulder disorders and the influence of different kinds of comorbidities on rotator cuff tendon echotextures.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Research Ethics Committee of National Taiwan University Hospital (IRB No. 201601091RIND). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

K-VC wrote the manuscript. W-TW and P-CH analyzed the data. D-SH interpreted the results. K-VC, W-TW, and K-CH enrolled eligible patients. H-CC edited and drew the pictures. All authors participated in the design of the study, reviewed the manuscript, contributed to the discussion, and read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.630009/full#supplementary-material

Supplementary Figure 1 | The line tool **(A)** and histogram **(B)** for measuring thickness and echogenicity.

Supplementary Figure 2 | Correlation of tendon thickness with grip strength **(A)** and skeletal muscle mass index **(B)**, ER_{TM} with grip strength **(C)** and skeletal muscle mass index **(D)** and ER_{TT} with grip strength **(E)** and skeletal muscle mass index **(F)** of the biceps long head tendons. The regression line is plotted on when p-value is < 0.05. The heat map with background color coding suggests clusters of observations. ER_{TM}, echogenicity ratio of the tendon vs. the overlying deltoid muscle; ER_{TT}, echogenicity ratio of the tendon vs. the overlying subcutaneous tissue.

Supplementary Figure 3 | Correlation of tendon thickness with grip strength **(A)** and skeletal muscle mass index **(B)**, ER_{TM} with grip strength **(C)** and skeletal muscle mass index **(D)** and ER_{TT} with grip strength **(E)** and skeletal muscle mass index **(F)** of the subscapularis tendons. The regression line is plotted on when p value is < 0.05. The heat map with background color coding suggests clusters of observations. ER_{TM}, echogenicity ratio of the tendon vs. the overlying deltoid muscle; ER_{TT}, echogenicity ratio of the tendon vs. the overlying subcutaneous tissue.

Supplementary Figure 4 | Correlation of tendon thickness with grip strength **(A)** and skeletal muscle mass index **(B)**, ER_{TM} with grip strength **(C)** and skeletal muscle mass index **(D)** and ER_{TT} with grip strength **(E)** and skeletal muscle mass index **(F)** of the infraspinatus tendons. The regression line is plotted on when p-value is < 0.05. The heat map with background color coding suggests clusters of observations. ER_{TM}, echogenicity ratio of the tendon vs. the overlying deltoid muscle; ER_{TT}, echogenicity ratio of the tendon vs. the overlying subcutaneous tissue.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Relationship Between Sarcopenia and Electrocardiographic Abnormalities in Older People: The Bushehr Elderly Health Program

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Background: Sarcopenia is characterized by low skeletal muscle mass and function, which is associated with cardiovascular risk factors and may even be related to adverse cardiovascular events and mortality. This study aimed to evaluate whether sarcopenia is related to electrocardiographic (ECG) abnormalities in a large sample of older adults.

Methods: We performed a cross-sectional study based on the data collected during the Bushehr Elderly Health (BEH) cohort study. Body composition was measured by dual X-ray absorptiometry (DXA) and muscle strength was measured using a digital dynamometer for each hand of every participant. A person who had low muscle strength, as well as low muscle mass was identified as having sarcopenia. The subjects were classified into three groups according to the Minnesota Code (MC) as major, minor ECG abnormalities and participants with no abnormalities ECG.

Results: Of the 2,426 participants, 354 (14.6%) had major ECG abnormalities and 193 (8%) had minor ECG abnormalities. Sarcopenia was associated with an increased risk of major ECG abnormality in all models. After adjustment for confounders of CHD in full model, the OR for major ECG abnormality was 1.47 (95% CI 1.11–1.95) in those with sarcopenia. Low muscle strength and low muscle performance were both with an increased risk of major ECG abnormality in all models. Sarcopenia and low muscle strength increased 28% and 62% risk of any ECG abnormality in the full models [sarcopenia: 1.28(1.01–1.63), low muscle strength: 1.62(1.30–2.03)], respectively.

Conclusions: This study showed that sarcopenia and its components are associated with ECG abnormalities in Iranian older people. Although some older adults have higher cardiovascular risk factors, these data showed that further factors such as sarcopenia may be identified as a particular risk factor for future cardiovascular events. Therefore, sarcopenia could be added to the screening of the older population to reduce the risk of cardiovascular events.

Keywords: sarcopenia, ECG abnormalities, older people, risk, components of sarcopenia

INTRODUCTION

Aging is related to changes in body composition, including decreases in muscle mass and bone mass and an increase in adipose tissue, which can lead to cardiovascular diseases and metabolic disorders (1).

Sarcopenia, an age-related muscle disorder characterized by a decline in muscle mass and function (2), is a major risk factor of falling, disability and death in old adults. Also, sarcopenia is associated with cardiometabolic risk factors such as glucose intolerance and metabolic syndrome and other diseases such as, cardiovascular diseases (CVD) and respiratory diseases (3).

Among all CVDs, Coronary Heart disease (CHD) is one of the most common and important causes of mortality, morbidity, and disability in older people (4).

Some studies determined cardiometabolic risk factors and comorbidities that associated with CHD (5, 6). The non-modifiable factors such age, sex, race, family history, and modifiable risk factors include obesity, physical inactivity, smoking, hyperlipidemia, hypertension, and diabetes are traditional cardiovascular disease risk factors (5). Also, electrocardiograms (ECG) abnormalities can predict of all-cause, CHD mortality independent of other cardiomeytabolic risk factors (7–11).

Few studies have shown that the association between low muscle mass or sarcopenia and various heart disease in older people (12–14). Some mechanisms including changes in anabolic androgenic hormones, insulin resistance, protein intake, physical activity and muscle structure can be common between CVDs and sarcopenia and can also impact the outcomes of patients with these diseases (15–17).

Although the prevalence and association of ECG abnormalities with chronic diseases such as diabetes and metabolic syndrome and its components have been studied (18, 19), this association has not been investigated in persons with sarcopenia. If ECG abnormalities are common and have associated with sarcopenia, these might help to identify of sarcopenic persons who are at especially high risk for the CVD events. Therefore, to identify subjects with increased risk of CVDs and study on the association between age-related diseases such as sarcopenia with CHD can improve public health problems in elderly.

Given the high prevalence of CHD and also sarcopenia in the Iranian elderly, in the present study, we investigated the association of sarcopenia and its components with ECG abnormalities in older people.

MATERIALS AND METHODS

The Study Population

This cross-sectional study was based on the Bushehr Elderly Health (BEH) program. The BEH study was a prospective population-based cohort study performed on a sample of older people ≥60 years in the urban population of Bushehr city, in the south of Iran. Overall 3,000 persons were recruited using a multistage, stratified cluster sampling method. BEH study aimed to assess non-communicable diseases in older people. The methodology and protocol of the BEH program were previously described elsewhere (20, 21).

The Research Ethics Committee of Bushehr and Tehran University of Medical Sciences approved the protocol of the BEH program (ID:IR.TUMS.EMRI.REC.1394.0036) and written informed consent was signed by all participants.

Data Collection

A comprehensive questionnaire including sociodemographic characteristics, medical history, smoking and lifestyle data was completed for each person through a personal interview. Anthropometric measurements were carried out using standard protocols. Height and weight were measured with a fixed stadiometer and a digital scale respectively. The body mass index (BMI) was calculated as weight in kg divided by the square of height in meters.

The measurement of Blood pressure (BP) was performed using a standardized mercury sphygmomanometeron the right arm after 15 min of rest in the seated position.

Standard 12-lead electrocardiograms (ECGs) were recorded at baseline in the resting supine position according to the standard procedures. Two qualified physicians coded the ECGs in parallel according to the Minnesota codes using a measuring loop, specially manufactured by the University of Minnesota (22). Any discordant results were resolved by a third qualified physician who was a cardiologist. The physical activity was evaluated by a validated questionnaire based on metabolic equivalent task (MET) (23, 24). A 24-h dietary recall was used for dietary assessment.

A trained operator measured the body composition using dual x-ray absorptiometry (DXA, Discovery WI, HologicInc, USA). The skeletal muscle mass index (SMI) was defined as the sum of the muscle masses of the four limbs as appendicular skeletal muscle mass divided by squared height. Maximum handgrip strength was measured in both hands by a digital grip strength dynamometer, 3 times, and the highest value was used as muscle strength. Walking speed over 4.57 m was used for estimating physical performance.

The biochemical parameters were measured by laboratory testing in a fasting condition, according to standard protocols. Serum lipid profiles and fasting plasma glucose (FPG) were measured by an enzymatic colorimetric technique using a commercial kit (Pars Azmun, Karaj, Iran).

Definition of Variables

According to the European Working Group on Sarcopenia in Older People 2 (EWGSOP- 2), sarcopenia was defined as low muscle strength plus reduced skeletal muscle mass (3). Also, the EWGSOP and Asia Working Group for Sarcopenia (AWGS) (25) recommend the use of reference data of the same population to determine cut- off points for muscle mass. Therefore, we used reference data from a normative Iranian population that was available for detecting sarcopenia for our study. Based on these data, the cut-off values for low skeletal muscle mass index (SMI) were 7.0 kg/m^2 and <5.4 kg/m^2 among men and women, respectively (26). The low muscle strength was handgrip strength <26 kg for men and <18 kg for women; while the cut-off value

for low physical performance was a usual walking speed < 0.8 m/s for both genders (25). According to these cut-off points, we identified sarcopenic persons (27). Current smoking was defined as smoking cigarettes or water pipes, at the time of study.

Diabetes mellitus was defined as fasting plasma glucose (FPG) ≥ 126 mg/dl or HbA1C ≥ 6.5 or current use of pharmacological medication. Hypertension (HTN) was defined as systolic blood pressure 140 mmHg and/or diastolic blood pressure 90 mmHg or current use of antihypertensive medication. Subjects with total cholesterol ≥200 mg/dl were named as hypercholesterolemia. High Fat Mass was outlined as total body percent fat >30 for men and >40 for women (28).

The Minnesota coding system and Whitehall criteria was used to classify ECG findings as having a major or minor abnormality (22, 29).

Criteria for major ECG abnormalities were any of the following: Q-QS wave abnormalities (MC 1-1 to 1-2-8); left ventricular hypertrophy (MC 3-1); Wolff–Parkinson–White syndrome (MC 6- 4-1 or 6-4-2); complete bundle branch block or intraventricular block (MC 7-1-1, 7-2-1, 7-4, or 7-8); atrial fibrillation or atrial flutter (MC 8-3); or major ST-T changes (MC 4-1, 4-2, 5-1, and 5-2).

Criteria for minor ECG abnormalities were minor ST-T changes (MC 4-3, 4-4, 5-3, and 5-4).

Participants with only minor ECG abnormalities were classified as having "minor abnormalities," and participants with major ECG abnormalities with or without coexisting minor ECG abnormalities were classified as having "major ECG abnormalities." Participants with both major and minor abnormalities were classified as having major abnormalities. Participants without minor or major ECG abnormalities were classified as having no abnormalities and their ECG was considered normal (22, 30).

Statistical Analysis

Normal distribution of continuous variables was assessed using the Shapiro-Wilks test and visual inspection of the group histograms. Continuous data that followed a normal distribution was described with means ± standard deviation (SD). Categorical variables are expressed as percentages. Comparisons between ECG abnormality categories were made using the *t*-test for continuous variables and the chi-squares tests for percentages. We used the best subset method with the Akaike Information Criterion (AIC), to select the final model from all possible subsets. The multinominal regression analyses were used to investigate the associations of sarcopenia and its components with ECG abnormality category. Results were presented as odds ratios and 95% confidence intervals. Data were analyzed using the Stata 14 software (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP) and $P \leq 0.05$ was considered as statistically significant in all tests.

RESULTS

General characteristics of the study group are shown in **Table 1**. Among 2,426 participants, 193 (8%) had minor ECG abnormalities and 354 (14.6%) had major ECG abnormalities. Subjects in the group with minor or major ECG abnormalities were older and had fewer years of education and also the prevalence of HTN and obesity was higher among these subjects ($P < 0.05$). Participants with minor or major ECG abnormalities walked more slowly and had lower means of SMI and muscle strength ($P < 0.001$).

Figure 1 shows that the prevalence major or any ECG abnormalities was higher in sarcopenic patients (major ECG abnormalities: 18.9 vs. 13.2%, any ECG abnormalities: 26.3 vs. 21.2%).

Table 2 presents the results of the multinomial logistic regression models to define the association sarcopenia and its components with minor and major ECG abnormalities. Sarcopenia was associated with an increased risk of major ECG abnormality in all models. After adjustment for confounders of CHD in full model, the OR for major ECG abnormality was 1.47 (95% CI 1.11–1.95) in those with sarcopenia. The associations between sarcopenia and minor ECG abnormality were not statistically significant in all models.

Low muscle strength and low muscle performance were both with an increased risk of major ECG abnormality in all models. Also, the results show that muscle strength and muscle performance decrease risk of major ECG abnormality in all models.

Table 3 demonstrates the association of sarcopenia and muscle components with any ECG abnormality. Sarcopenia and low muscle strength increased 28 and 62% risk of any ECG abnormality in the full models [sarcopenia: 1.28(1.01–1.63), low muscle strength: 1.62(1.30–2.03)], respectively. The relationship between low muscle performance and any ECG abnormality was significant only in crude and age, sex adjusted model. The associations between low SMI and any ECG abnormality were not statistically significant in all models.

Also, we observed statistically significant associations of SMI, muscle strength and muscle performance with any ECG abnormality in all models especially in full models.

DISCUSSION

This cross-sectional study aimed to assay the association of sarcopenia and components of muscle with major and minor ECG abnormalities. The results of the present study demonstrated sarcopenia to be independently and strongly associated with major ECG abnormalities in older people. Furthermore, participants with low muscle strength or low muscle performance had higher risk of major ECG abnormality than those with normal ECG.

Studies explained that skeletal muscle, as the most tissue in the human body, is involved in some metabolic functions including energy expenditure, protein metabolism and insulin sensitivity (31, 32). Also, these muscles have endocrine actions with releasing some myokines and play in regulation inflammation and immune function. Therefore, decline of muscle mass and muscle function, as named sarcopenia can lead to several age-related metabolic disorders and some diseases such as CHD, hypertension and heart failure (33–35).

TABLE 1 | General characteristics of the study population according to ECG status.

	ECG Category			
	Normal (No ECG abnormality) (*n* = 1,879)	**Minor ECG abnormality (*n* = 193)**	**Major ECG abnormality (*n* = 354)**	***P*-value**
Sex(Men),%	939(50.0)	50(25.9)	177(50.0)	0.104
Age, Years	69.14 ± 6.32	69.95 ± 6.69	70.12 ± 6.60	0.012
BMI, Kg/m^2	27.50 ± 4.90	27.92 ± 5.22	27.37 ± 4.73	0.436
Education, Years	5.37 ± 5.05	4.58 ± 4.87	4.64 ± 4.92	0.008
Physical activity, %	439(23.4)	46(23.8)	70(19.8)	0.186
Current Smoking, %	387(20.6)	39(20.2)	78(22.1)	0.584
Diabetes, %	587(31.8)	61(32.3)	129(36.9)	0.177
Hypercholesterolemia, %	628(33.4)	67(34.7)	99(28.0)	0.110
Hypertension, %	1349(71.9)	144(74.6)	277(78.5)	0.033
High Fat mass, %	1,263(68.5)	145(77.1)	253(73.3)	0.016
Sarcopenia,%	414(22.3)	42(22.2)	106(30.5)	0.004
Low muscle performance, %	867(46.4)	104(54.7)	202(57.9)	<0.001
Low muscle Strength, %	754(40.2)	102(52.8)	191(54.3)	<0.001
Low SMI, %	907(49.2)	82(43.6)	184(53.5)	0.089
SMI, kg/m^2	6.28 ± 0.98	5.95 ± 0.89	6.18 ± 0.99	<0.001
Muscle strength, Kg	24.32 ± 9.66	20.22 ± 8.30	22.21 ± 9.09	<0.001
Muscle Performance, m/s	0.86 ± 0.31	0.80 ± 0.31	0.78 ± 0.29	<0.001

Data are n (%) or mean ± standard deviation.
CHD, coronary heart disease; BMI, body mass index; SMI, skeletal muscle index.

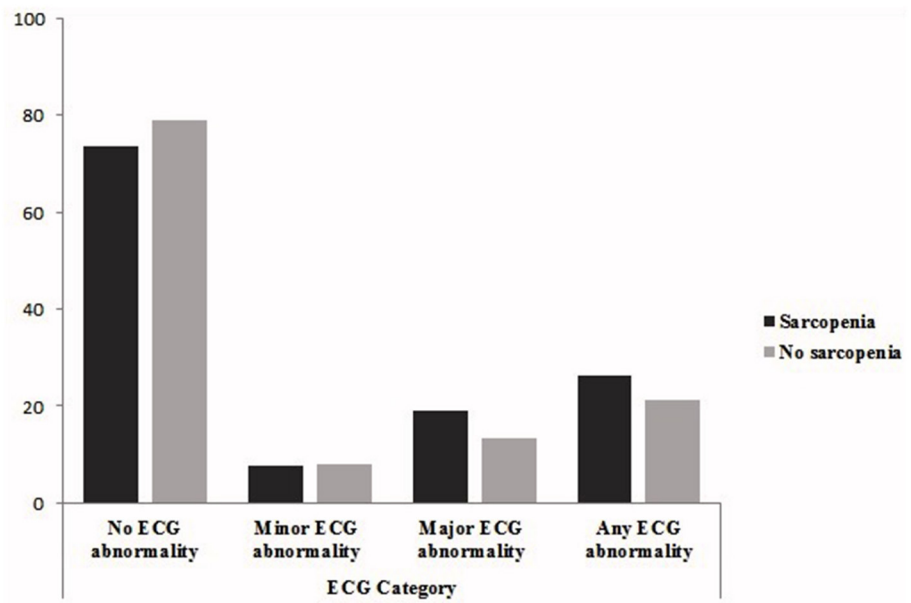

FIGURE 1 | Prevalence rates of sarcopenia according to ECG abnormality category.

CHD is a major cause of death and disability in the world. Understanding the risk factors and comorbidities is essential for prevention, early diagnosis, reduction of mortality and to evaluate management effectiveness (4). Among comorbidities, sarcopenia with common mechanisms can associate with CHD. Previous reports have shown that the associations of sarcopenia and its parameters with carotid atherosclerosis, myocardial infarction (MI), chronic heart failure and other heart diseases (14, 33). A recent study found that sarcopenia was associated with MI and atrial fibrillation. However, in the mention study, sarcopenia was defined based on the skeletal muscle mass and muscle strength did not assay in their population (14). In another

TABLE 2 | Association of sarcopenia and muscle components with minor and major ECG abnormalities.

	No ECG abnormality	Minor ECG abnormality	Major ECG abnormality
Sarcopenia			
Crude model	1.00	0.99(0.69–1.43)	**1.53(1.19–1.97)**
Model 1	1.00	0.90(0.61–1.31)	**1.43(1.09–1.87)**
Model 2	1.00	0.96(0.65–1.43)	**1.47(1.11–1.95)**
SMI			
Crude model	1.00	**0.70(0.60–0.82)**	0.90(0.80–1.01)
Model 1	1.00	0.90(0.75–1.08)	0.88(0.77–1.02)
Model 2	1.00	0.87(0.72–1.06)	**0.82(0.71–0.96)**
Muscle strength			
Crude Model	1.00	**0.95(0.93–0.97)**	**0.98(0.96–0.99)**
Model 1	1.00	0.98(0.96–1.01)	**0.96(0.94–0.98)**
Model 2	1.00	0.98(0.95–1.00)	**0.96(0.94–0.97)**
Muscle performance			
Crude Model	1.00	**0.52(0.31–0.85)**	**0.41(0.28–0.60)**
Model 1	1.00	1.06(0.59–1.90)	**0.38(0.25–0.60)**
Model 2	1.00	1.09(0.59–2.02)	**0.45(0.29–0.72)**
Low SMI			
Crude model	1.00	0.80(0.59–1.08)	1.18(0.94–1.49)
Model 1	1.00	0.98(0.71–1.34)	1.13(0.89–1.45)
Model 2	1.00	1.01(0.72–1.41)	1.25(0.97–1.61)
Low muscle strength			
Crude model	1.00	**1.66(1.24–2.24)**	**1.76(1.40–2.22)**
Model 1	1.00	1.20(0.86–1.67)	**1.78(1.38–2.31)**
Model 2	1.00	1.33(0.94–1.88)	**1.82(1.39–2.37)**
Low muscle performance			
Crude model	1.00	**1.39(1.03–1.88)**	**1.58(1.26–1.20)**
Model 1	1.00	0.93(0.66–1.29)	**1.60(1.23–2.07)**
Model 2	1.00	0.90(0.64–1.28)	**1.39(1.07–1.82)**

Data are OR and 95% confidence interval. SMI, skeletal muscle index.
Model 1; adjusted for age, sex.
Model 2; adjusted for age, sex, smoking, physical activity, Education, hypertension, Diabetes, high fat mass, hyperchoesterolemia.
The bold values show that the ORs are significant.

TABLE 3 | Association of sarcopenia and muscle components with any ECG abnormalities.

	No ECG abnormality	Any ECG abnormality
Sarcopenia		
Crude model	1.00	**1.33(1.07–1.65)**
Model 1	1.00	1.22(0.97–1.54)
Model 2	1.00	**1.28(1.01–1.63)**
SMI		
Crude model	1.00	**0.82(0.75–0.91)**
Model 1	1.00	0.89(0.79–1.00)
Model 2	1.00	**0.84(0.74–0.95)**
Muscle strength		
Crude Model	1.00	**0.97(0.96–0.98)**
Model 1	1.00	**0.97(0.95–0.98)**
Model 2	1.00	**0.96(0.95–0.98)**
Muscle performance		
Crude model	1.00	**0.44(0.32–0.61)**
Model 1	1.00	**0.54(0.37–0.79)**
Model 2	1.00	**0.61(0.42–0.91)**
Low SMI		
Crude Model	1.00	1.03(0.85–1.25)
Model 1	1.00	1.08(0.88–1.32)
Model 2	1.00	1.16(0.94–1.43)
Low muscle strength		
Crude Model	1.00	**1.73(1.43–2.09)**
Model 1	1.00	**1.55(1.251.92)**
Model 2	1.00	**1.62(1.30–2.03)**
Low muscle performance		
Crude model	1.00	**1.51(1.25–1.84)**
Model 1	1.00	**1.32(1.06–1.63)**
Model 2	1.00	1.19(0.95–1.49)

Data are OR and 95% Confidence Interval. SMI; Skeletal Muscle Index.
Model 1; adjusted for age, sex.
Model 2; adjusted for age, sex, smoking, physical activity, education, hypertension, diabetes, high fat mass, hyperchoesterolemia.
The bold values show that the ORs are significant.

study, researchers showed that sarcopenia was as prognostic predictor in older people with acute MI (12).

ECG is an available, low cost and useful tool for risk prediction of asymptomatic subjects with CHD, especially in older people given their higher prevalence of CVD events (36, 37). In some studies, CHD was defined as a symptom of angina pectoris based on the Rose Angina Questionnaire, a positive history of CHD, or a positive ECG for CHD. There are also studies that use only one definition of CHD separately. Therefore, CHD could be defined based on ECG abnormalities (29, 38, 39).

In this study, we revealed the relationship between sarcopenia and major ECG abnormalities. The model analysis indicated that the risk of major ECG abnormality was increased in sarcopenic participants (OR = 1.47, 95% CI: 1.11–1.95) even after adjustment for several risk factors. Also, among components of sarcopenia, we found the independent association between muscle strength and muscle performance with ECG abnormalities. Considerable evidence supports muscle strength, an important component of sarcopenia, has an independent role in the prevention of cardiovascular events and mortality (40–42). A systematic review of 23 selected publications showed that muscle strength was inversely and independently associated with all cause and cardiovascular mortality. Furthermore, a strong and inverse association of muscle strength with mortality had been confirmed in patients with chronic diseases such as CHD, cancer, and peripheral artery disease (43).

Our findings also supported that low muscle mass alone may not completely reveal muscle performance and that muscle strength should be considered an important parameter in defining sarcopenia. This issue has also been considered by

the EWGSOP and in the recent definition of sarcopenia, the importance of muscle strength over muscle mass has been emphasized (3). Furthermore, the present study demonstrated the important of muscle performance as a risk factor for CHD. It implied that the muscle function of the lower extremities may be important in cardiovascular outcomes. Consistent with our findings, recent studies revealed gait speed was associated with an increased HRs for death and cardiovascular mortality (44, 45).

Both muscle strength and muscle performance are used to assess the function of skeletal muscle and these tests are simple and rapid and can be performed in older people. On the other hand, due to the relevance of these parameters with health outcomes, these are useful for predicting CVD and all- cause mortality. This may, at least in part, explain our observations that muscle strength and muscle performance are independently and significantly associated with health outcomes regardless of muscle mass (45, 46).

The principal mechanism for the relationships between sarcopenia and its components, especially muscle strength or muscle performance, with CHD has not been clearly explored. Muscle mitochondrial dysfunction, which is involved in the pathogenesis of sarcopenia, may also play a role to develop of cardiovascular disease by increasing oxidative stress production and damage of vascular endothelium (47). In addition, insulin resistance, chronic inflammation, and abnormalities in anabolic hormones such as low testosterone levels are other common mechanisms involve in sarcopenia especially low muscle function and atherosclerosis diseases (48–50). Physical activity and activities of daily living may be reduced after developing CVDs and also muscle atrophy occurs by reducing blood flow in skeletal muscle and infiltration of adipocytes into muscle fibers (50). The above mechanisms suggest that sarcopenia and its parameters associate with CVDs and prevention and treatment of sarcopenia would decrease the risk of atherosclerosis and death in older people.

In this study, some limitations should be considered. The cross-sectional design limited the possibilities of determining the causal inferences and further longitudinal designs are needed to clarify any causal relationship. However, ECG is an easy screening test for CHD, but not the gold standard method such as coronary angiography. Therefore, this issue might be impacted on our results. Despite these limitations, the strength of this study is that our findings were based on a great sample size from a population-based study provided data on musculoskeletal disorders such as sarcopenia among older people in Iran. Also, skeletal muscle mass was directly measured with DXA as a gold standard for diagnosing low muscle mass.

CONCLUSIONS

This study highlighted that sarcopenia was associated with ECG abnormalities independent of the well-known cardiovascular risk factors in Iranian older people. Among parameters of sarcopenia, muscle strength and muscle performance were the most important factors to associate with ECG abnormalities.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Bushehr University of Medical Sciences. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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The Relationship Between Food-Based Pro-inflammatory Diet and Sarcopenia: Findings From a Cross-Sectional Study in Iranian Elderly People

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Background: Sarcopenia has rarely been linked to Food-based Inflammatory Potential of the Diet (FIPD) in earlier studies. This study was performed to examine the association of FIPD and sarcopenia and its components.

Method: In the cross-sectional research, dietary intakes of 300 randomly-selected elderly adults aged 55 years or older were collected through a validated food frequency questionnaire. We constructed FIPD score based on average consumptions of 28 food items. According to The European Working Group on Sarcopenia definition, sarcopenia and its components such as muscle strength, muscle mass, and gait speed were defined.

Result: No significant difference was found between the prevalence of sarcopenia ($P = 0.05$), low muscle mass ($P = 0.27$), low handgrip strength ($P = 0.72$), and lower gait speed ($P = 0.14$) across tertiles of FIPD score. Moreover, we did not find significant differences among means of handgrip strength ($P = 0.65$), muscle mass ($P = 0.33$), and walking speed ($P = 0.89$) across FIPD categories. However, binary logistic regression analysis indicated a significant positive relationship between FIPD score and odds of sarcopenia; such that subjects in the top vs. those in the bottom FIPD tertile had 155% greater chance of having sarcopenia (OR: 2.55; 95% CI: 1.17–5.55). After controlling for all confounding factors, this association strengthened (OR: 2.67; 95% CI: 1.18–6.01).

Conclusion: We found that greater FIPD score, which means a more pro-inflammatory diet, was positively linked with sarcopenia.

Keywords: food-based inflammatory potential of the diet, sarcopenia, muscle mass, muscle strength, gait speed

INTRODUCTION

Sarcopenia is a generalized and progressive skeletal muscle disease that causes rapid loss of muscle health (1). It is related to chronic disease and known as a public health problem (1, 2). The projection for number of people with sarcopenia is its increasing rate from 50 million in 2010 to more than 200 million in 2050 worldwide (3). It is estimated that Iran's aging population will approximately reach 10% of the population in 2026 (4). Additionally, the prevalence of sarcopenia in Iran was 17 to 33% (5). Thus, diagnosis of underlying factor contributing to this condition is essential.

Aging, inactivity, poor diet, chronic disease, inflammation, and iatrogenic factors are the underlying causes of sarcopenia (1). Inflammation activates many molecular pathways involved in this disease by stimulating protein catabolism and suppressing muscle synthesis (6, 7). Therefore, high levels of inflammatory cytokines have a harmful effect on muscle strength and mass (8). Diet is a modifiable factor for both sarcopenia and inflammation (9). Although dietary inflammatory index (DII) has earlier been designed to evaluate the inflammatory properties of the diet, it mostly based on nutrients (10). There are the complex mixture of nutrients and chemicals in the diet and their effect on each other (11). This can distort the known potential of their anti- or pro-inflammatory nature. Thus, studies of single nutrients and even single foods may not fully address the complex nature of a diet (12). Therefore, the use of food-based inflammatory potential of the diet (FIPD) that considers foods together is suggested (13, 14). According to this idea, Tabung et al. constructed FIPD index based on dietary intakes of foods or food groups to survey the inflammatory capacity of the diet (14). This food-based dietary pattern could be conveniently interpreted for disease prevention and health improvement as dietary guidelines (14). Such dietary patterns have been shown to predict concentrations of plasma inflammatory factors better than DII (13).

Despite some studies on the link between food-based inflammatory potential of the diet (FIPD) and risk of some chronic disease including colorectal (15) and ovarian cancer (16), irritable bowel syndrome (17), and psychological illnesses (18), to our knowledge there is no study explored the association of this dietary index and risk of sarcopenia. Moreover, scarce data are available about the association of diet and sarcopenia in the Middle East. Therefore, this study was designed to examine the relationship between FIPD and sarcopenia and its components.

MATERIALS AND METHODS

Participants

We carried out a population-based cross-sectional study from May to October 2011 in Tehran, Iran. Tehran is the largest city and capital of Iran. This metropolitan region accounts for 10.8% of Iran's total population (19). The data collection and sampling method with more details have earlier been published (20). Briefly, we recruited 300 elderly adults (150 women and 150 men) aged 55 years or older who were selected through a cluster random selection method in district 6 of Tehran. According to the postal code address, the head of each cluster was determined. It should be noted that age and gender distribution, as well as demographic status in the population of district 6 of Tehran, where the current study's population came from, are representative of Tehran's population (19). To avoid heterogeneity in the data, persons whose major cause of sarcopenia did not due to aging were not included. Subjects who had sarcopenia due to lack of moving as well as those with artificial limbs or limb prostheses were not included. In addition, subjects with debilitating diseases (for instance malignancy and organ failure) that might predispose an individual to sarcopenia were not included as well. Tehran University of Medical Sciences Ethics' Committee accepted the protocol study. First, the settings of study were elucidated to the participants and then the informed written consent were obtained.

Dietary Intake Assessment

Dietary data of study participants were gathered with a Block-format 117-item Food Frequency Questionnaire (FFQ), for which detailed information about the validity and reliability has been given elsewhere (20, 21). Trained nutritionist administered the FFQs through in-person meeting. The questionnaire contained a list of food items that their portion sizes were specified. The booklet of "household measures" was used to convert the dietary items to grams per day. We calculated daily nutrients and energy intake of each participant with Iranian modified version of Nutritionist IV software.

Development of a Food-Based Inflammatory Potential of Diet

For construction of FIPD, we used the earlier database on 486 Tehrani female adults about the association of food and food groups contributed to systemic inflammation (22). In the mentioned study, the level of inflammatory markers was assessed with serum interleukin-6 (IL-6), Tumor Necrosis Factor alpha (TNF alpha), and high-sensitivity C-reactive protein (hs-CRP) level (22). Dietary items that loaded in the western dietary pattern were determined as pro-inflammatory foods and other food items loaded in the healthy dietary pattern were determined as anti-inflammatory items. We used this approach because that study observed the healthy dietary pattern could significantly decrease inflammatory markers as well as the western dietary pattern could significantly elevated inflammatory markers (22). First, average daily consumptions of 28 food groups including 12 anti-inflammatories (e.g., poultry, fish, tomatoes, legumes, yellow vegetables, cruciferous vegetables, other vegetables, fruits, fruit juices, green leafy vegetables, tea, and whole grains) and 16 pro-inflammatory items (eggs, dairy, potatoes, pizza, butter, red meats, coffee, French fries, sweets and desserts, refined grains, snacks, hydrogenated oils, processed meats, hydrogenated fats, soft drinks, and mayonnaise) were calculated. Then, amounts of these foods items were controlled for energy with the residual analysis (23). For each individual, we multiplied average daily consumption of each food items through the factor loadings attained in the aforementioned paper (22). Then, total FIPD score of each individual was calculated through summation of

each dietary item scores. Lastly, to decrease the magnitude of the scores, the final FIPD score was divided by 100. A lower FIPD or more negative score shows a less pro-inflammatory diet, and vice versa.

Assessment of Sarcopenia

Sarcopenia was determined according to the definition suggested by the European Working Group on Sarcopenia (EWGSOP) (3). We considered the combination of both low muscle mass and either weak grip strength or slow gait speed to determine sarcopenia. The ratio of whole lean mass of arms and legs of each individuals known as ASM (Appendicular Skeletal Muscle) (24) divided to their height^2 (ASM/height^2) was considered as the muscle mass. A dual-energy X-ray absorptiometry (DEXA) (Discovery W S/N 84430) was applied for this assessment. The muscle mass lower than 5.45 kg/m^2 for women and lower than 7.26 kg/m^2 for men were diagnosed as low muscle mass (3).

Muscle strength of each participant was determined by handgrip test. A pneumatic squeeze bulb dynamometer (named: c7489-02 Rolyan) adjusted in pound per inch^2 (psi) was used to obtained handgrip strength. Participants had to squeeze 3 times for both hands with a 30 s rest after each squeeze. Next, the mean result of all measurement was recorded. Finally, the handgrip strength lower than 30 kg for men and lower than 20 kg for women was determined as low muscle strength (25). We applied a 4-m walk gait speed exam to evaluate physical performance of participants (3). Participants with gait speeds < 0.8 m/s was diagnosed as slow gait speed (3).

Assessment of Other Variables

Required information about non-dietary data including age, sex, socio-economic status, alcohol consumption, and smoking habits were obtained with a general questionnaire. The former medical history including history of arthritis, stroke, asthma, myocardial infarction, and diabetes, and also a history of medicine use including statins, insulin angiotensin-converting enzyme inhibitors, sexual hormones, and corticosteroid were collected as well. The physical activity performance was evaluated by the short form of the International Physical Activity Questionnaire (IPAQ) (26). Next, in accordance with recommendation of IPAQ, we calculated a metabolic equivalent-hour per week (MET-h/week) for all contributors (27). We used a digital scale to measure weight while participants were minimally clothed. We measured height in a standing position without shoes by a wall tape meter. While contributors were standing and usually breathe, their waist circumference was measured in the middle of the iliac crest and lower rib margin. Weight (kg) divided by height squared (m2) was applied to compute body mass index (BMI).

Statistical Analysis

Participants were categorized based on tertile cut-off points of FIPD score. We used tertiles instead of quartiles or quintiles due to not having a large sample size. In addition, we reached the best associations when we considered participants across tertiles of FIPD score. To examine the differences in distribution of the participant's characteristics across tertiles of FIPD, we used Chi-square and ANOVA analyses for categorical and continuous variables, respectively. Dietary intakes were assessed through ANCOVA across FIPD score categories, in which we adjusted for sex, age, and energy. Binary logistic regression was applied to find the link of FIPD score with sarcopenia in crude and multivariable-adjusted models. In the first model, energy intake (kcal/d), sex (male/female), and age (continuous) were controlled for. In the second model, further adjustments were performed for alcohol consumption (yes/no), smoking (yes/no), history

TABLE 1 | Characteristics of study participants in FIPD categories*.

	Tertiles of FIPD score			$P^{\dagger}$
	T_1 ($n = 100$)	T_2 ($n = 100$)	T_3 ($n = 100$)	
FIPD range	<-11.25	−11.25, −7.37	>-7.37	
Age (y)	66.33 ± 7.50	66.82 ± 7.37	67.24 ± 8.26	0.70
BMI (kg/m^2)	27.51 ± 4.12	27.28 ± 4.47	27.34 ± 4.05	0.92
Physical activity (MET-h/w)	1626.1 ± 1665.9	1279.71 ± 1358.2	977.7 ± 1157.3	0.005
Female (%)	55	49	49	0.61
Alcohol use (%)	12	16	12	0.63
Smoking (%)	13	15	10	0.56
Medical history				
Yes (%)	16	20	16	0.68
No (%)	84	80	84	
Drug history				
Sexual hormone use (%)	2	3	4	0.70
Statin use (%)	41	30	39	0.22
Corticosteroid use (%)	3	1	4	0.40

All values are mean ± SD, unless indicated.
†P-value for quantitative variables and qualitative variables were obtained from ANOVA and chi-square, respectively.
FIPD, food-based inflammatory potential of diet.

TABLE 2 | Dietary intakes of study participants by FIPD categories*.

Variables	Tertiles of FIPD score			P†
	T_1 ($n = 100$)	T_2 ($n = 100$)	T_3 ($n = 100$)	
Fruits (g/d)	861.41 ± 21.09	589.92 ± 20.58	465.11 ± 20.74	< 0.001
Fruit juices (g/d)	52.53 ± 7.63	36.12 ± 7.45	35.72 ± 7.51	0.21
Poultry (g/d)	26.30 ± 1.80	23.33 ± 1.75	22.61 ± 1.77	0.32
Legumes (g/d)	37.10 ± 3.37	45.93 ± 3.29	39.17 ± 3.31	0.14
Cruciferous vegetables (g/d)	14.57 ± 1.71	9.65 ± 1.67	7.90 ± 1.68	0.02
Green leafy vegetables (g/d)	44.30 ± 2.64	30.06 ± 2.58	27.66 ± 2.60	< 0.001
Yellow vegetables (g/d)	35.68 ± 2.23	23.75 ± 2.18	19.53 ± 2.20	< 0.001
Other vegetables (g/d)	454.95 ± 14.75	296.19 ± 14.39	241.03 ± 14.51	< 0.001
Tea (g/d)	910.52 ± 56.28	839.30 ± 54.92	578.18 ± 55.36	< 0.001
Tomatoes (g/d)	220.91 ± 9.78	153.80 ± 9.54	115.61 ± 9.62	< 0.001
Whole grains (g/d)	111.47 ± 8.60	93.62 ± 8.39	98.20 ± 8.46	0.32
Butter (g/d)	2.89 ± 0.45	1.79 ± 0.43	2.61 ± 0.44	0.19
Potatoes (g/d)	18.48 ± 3.26	31.20 ± 3.18	31.55 ± 3.20	0.007
Low fat dairy (g/d)	314.51 ± 22.81	254.65 ± 22.25	192.60 ± 22.43	0.001
High fat dairy (g/d)	240.39 ± 19.96	313.28 ± 19.48	362.44 ± 19.63	< 0.001
Fish (g/d)	20.26 ± 2.36	12.27 ± 2.30	11.67 ± 2.32	0.01
Refined grains (g/d)	137.03 ± 14.30	195.69 ± 13.95	287.01 ± 14.07	< 0.001
Red meats (g/d)	29.12 ± 2.96	34.70 ± 2.88	42.41 ± 2.91	0.007
Processed meats (g/d)	1.11 ± 0.73	2.58 ± 0.71	3.01 ± 0.71	0.16
Sweets and desserts (g/d)	6.16 ± 0.96	6.15 ± 0.94	6.96 ± 0.95	0.79
Pizza (g/d)	7.97 ± 1.75	4.81 ± 1.71	6.60 ± 1.73	0.44
Eggs (g/d)	18.99 ± 2.82	15.48 ± 2.76	14.71 ± 2.78	0.53
Soft drinks (g/d)	22.27 ± 7.66	25.80 ± 7.47	54.81 ± 7.53	0.004
French fries (g/d)	2.76 ± 0.54	3.40 ± 0.53	4.65 ± 0.53	0.04
Coffee (g/d)	31.51 ± 6.39	19.59 ± 6.23	13.30 ± 6.28	0.13
Mayonnaise (g/d)	1.80 ± 0.49	1.93 ± 0.48	2.47 ± 0.48	0.59
Hydrogenated fats (g/d)	2.10 ± 0.97	5.04 ± 0.94	3.80 ± 0.95	0.10
Vegetables oils (g/d)	7.51 ± 0.59	6.81 ± 0.58	6.87 ± 0.58	0.66

*All values are mean ± SE; all values are adjusted for energy intake, sex, and age. †ANCOVA for all variables.
FIPD, food-based inflammatory potential of diet.

of chronic illness (cerebrovascular accident, arthritis, asthma, diabetes, and myocardial infarction), physical activity (MET-h/wk), and medication use (corticosteroid, statin, testosterone, and estrogen). Moreover, the odds ratio for sarcopenia in the second and third tertiles were compared with the lowest tertile (reference category). We included the tertile categories of the FIPD score as an ordinal variable in the logistic regression analysis to attain *P* for trends. All aforementioned analyses were done with SPSS (version 26). *P*-values lower than 0.05 were considered significant.

RESULTS

In the present investigation, total FIPD score was between −48.4 and −0.45. The cut-off points of FIPD score across increasing tertiles was <-11.25, −11.25 to −7.37, and >-7.37, respectively. Distribution of participants as well as mean values of continuous variables across tertiles of FIPD is shown in **Table 1**. Subjects in the third tertile compared to subjects in the first tertile of FIPD had less physical activity ($P = 0.005$). No significant difference was detected in mean age and BMI across FIPD categories. The distribution of subjects in alcohol use, smoking, medical or medication history between the highest vs. lowest categories of FIPD was not significantly different.

Age-, gender- and energy-adjusted means of selected food items throughout FIPD categories are displayed in **Table 2**. We observed a higher score of FIPD significantly related with a lower intake of cruciferous vegetables, fruits, yellow vegetables, green leafy vegetables, tomatoes, other vegetables, fish, tea, and low-fat dairy. Moreover, subjects in the highest rank of FIPD score had significantly greater consumptions of refined grains, high-fat dairy, soft drinks, red meats, potatoes, and French fries than subjects in the lowest rank.

Table 3 indicates the distribution of sarcopenia, low muscle mass, low muscle strength, and low gait speed across FIPD categories. We did not find a significant difference in the distribution of sarcopenia ($P = 0.05$), low muscle mass ($P = 0.27$), low handgrip strength ($P = 0.72$), and lower gait speed

TABLE 3 | Distribution of sarcopenia and its components across tertile FIPD categories.

	Tertiles of FIPD score			P^*
	T_1 ($n = 100$)	T_2 ($n = 100$)	T_3 ($n = 100$)	
Sarcopenia (%)	11	19	24	0.05
Low muscle mass (%)†	34	38	45	0.27
Low hand grip strength (%)‡	35	30	31	0.72
Low gait speed (%)§	33	43	46	0.14
Means of components				
Muscle mass [ASM/h2] (kg)				
Crude	6.62 ± 0.09	6.67 ± 0.09	6.53 ± 0.09	0.63
Model 1	6.66 ± 0.08	6.64 ± 0.08	6.51 ± 0.08	0.39
Model 2	6.67 ± 0.08	6.65 ± 0.08	6.51 ± 0.08	0.33
Hand grip strength (psi)				
Crude	10.77 ± 0.35	11.38 ± 0.35	10.98 ± 0.35	0.47
Model 1	10.92 ± 0.24	11.28 ± 0.23	10.93 ± 0.23	0.48
Model 2	10.91 ± 0.24	11.22 ± 0.23	11.02 ± 0.24	0.65
Gait speed (m/s)				
Crude	0.85 ± 0.02	0.84 ± 0.02	0.83 ± 0.02	0.71
Model 1	0.85 ± 0.02	0.83 ± 0.02	0.83 ± 0.02	0.74
Model 2	0.85 ± 0.02	0.84 ± 0.02	0.85 ± 0.2	0.89

**P-value for quantitative variables and qualitative variables were obtained from ANCOVA and chi-square, respectively ($P < 0.05$ significant).*
†Muscle mass < 5.5 (kg/m^2) for women and < 7.0 (kg/m^2) for men (3).
‡Muscle strength < 30 kg for men and < 20 kg for women (25).
§Gait speeds ≤ 0.8 m/s (3).
Model 1: Adjusted for energy, age and sex.
Model 2: Further adjusted for smoking, physical activity, medication use (estrogen, testosterone, corticosteroid, and statin), alcohol consumption, and history of disease.
FIPD, food-based inflammatory potential of diet.

TABLE 4 | Multivariable-adjusted odds ratios (95% CIs) for sarcopenia across tertile FIPD categories.

	Tertiles of FIPD score			*P* trend
	T_1	T_2	T_3	
Sarcopenia				
n (case)	11	19	24	
Crude	1	1.89 (0.85–4.22)	2.55 (1.17–5.55)	0.01
Model 1	1	1.97 (0.86–4.51)	2.67 (1.18–6.01)	0.01
Model 2	1	2.06 (0.88–4.82)	2.57 (1.11–5.89)	0.02

Model 1: Adjusted for energy, age and sex. Model 2: Further adjusted for smoking, physical activity, medication use (estrogen, testosterone, corticosteroid, and statin), alcohol consumption, and history of disease.
FIPD, food-based inflammatory potential of diet.

($P = 0.14$) throughout categories of FIPD score. In addition, no significant differences were found among means of handgrip strength, muscle mass, and walking speed across FIPD categories even after adjusting for all covariates.

Odds ratios (ORs) and 95% CIs from crude and multivariable-adjusted model for sarcopenia across FIPD tertiles are depicted in **Table 4.** A significant relationship between a higher FIPD score and increasing odds of sarcopenia (OR: 2.55; 95% CI: 1.17–5.55) was identified in the unadjusted model. After controlling for energy intake, sex, and age (model 1), the relationship remained significant (OR: 2.67; 95% CI: 1.18–6.01). Even after additional controlling for all covariates, we found that subjects in the top vs. the bottom FIPD tertile had higher odds of sarcopenia (OR: 2.57; 95% CI: 1.11–5.89).

DISCUSSION

We evaluated the relationship between the food-based inflammatory potential of diet and sarcopenia and its components. A higher FIPD score or a more pro-inflammatory diet was linked with elevated likelihood of sarcopenia. Nevertheless, we did not find any relationship between FIPD and low gait speed, low muscle strength, and low muscle mass.

As far as we know, this is the first study elucidate the role of the food-based inflammatory score in sarcopenia.

Sarcopenia is known as a disease, associated with increment hazard of disability, mortality, and fall (28, 29). It appears that level of inflammatory marker has been increased during the aging period that might cause muscle weakness or sarcopenia (30); however, dietary intakes can also contribute to elevated inflammation and muscle deterioration (9). FIPD was validated and expanded to clarify the whole dietary inflammatory capacity (14). We found that subjects with high FIPD score had a greater chance of having sarcopenia. It must be mentioned that data are very limited on the association between diet and sarcopenia especially about the inflammatory capacity of the diet. A large cross-sectional study from the United State demonstrated that higher nutrient-based DII score was related to increased risk of sarcopenia (31). Our recent publication in the current population revealed that nutrient-based DII was positively associated with sarcopenia (32). However, the current analysis is different from previous ones because unlike previous one (32), here we considered foods to compute dietary inflammatory capacity. Although both DII based on nutrient and food-based FIPD indexes evaluate the inflammatory properties of diet, nutrient-based index might have some limitations to assess this potential due to the complex synergistic and interactions effect of nutrients and chemicals in the diet (11, 14). The FIPD is a novel index constructed based on foods and food groups and is more appropriate for clinical practice and public recommendations (14). Earlier studies have shown that the food-based assessment of dietary inflammatory potential predicts systemic inflammation better than nutrient-based DII (13). However, additional investigation is needed to elucidate the association between dietary inflammatory capacity and components of sarcopenia.

As expected, we found individuals with high adherence to pro-inflammatory diet (the top FIPD tertile) had significantly lower consumptions of food groups with anti-inflammatory properties including fish, tomatoes, cruciferous vegetables, yellow vegetables, green leafy vegetables, other vegetables, fruits, tea, and low-fat dairy. Additionally, subjects in the third vs. the first FIPD tertile had significantly greater consumptions of potatoes, high-fat dairy, refined grains, red meats, soft drinks, and French fries. Based on these findings, a dietary pattern with a high intake of fish, vegetables, fruit, and low-fat dairy along with a fewer intake of red meats, refined grains, potatoes, high-fat dairy, and soft drinks might be beneficial for maintaining muscles. In line with this results, a cohort study conducted in England, Wales, and Scotland reported that a healthy dietary pattern (means greater consumption of leafy vegetables, fresh fruit, and whole-grain bread, but lesser consumption of processed meat, white bread, and added sugar) in adulthood (ages 36, 43, 53) was linked with improved muscle performance in older age (60–64) (33). A Swedish cohort study (34), that investigated the relationship of dietary patterns at study baseline with average age 71 years, suggested that eating a healthy dietary pattern especially "the Mediterranean diet" tended to reduce the progress of sarcopenia 16 years later.

There is growing evidence that increasing pro-inflammatory markers such as TNF-α, IL-1β, IL-6 are the main cause of skeletal muscle wasting and sarcopenia (35). High serum levels of these inflammatory markers can negatively influence skeletal muscle by inhibiting the expression and activity of GH and IGF-I (35, 36). Of note, studies conducted to determine the effect of anti-inflammatory medications on skeletal muscle and inflammation, showed that these anti-inflammatory drugs can significantly reduce loss of muscle mass and keep muscle strength (37). It appears that our findings provide further evidence on the contribution of dietary inflammatory potential to sarcopenia.

This study had some strengths and limitations. For the first time, we used a novel food-based IPD to predict sarcopenia and its components. Evidence found that FIPD better predicts the body's inflammation and its related co-morbidities than nutrient-based dietary inflammatory index (13). Several potential confounders were considered in the analyses. Moreover, we used a validated FFQ for the evaluation of participants dietary intakes. Along with strengths, our study had some limitations as well. First, the cross-sectional design of the study prohibits us to reach a causal relationship, because longitudinal data is not available as well as exposure and outcome are identified in each individual simultaneously. Second, the possibility of misclassification of study subjects, due to measurement errors, cannot be avoided. Third, despite considering numerous confounding factors, residual confounders cannot be ignored. Fourth, we did not measure inflammatory cytokines in the current study. The FIPD was constructed based on factor loadings of food items in healthy or Western dietary patterns among Iranian female teachers, not the current study population. It is better to construct FIPD based on coefficients between food groups and inflammatory biomarkers obtained in the same study population. Finally, the study was performed on a small sample (maximum 300 cases), due to inaccessibility to more DEXA machine in Tehran and budget limitations. Thus, caution is required to the extrapolation of our findings to the total Iranian population.

CONCLUSION

Findings from this population-based cross-sectional investigation support the role of food-based inflammatory potential of the diet in sarcopenia. Strategies to reduce consumption of foods with a greater pro-inflammatory capacity along with increasing consumption of foods with anti-inflammatory features may have benefits for older adults to prevent muscle loss. Prospective studies however are needed to verify these findings.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, on reasonable request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Tehran University of Medical Sciences Ethics' Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AB, RHa, AD, BL, RHe, SS, and AE participated to the data collection, statistical analyses, design, conception, data explanation, manuscript writing, and approval of the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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Effects and Moderators of Exercise on Sarcopenic Components in Sarcopenic Elderly: A Systematic Review and Meta-Analysis

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Background: Sarcopenia is a muscle disease in loss of muscle strength, mass, and function associated with aging. Although protective effects of exercise on muscle mass and function are generally recognized, research findings in sarcopenic adults are inconsistent. It is necessary to conduct a systematic review to determine the effects of exercise on muscle strength, body composition, and physical performance in older adults with sarcopenia, and to examine the potential moderators including sociodemographic characteristics and exercise-related factors.

Methods: Six electronical academic databases (Medline, Embase, CINAHL, Scopus, Cochrane Library, and SPORTDiscus) were used to retrieve the eligible studies from inception to May 2020. Two reviewers independently selected and extracted the data from each included study, and effect sizes were calculated by employing random-effect models with 95% confidential interval (CI). The Physiotherapy Evidence Database (PEDro) scale was used to assess study quality.

Results: Seventeen studies (985 participants with sarcopenia, aged 67.6–86 years) were included in this review study. The meta-analytic results showed significant improvements in muscle strength [grip strength, SMD = 0.30, 95% CI (0.15, 0.45), $I^2 = 6\%$, $p < 0.01$; knee extension, SMD = 0.32, 95% CI (0.15, 0.50), $I^2 = 0\%$, $p < 0.01$; and chair and stand, SMD = 0.56, 95% CI (0.30, 0.81), $I^2 = 36\%$, $p < 0.01$], in physical performance [timed up and go, SMD = 0.74, 95% CI (0.48, 1.00), $I^2 = 0\%$, $p < 0.01$; and gait speed, SMD = 0.59, 95% CI (0.35, 0.82), $I^2 = 62\%$, $p < 0.01$], and in body composition [skeletal muscle mass index, SMD = 0.37, 95% CI (0.15, 0.58), $I^2 = 16\%$, $p < 0.01$; and appendicular skeletal muscle, SMD = 0.31, 95% CI (0.13, 0.49), $I^2 = 20\%$, $p < 0.01$]. However, there were no significant differences in other body composition (SMD = 0.20–0.36). Additionally, meta-regression revealed that the higher percent of female participants was significantly associated with improved gait speed ($\beta = 0.0096$, $p = 0.03$) and decreased skeletal muscle mass index ($\beta = -0.0092$, $p = 0.01$).

Conclusions: The current meta-analysis suggests that exercise is a beneficial therapy, which has protective effects for older adults with sarcopenia. Some beneficial effects may be moderated by gender and exercise intensity.

Keywords: physical exercise, muscle function, physical performance, sarcopenia, meta—analysis

INTRODUCTION

Aging-related health leads to many issues in the 21st century. One of the major public health challenges is to preserve older adults' physical ability and quality of life, to achieve successful aging in the whole society (1). However, due to internal physiological changes in the human body, gradual declines in skeletal muscle strength, losses of muscle mass, and reductions in physical capacity are inevitable during the aging process. These reductions are commonly known as sarcopenia (2, 3). Despite no consistent diagnostic criteria for sarcopenia, the prevalence and harmfulness of sarcopenia in older adults have been shown to be ubiquitous. For example, a previous review study using the European Working Group on Sarcopenia in Older People (EWGSOP) optional definition found that the prevalence of sarcopeina was between 11 and 20% in old adults (4). Subsequently, a series of adverse health outcomes such as mental illness, physical limitations, fractures, poor therapeutic efficacy, poor quality of life, cancer, and even cachexia in adults, have been shown to be associated with the presence of a high-risk of sarcopenia (5–9). Therefore, to reduce the prevalence of sarcopenia, there is a growing interest in non-pharmacological treatments, such as physical exercise, in which researchers can determine the effects and design optimal interventional strategies.

A wealth of evidence supports that exercise, an important modified lifestyle factor, is feasible and efficacious in improving psychological outcomes (e.g., cognition, mood) in older adults (10–14). Moreover, the literature supports that exercise improves physiology-related muscle strength, muscle strength, and physical performance in older adults, and the associated studies are also growing rapidly (15–17). For example, the randomized study of Liu et al. consisting of older adults, found that physical exercise could elevate physical performance (18). A systematic review study examining the impact of resistance exercise showed that low-load exercise benefited the muscle strength and muscle mass in older adults (19). However, in the literature, health benefits of exercise in sarcopenic adults yields mixed findings. For example, a recently published systematic review including five randomized controlled trials (RCTs) suggested that resistant exercise can improve muscle strength, muscle quality, and muscle function in older adults with sarcopenia or dynapenia compared with the controlled group (20). Similarly, the systematic review of Beckwée et al. concluded that exercise contributed to improving muscle strength, muscle mass and physical performance of sarcopenic adults (21). Conversely, the work of Yoshimura et al. demonstrated that exercise had no significant effects on muscle strength, muscle mass, and physical performance in older adults with sarcopenia (22). A systematic review study including six studies indicated that exercise did not significantly increase muscle strength, muscle mass, and balance ability among sarcopenic adults (23). These discrepant research findings imply that more synthesized studies should confirm the roles of exercise on health outcomes in older adults with sarcopenia. In response to this, a meta-analysis based on multiple studies is necessary to demonstrate the effects of exercise on sarcopenia.

Additionally, it is important for sarcopenic older adults to have optimized exercise programs that can promote their physical health. A previous study has found that the exercise modalities (e.g., duration, intensity, and type) were not met to counteract sarcopenia (24). Denison and colleagues found that demographics (e.g., age and sex) can moderate the effects of exercise in older adults with sarcopenia (25). Considering rapid growth in the research field of exercise and sarcopenia, aggregating sufficient quality studies for meta-analysis cannot only make up the limitations across previous reviews but also comprehensively determine the effects of exercise and then examine the influences of moderating factors.

Therefore, the current study was conducted: 1) to determine the effects of exercise on muscle strength, physical performance, and body composition in older adults with sarcopenia and 2) to investigate whether the potential moderators including sociodemographic characteristics and exercise-related factors that influence the intervention effects, as these moderators have been found affecting the sarcopenia-related health outcomes (25).

METHODS

Search Strategy

This systematic review was prospectively registered at PROSPERO (ID: CRD42020184130; https://www.crd.york.ac.uk/) and performed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (26). Articles were retrieved from six databases (Medline, Embase, CINAHL, Scopus, Cochrane Library, and SPORTDiscus) on May 2020. The following keywords were used: 1) "physical activity" OR "physical therapy" OR "aerobic exercise" OR "exercise*" OR "resistance training" OR "train*; AND 2) "sarcopenia" OR "sarcopenic" OR "dynapenia" OR "muscular atrophy" OR "muscular weight" OR "grip strength"; AND 3) "older adults" OR "aged" OR "elder*"; AND 4) "randomized controlled trials" OR "clinical trial" OR "random allocation." To retrieve more eligible articles, manual searching was conducted from the bibliographies of the included studies.

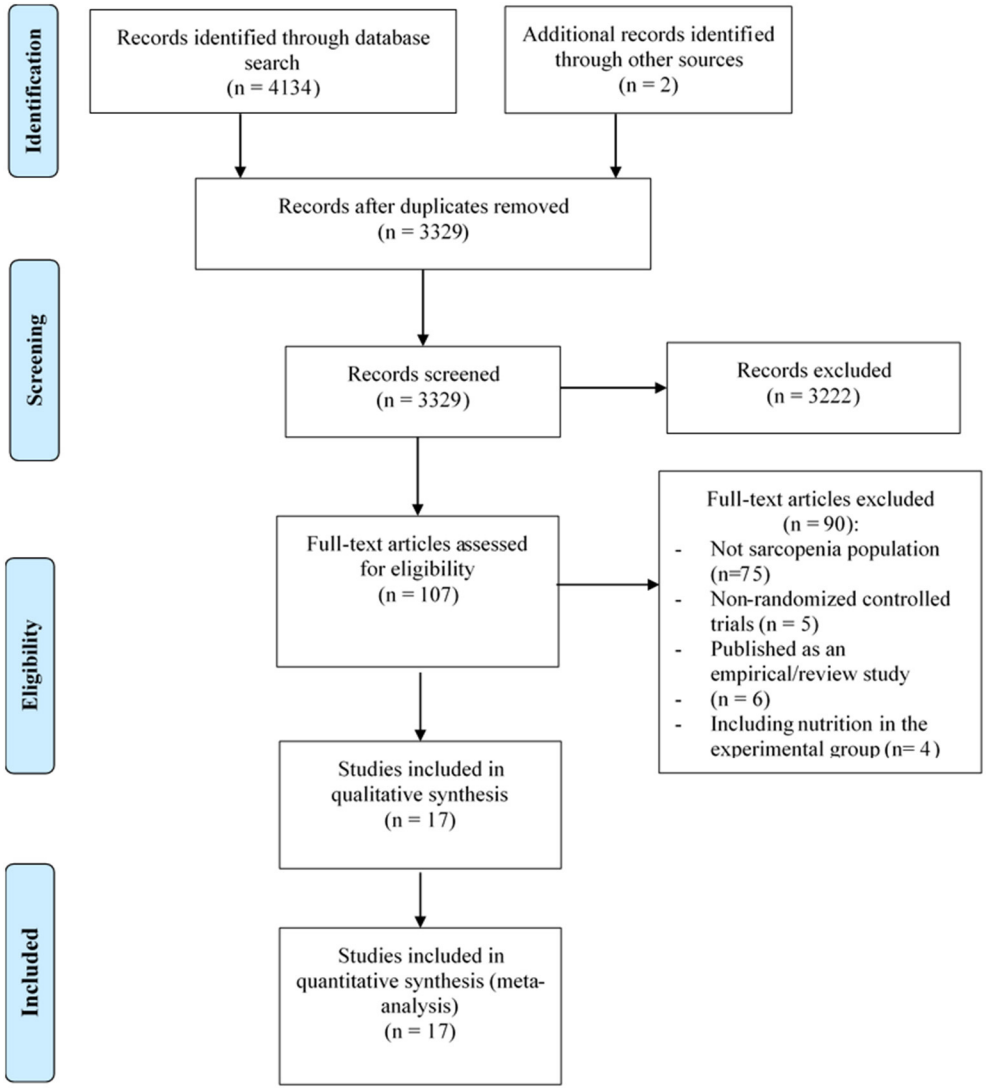


FIGURE 1 | Process of study selection following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Inclusion and Exclusion Criteria

Articles were included if they met the following criteria: (i) Participants aged over 65 years were diagnosed as sarcopenia based on the definition of EWGSOP, Asia Working Group for Sarcopenia (AWGS) or other clinical diagnosis. (ii) The study was designed as an RCT. (iii) Exercise (e.g., aerobic exercise, resistance training, whole-body variation, or a combination of strength and aerobic exercise program) was used in the intervention group. (iv) No exercise intervention (e.g., usual care or waitlist) was given in the control group. (v) The outcomes were muscle strength, body composition (skeletal muscle mass index, appendicular muscle mass, lean mass, body fat, and fat-free mass), and physical performance (gait speed and timed up and go test). (vi) The study was published in the English language.

Exclusion criteria were: (i) *in vitro* with an animal trial, (ii) participants with sarcopenia obesity, (iii) insufficient information for calculating the effect size (ES), And (iv) case-study, observational studies, editorials, or review articles.

Data Extraction and Quality Assessment

Detailed information was extracted from each study through a pre-created extraction table by two authors (YZ and LZ). The presenting information included the author and year of publication, study design, participants' characteristics, interventions, sarcopenia diagnostic criteria, assessment tool for body composition, outcomes, and safety.

Assessment of study quality was conducted using the Physiotherapy Evidence Database (PEDro) scale (27) by two authors (YZ and LZ). This assessment tool consists of 11 items: eligibility criteria, random allocation, concealed allocation, similar measures between groups at baseline, instructor blinding, assessor blinding, participant blinding, more than 85% dropout

TABLE 1 | Characteristics of randomized controlled trials included in the meta-analysis.

Study/country	Participants/living status	Sample size Female (%)	Age (years)	Intervention(s)		Sarcopenia criteria	Assessment tool for body composition	Outcomes	Adverse effect
				Experiment group	Control group				
Chen et al. (2018) (31) China	Sarcopenia residents of community dwelling	33 E = 17 C = 16 Female (100%)	67.5	2 × 60 min/week 8 weeks Resistance training	Waitlist	AWGS	BIA	Grip strength SMI ASM Body fat	No
Hassan et al. (2016) (32) Australia	Sarcopenia residents of nursing care facilities	41 E = 20 C = 21 Female (71%)	85.9	2 × 60 min/week 24 weeks Progressive resistance and balance training	Usual care	EWGSOP	BIA	Grip strength Gait speed SMI Lean mass Body fat	No
I Iranzo et al. (2018) (40) Spain	Sarcopenia residents in institution	28 E = 11 C = 17 Female (75%)	81.9	3 × 30–40 min/week 12 weeks Resistance training	Waitlist	EWGSOP	BIA	Grip strength Gait speed SMI	No
Jung et al. (2019) (41) Korea	Sarcopenia residents of community dwelling	26 E = 13 C = 13 Female (100%)	75	3 × 25–75 min/week 12weeks Resistance training and walking	Usual care + education	AWGS	DXA	Knee extension strength SMI Lean mass body fat	No
Kim et al. (2012) (42) Japan	Sarcopenia residents of community dwelling	117 E = 39 C1 = 39 C2 = 39 Female (100%)	79	2 × 60 min/week, 12 weeks Resistance training	C1: Nutrition C2: Health education	AWGS	BIA	Knee extension strength Gait speed ASM	No
Kim et al. (2013) (43) Japan	Sarcopenia residents of community dwelling	96 E = 32 C1 = 32 C2 = 32 Female (100%)	80	2 × 60 min/week, 12 weeks Resistance training	C1: Nutrition C2: Health education	AWGS	BIA	Grip strength Knee extension strength Gait speed TUG ASM	No
Lichtenberg et al. (2019) (44) Germany	Sarcopenia residents of community dwelling	43 E = 21 C = 22 Female (0%)	78.5	2 × 50 min/week 12 weeks Resistance training	Nutrition	EWGSOP	DXA	Grip strength Gait speed SMI	
Mafi et al. (2019) (45) Iran	Sarcopenia residents of community dwelling	47 E = 14 C1 = 17 C2 = 16 Female (0%)	68.5	3 × 60 min/week 8 weeks Resistance training	C1: Nutrition C2: Waitlist	EWGSOP	DXA	TUG ASM	No
Makizako et al. 2020 (46) Japan	Sarcopenia residents of community dwelling	72 E = 36 C = 36 Female (70.8%)	75	1 × 60 min/week 12 weeks Resistance training and aerobic exercise	C1: Waitlist	AWGS	BIA	Grip strength Chair and stand Gait speed TUG	No

(Continued)

TABLE 1 | Continued

Study/country	Participants/living status	Sample size Female (%)	Age (years)	Intervention(s)		Sarcopenia criteria	Assessment tool for body composition	Outcomes	Adverse effect
				Experiment group	Control group				
Maruya et al. (2016) (47) Japan	Sarcopenia residents of community dwelling	52 E = 34 C = 18 Female (56%)	69	1 × 90 min/week, 24 weeks Walking and resistance training	Usual daily activity	AWGS	BIA	Grip strength Knee extension strength Gait speed SMI Body fat	No
Piastra et al. (2018) (33) Italy	Sarcopenia residents of community dwelling	72 E = 35 C = 37 Female (100%)	70	2 × 60 min/week, 36 weeks Resistance training	Postural activation	EWGSOP	BIA	Grip strength SMI ASM Lean mass	No
Strasser et al. (2018) (34) Austria	Sarcopenia residents of institution	33 E = 16 C = 17 Female (91%)	83	2 × 60 min/week 24 weeks Resistance training	Cognitive training	EWGSOP	DXA	SMI ASM	No
Tsekoura et al. (2018) (35) Greece	Sarcopenia residents of community dwelling	54 E1 = 18 E2 = 18 C = 18 Female (84%)	73	E1: 2 × 60 min/week, 12 weeks Resistance training and 3 × 30–35 min/week, walking E2: same E1, home therapeutic exercises	Health education	EWGSOP	BIA	Grip strength Knee extension strength Chair and stand Gait speed TUG SMI Fat-free mass	No
Vikberg et al. (2019) (36) Sweden	Sarcopenia residents of community dwelling	70 E = 36 C = 34 Female (54%)	70.5	3 × 45 min/week, 10 weeks Resistance training	Waitlist	EWGSOP	DXA	Grip strength Chair and stand TUG Gait speed SMI ASM Lean mass Fat mass	No
Wei et al. (2016) (37) China	Sarcopenia residents of community dwelling	40 E = 20 C = 20 Female (70%)	76	3 × 24 min/week 12 weeks Whole-body vibration training	Waitlist	EWGSOP	BIA	Knee extension strength TUG Chair and stand	No
Yamada et al. (2019) (38) Japan	Sarcopenia residents of community dwelling	84 E = 28 C1 = 28 C2 = 28 Female (63%)	83.9	2 × 30 min/week 12 weeks Resistance exercise	C1: nutrition C2: waitlist	AWGS	BIA	Grip strength Knee extension strength Chair and stand Gait speed ASM	
Zhu et al. (2019) (39) China	Sarcopenia residents of community dwelling	77 E = 40 C = 37 Female (75%)	73	2 × 45–60 min/ week 12 weeks Resistance training and aerobic exercise +1 time/week home exercise	Waitlist	AWGS	DXA	Grip strength Knee extension strength Chair stand test Gait speed ASM	No

ASM, appendicular skeletal muscle; AWGS, Asia Working Group for Sarcopenia; EWGSOP, European Working Group on Sarcopenia in Older People; SMI, skeletal muscle mass index; BIA, bioelectrical impedance analysis; DXA, Dual-energy X-ray absorptiometry; TUG, Timed up and go.

TABLE 2 | Methodological quality of the included studies [The Physiotherapy Evidence Database (PEDro analysis)].

Study	Score	Methodological quality	PEDro item number										
			1	2	3	4	5	6	7	8	9	10	11
Chen et al. 2018 (31)	6	Good	1	1	0	1	0	0	0	1	1	1	1
Hassan et al. 2016 (32)	6	Good	1	1	0	1	0	0	0	1	1	1	1
I Iranzo et al. 2018 (40)	6	Good	1	1	0	1	0	0	1	1	0	1	1
Jung et al. 2019 (41)	6	Good	1	1	0	1	0	0	0	1	1	1	1
Kim et al. 2012 (42)	7	Good	1	1	1	1	0	0	1	1	0	1	1
Kim et al. 2013 (43)	7	Good	1	1	1	1	0	0	1	1	0	1	1
Lichtenberg et al. 2019 (44)	7	Good	1	1	0	1	0	0	1	1	1	1	1
Mafi et al. 2019 (45)	6	Good	1	1	1	1	0	0	0	1	0	1	1
Makizako et al. 2020 (46)	7	Good	1	1	0	1	0	0	1	1	1	1	1
Maruya et al. 2016 (47)	5	Fair	1	1	0	1	0	0	0	1	0	1	1
Piastra et al. 2018 (33)	5	Fair	1	1	0	1	0	0	0	1	0	1	1
Strasser et al. 2018 (34)	6	Good	1	1	0	1	0	0	1	1	0	1	1
Tsekoura et al. 2018 (35)	6	Good	1	1	1	1	0	0	0	1	0	1	1
Vikberg et al. 2019 (36)	7	Good	1	1	1	1	0	0	1	1	0	1	1
Wei et al. 2016 (37)	6	Good	1	1	1	1	0	0	0	1	0	1	1
Yamada et al. 2019 (38)	7	Good	1	1	0	1	0	0	1	1	1	1	1
Zhu et al. 2019 (39)	8	Good	1	1	1	1	0	0	1	1	1	1	1

Studies were classified as having excellent (9–10), good (6–8), fair (4–5), or poor (<4).

Scale of item score: 0, absent; 1, present. The PEDro scale criteria are (1) eligibility criteria, (2) random allocation, (3) concealed allocation, (4) similarity at baseline on key measures, (5) subject blinding, (6) therapist blinding, (7) assessor blinding, (8) more than 85% follow-up of at least 1 key outcome, (9) intention-to-treat analysis, (10) between-group statistical comparison for at least one key outcome, and (11) point estimates and measures of variability provided for at least one key outcome.

rate, intention-to-treat analysis, statistical comparison between groups, and ≥1 key outcome estimated. Each item is scored as 0 (absent) or 1 (present). The total score is in the 0–10 point range after summing scores of all items. The study quality was classified as excellent (9–10 points), good (6–8 points), fair (4–5 points), and poor (<4 points).

Statistical Analysis

The Comprehensive Meta-Analysis program (version 2.2) was used for analyzing the extracted data. Since all extracted outcome data were continuous variables with variability between studies, standard mean differences (SMDs) were used for representing the ESs by calculating the mean change from baseline to post-intervention for the intervention and control groups. If there were two exercise groups (or control group) in one study, we halved the number of participants in the control group (or exercise group), while the mean and SD were unchanged. The random effects model, which can avoid the high risk of false-positive results, (28) was used with 95% confidence interval (CI) in overall ESs estimated. According to the Cochrane handbook, the ES was classified as small (0.2–0.49), moderate (0.50–0.79), and large (≥0.8) (29). A positive ES value indicated that the results were more favorable to the intervention group, otherwise the control group. Study heterogeneity was evaluated using the I^2 test, which was classified as three levels: low, moderate, and high heterogeneity with cutoff points ($I^2 = 25$, $I^2 = 50$, and $I^2 = 75\%$). We assessed the publication bias using Egger's regression test and Funnel plot. The Duval and Tweedie's trim and fill method was used to assess the potential impact of this publication bias. A two—side analysis with a significant level of 0.05 was used in all analyses.

Additionally, the continuous and categorical moderator analyses were performed using random effects model to investigate the influences of potential moderators on the overall ESs. Continuous moderators included mean age, exercise duration, and dose of exercise intervention (overall number of weeks of exercise × mean exercise frequency weekly × mean exercise time of each session in minutes). Potential categorical moderators included sex, diagnosis criteria, and exercise characteristics (exercise type, exercise frequency, exercise duration, exercise time, and exercise intensity). The coding of diagnosis criteria was categorized as the AWGS and EWGSOP. According to the classification of exercise prescription in a previous study (10), the type of exercise was coded as aerobic exercise, resistance exercise, and mixed exercises. Exercise frequency was coded as <3 and ≥3 times. Exercise duration was defined as ≤12 weeks (short term) and >12 weeks (long term) in this study. Exercise time was coded as <45 min (short) and 45–60 min (medium). Exercise intensity was coded from light to vigorous intensity according to the American College of Sports Medicine (30). The control group was coded as active control (e.g., nutrition, health education) and passive control (e.g., waitlist).

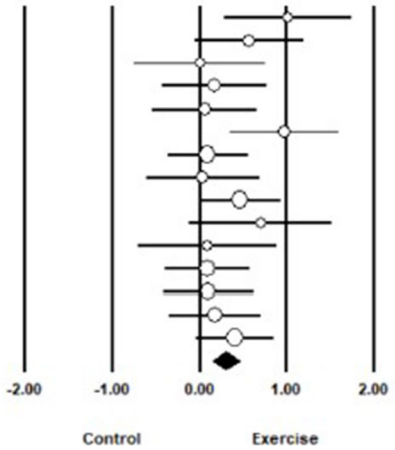
RESULTS

Search Results

Figure 1 depicts the process of study selection of this review. A total of 4,136 studies were retrieved from the electronic databases,

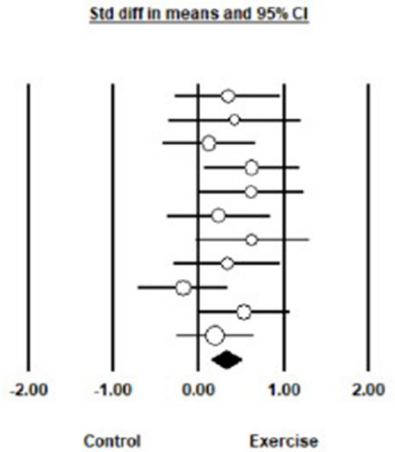
A Grip strength

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Chen 2018	1.01	0.37	0.14	0.28	1.73	2.73	0.01
Hassan 2016	0.57	0.32	0.10	-0.06	1.19	1.78	0.08
Iranzo 2018	0.00	0.39	0.15	-0.76	0.76	0.00	1.00
Kim 2013 1	0.16	0.31	0.09	-0.44	0.77	0.54	0.59
Kim 2013 2	0.06	0.31	0.09	-0.54	0.66	0.20	0.84
Lichtenberg 2019	0.97	0.32	0.10	0.34	1.60	3.01	0.00
Makizako 2020	0.09	0.24	0.06	-0.37	0.55	0.39	0.70
Maruya 2016	0.03	0.33	0.11	-0.62	0.68	0.09	0.92
Piastra 2018	0.46	0.24	0.06	-0.01	0.93	1.93	0.05
Tsekoura 2018 1	0.70	0.42	0.18	-0.12	1.52	1.66	0.10
Tsekoura 2018 2	0.08	0.41	0.17	-0.72	0.88	0.21	0.84
Vikberg 2019	0.08	0.25	0.06	-0.41	0.57	0.33	0.74
Yamada 2019 1	0.10	0.27	0.07	-0.42	0.63	0.38	0.70
Yamada 2019 2	0.17	0.27	0.07	-0.35	0.70	0.65	0.52
Zhu 2019	0.40	0.23	0.05	-0.05	0.85	1.73	0.08
	0.30	0.08	0.01	0.15	0.45	3.81	0.00



B Knee extension

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Hassan 2016	0.35	0.31	0.10	-0.27	0.96	1.10	0.27
Jung 2019	0.43	0.40	0.16	-0.35	1.20	1.07	0.28
Kim 2012 1	0.12	0.28	0.08	-0.42	0.66	0.44	0.66
Kim 2012 2	0.62	0.29	0.08	0.06	1.18	2.17	0.03
Kim 2013 1	0.62	0.31	0.10	0.00	1.23	1.97	0.05
Kim 2013 2	0.23	0.31	0.09	-0.37	0.84	0.76	0.45
Maruya 2016	0.63	0.34	0.11	-0.04	1.29	1.85	0.06
Wei 2016	0.34	0.32	0.10	-0.29	0.96	1.06	0.29
Yamada 2019 1	-0.18	0.27	0.07	-0.71	0.34	-0.69	0.49
Yamada 2019 2	0.54	0.27	0.07	0.01	1.07	1.99	0.05
Zhu 2019	0.19	0.23	0.05	-0.25	0.64	0.85	0.40
	0.32	0.09	0.01	0.15	0.50	3.67	0.00



C Chair and stand test

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Makizako 2020	0.43	0.24	0.06	-0.03	0.90	1.82	0.07
Tsekoura 2018 1	0.71	0.42	0.18	-0.11	1.53	1.69	0.09
Tsekoura 2018 2	0.44	0.41	0.17	-0.37	1.25	1.06	0.29
Vikberg 2019	0.33	0.25	0.06	-0.16	0.82	1.34	0.18
Wei 2016	0.88	0.33	0.11	0.23	1.53	2.65	0.01
Yamada 2019 1	0.05	0.27	0.07	-0.47	0.58	0.19	0.85
Yamada 2019 2	0.56	0.27	0.07	0.02	1.09	2.04	0.04
Zhu 2019	1.11	0.25	0.06	0.63	1.60	4.55	0.00
	0.56	0.13	0.02	0.30	0.81	4.31	0.00

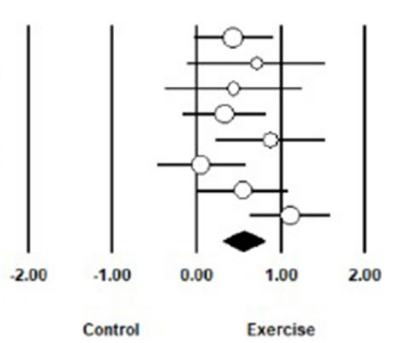


FIGURE 2 | Forest plot showing the effects of exercise vs. control on muscle strength: **(A)** grip strength, **(B)** knee extension, **(C)** chair and stand test.

TABLE 3 | Synthesized results for the effects of exercise vs control intervention.

Variables	*k*	*SMD*	95% CI	I^2%	Between-group homogeneity			Publication bias
					Q-value	df(*Q*)	*p*-value	Egger's test (*p*)
Muscle strength								
Grip strength	15	0.30	0.15–0.45	6	14.90	14	0.39	0.39
Knee extension	11	0.32	0.15–0.50	0	7.99	10	0.63	0.19
Chair and stand	8	0.56	0.30–0.81	36	10.95	7	0.14	0.86
Physical performance								
TUG	9	0.74	0.48–1.00	31	11.63	8	0.17	0.01
Gait speed	17	0.59	0.35–0.82	62	41.74	16	0.001	0.01
Body composition								
Skeletal mass index	11	0.37	0.15–0.58	16	11.90	10	0.29	0.92
ASM	13	0.31	0.13–0.49	20	15.07	12	0.24	0.21
Lean mass	4	0.20	−0.07 to 0.48	0	0.80	3	0.85	0.20
Body fat	5	0.24	−0.04 to 0.53	3	4.12	4	0.39	0.15
Fat-free mass	3	0.36	−0.10 to 0.82	0	0.36	2	0.84	0.39

ASM, appendicular skeletal muscle; SMD, standard mean difference; TUG, timed up and go; k, number of trials.

807 of them were excluded because of duplicates, and 107 full-text articles were identified for further confirmation after screening the titles or abstracts. Subsequently, the remaining 107 studies were reviewed for eligibility through reading the full-texts. Finally, 17 studies (31–47) were considered as eligible studies that were included in the meta-analysis.

Characteristics of Included Studies

The characteristics of the included 17 studies are summarized in **Table 1**. The included studies were published between 2012 and 2020, locating at 12 countries Australia (32), Spain (40), Korea (41), Germany (44), Iran (45), Japan (42, 43, 47), Italy (33), Malaysia (48), Austria (34), Greece (35), Sweden (36), and China (37, 39). A total of 985 participants with sarcopenia were included in the included 17 studies, and the mean age ranged from 67.6 to 86 years. Of note, the diagnostic sarcopenia was based on the two criteria, EWGSOP and AWGS. Eleven studies (31–33, 35, 37, 38, 40, 42, 43, 46, 47) used BIA, and six studies (34, 36, 39, 41, 44, 45) used dual-energy X-ray absorptiometry (DXA) to measure the body composition. A large proportion (74%) of females was evaluated in the included studies (7/17 studies were all females). Participants in the experimental group were given aerobic exercise, resistance exercise, or mixed exercises. These participants were concurrently given 30–60 min of exercise in each session, one to seven times per week for 8–36 weeks. Usual care or waitlist were provided in the control group. The outcomes in these 17 studies were grip strength, knee extension, chair and stand test, gait speed, timed up and go (TUG), appendicular skeletal muscle (ASM), skeletal muscle mass index (SMI), lean mass, body fat, and fat-free mass. There were no reports on side effects related to the exercises.

The results for methodological quality assessment are summarized in **Table 2**. The study quality scores ranged from 4 to 8, of which 88% of studies were rated as good quality, 12% of studies were rated as fair quality, and all studies were RCTs. The process of concealed allocation was used in seven studies. The methods of single- or double-blinding of assessor and intention-to-treat analysis were used in nine studies (34, 36, 38–40, 42–44, 46) and seven studies (31, 32, 38, 39, 41, 44, 46), respectively. As for the other characteristics, such as similarity on key measures at baseline, comparison with more than one outcome was fully reported in the included studies.

Synthetic Results

In terms of muscle strength (**Figure 2** and **Table 3**), there were 12 studies, including 15 parallel comparisons on exercise and control conditions (as three studies included two paired trials, respectively), on measuring the grip strength. A pooled comparison revealed that exercise intervention had significant improvement in grip strength (SMD = 0.30, 95% CI [0.15, 0.45], $I^2 = 6\%$, $p < 0.01$). Pooled results from eight trials revealed a significant improvement in chair and stand [SMD = 0.56, 95% CI (0.30, 0.81), $I^2 = 36\%$, $p < 0.01$] compared with the control group. Moreover, pooled analysis from 11 parallel trials showed a significant improvement in knee extension in favor of exercise intervention [SMD = 0.32, 95% CI (0.15, 0.50), $I^2 = 0\%$, $p < 0.01$) compared with the control group.

In terms of physical performance (**Figure 3** and **Table 3**), the pooled results showed that exercise produced significant improvements in TUG [SMD = 0.74, 95% CI (0.48, 1.00), $I^2 = 0\%$, $p < 0.01$], and gait speed [SMD = 0.59, 95% CI (0.35, 0.82), $I^2 = 62\%$, $p < 0.01$] compared with the control group.

In terms of body composition (**Figure 4** and **Table 3**), the meta-analysis presented that exercise had significant improvements in SMI [SMD = 0.37, 95% CI (0.15, 0.58), $I^2 = 16\%$, $p < 0.01$] and ASM [SMD = 0.31, 95% CI (0.13, 0.49), $I^2 = 20\%$, $p < 0.01$] compared with the control group, but there were no significant differences on lean mass [SMD = 0.20, 95% CI (−0.07, 0.48), $I^2 = 0\%$, $p = 0.15$], body fat [SMD = 0.24, 95% CI (−0.04, 0.53), $I^2 = 3\%$, $p = 0.09$], and fat-free mass [SMD = 0.36, 95% CI (−0.10, 0.82), $I^2 = 0\%$, $p = 0.13$] between the exercise group and control group.

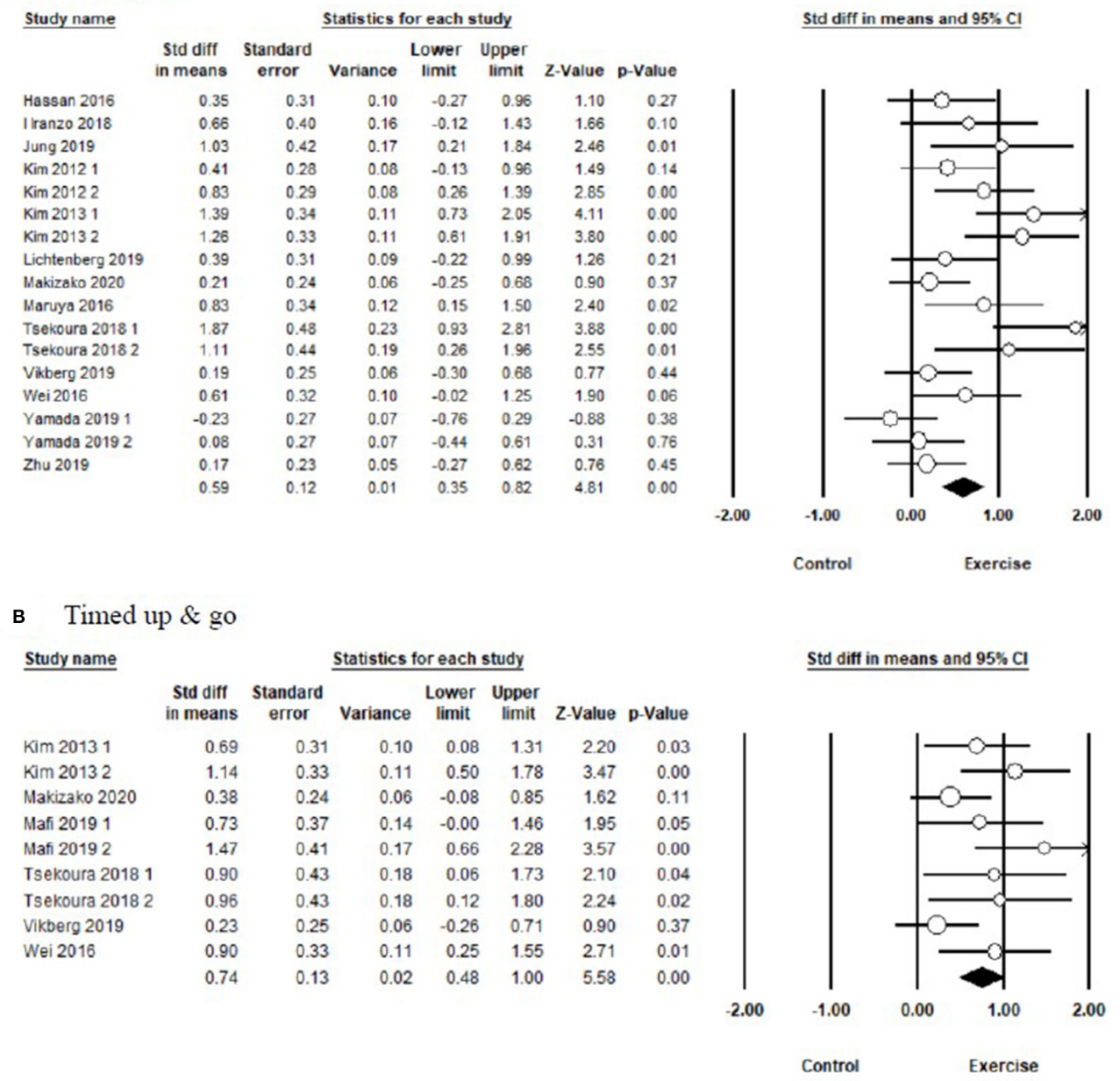


FIGURE 3 | Forest plot showing the effects of exercise vs. control on physical performance: **(A)** gait speed, **(B)** timed up and go test.

Moderator Analysis

To investigate the moderator effects of exercise on interested outcomes, moderator analyses were conducted according to the categorical and continuous variables in **Table 4**. The effects of exercise on TUG ($Q = 4.45$, $df = 1$, $p = 0.04$) and SMI ($Q = 7.90$, $df = 2$, $p = 0.02$) were significantly moderated by exercise intensity. Moderate–vigorous intensity [SMD = 0.81, 95% CI (0.57, 1.05), $p < 0.01$] of exercise significantly improved TUG compared with the high intensity [SMD = 0.23, 95% CI (−0.26, 0.71), $p = 0.37$] of exercise. The high intensity [SMD = 1.39, 95% CI (0.73, 2.06), $p < 0.01$] and moderate intensity [SMD = 0.41, 95% CI (0.10, 0.72), $p < 0.01$] of exercise significantly improved SMI compared with the light-to-moderate intensity [SMD = 0.29, 95% CI (−0.20, 0.79), $p = 0.25$] of exercise. In the meta-regression, the percent of female participants in the original studies was significantly associated with the gait speed ($\beta = 0.0096$, 95%CI: 0.0006 to 0.0186, $p = 0.03$) (**Figure 5** and **Table 5**) and skeletal muscle index ($\beta = -0.0092$, 95%CI: −0.0162 to −0.0021, $p = 0.01$) (**Figure 6** and **Table 5**). In addition, there were no significant moderator effects in age,

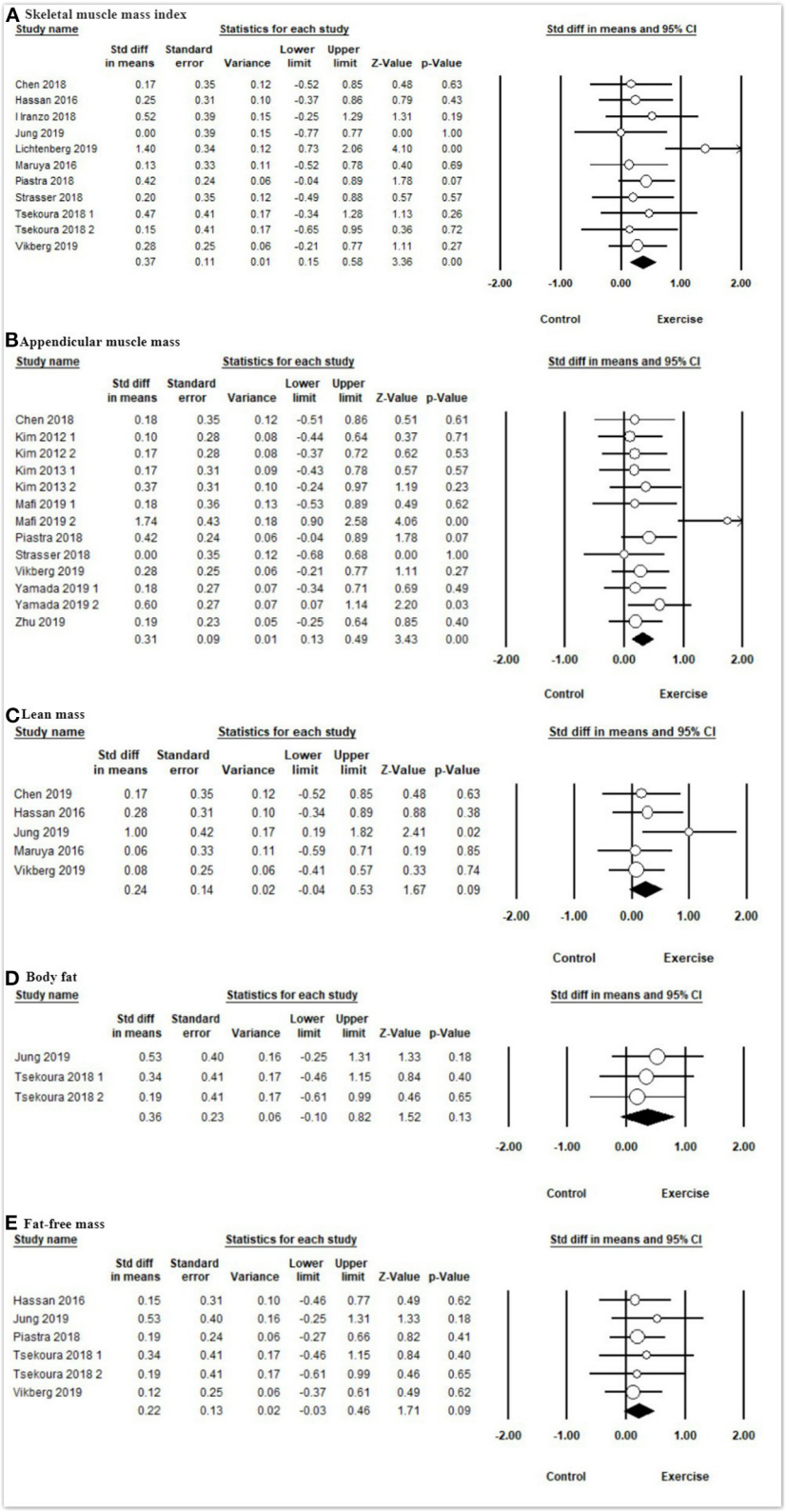


FIGURE 4 | Forest plot showing the effects of exercise vs. control on body composition: **(A)** skeletal muscle mass index, **(B)** appendicular muscle mass, **(C)** lean mass, **(D)** body fat, **(E)** fat-free mass.

TABLE 4 | Moderator analysis for the effects of exercise on measurement outcomes.

Variables	Muscle Strength			Physical Performance		Body Composition				
	Grip Strength	Knee Extension	Chair and Stand	TUG	Gait Speed	ASM	SMI	Muscle Mass	Lean Mass	BODY FAT
	SMD (95% CI)	SMD (95% CI)	SMD (95% CI)	SMD (95% CI)	SMD (95% CI)	SMD (95% CI)	SMD (95% CI)	SMD (95% CI)	SMD (95% CI)	SMD (95% CI)
Criteria										
AWGS	0.23 (0.03–0.43)	0.32 (0.13–0.51)	0.55 (0.11–0.98)	0.69 (0.26–1.13)	0.55 (0.23–0.88)	0.25 (0.05–0.44)	0.18 (−0.13 to 0.49)	0.08 (−0.21 to 0.36)	0.53 (−0.25 to 1.31)	0.36 (−0.18 to 0.91)
EWGSOP	0.41 (0.15–0.67)	0.34 (−0.10 to 0.78)	0.54 (0.22–0.87)	0.79 (0.43–1.16)	0.64 (0.28–1.00)	0.47 (0.00–0.94)	0.49 (0.18–0.80)	0.19 (−0.20 to 0.57)	0.16 (−0.14 to 0.45)	0.16 (−0.22 to 0.54)
Sex										
Female	0.39 (0.03–0.76)	0.39 (0.12–0.66)	–	0.91 (0.46–1.35)	0.95 (0.59–1.31)	0.25 (0.02–0.48)	0.27 (−0.07 to 0.62)	0.13 (−0.11 to 0.37	0.28 (−0.12 to 0.68)	0.55 (−0.26 to 1.37)
Male	0.97 (0.34–1.60)	–	–	1.08 (0.35–1.81)	0.39 (−0.22 to 0.99)	0.94(−0.59 to 2.48)	1.40 (0.73–2.06)*	–	–	–
Mixed	0.21 (0.03–0.39)	0.28 (0.05–0.51)	0.5 (0.30–0.81)	0.26 (0.26–0.86)	0.43 (0.15–0.70)	0.27 (0.03–0.50)	0.27 (0.02–0.52)	0.001 (−0.68 to 0.68)	0.13 (−0.25 to 0.52)	0.13 (−0.20 to 0.46)
Exercise type										
RT	0.33 (0.14–0.51)	0.32 (0.09–0.54)	0.31 (0.02–0.61)	0.80 (0.37–1.23)	0.50 (0.19–0.81)	0.33 (0.13–0.52)	0.54 (0.15–0.74)	0.11 (−0.11 to 0.34)	0.16 (−0.14 to 0.45)	0.16 (−0.17 to 0.49)
RT+AE	0.24 (−0.02 to 0.50)	0.35 (0.01–0.68)	0.71 (0.33–1.08)	0.59 (0.23–0.96)	0.92 (0.35–1.50)	0.19 (−0.25 to 0.64)	0.18 (−0.20 to 0.55)	–	0.53 (−0.25 to 1.31)	0.50 (−0.42 to 1.42)
WBV	–	0.34 (−0.29 to 0.96)	0.88 (0.23–1.53)	0.90 (0.25–1.55)	0.61 (−0.02 to 1.25)	–	–	–	–	–
Exercise frequency										
≥3 times/week	0.14 (−0.16 to 0.44)	0.46 (0.07–0.85)	0.72 (0.39–1.04)	0.79 (0.43–1.16)	0.85 (0.41–1.29)	0.68 (−0.18 to 1.55)	0.25 (−0.02 to 0.53)		0.24 (−0.18 to 0.65)	0.31 (−0.22 to 0.83)
<3 times/week	0.36 (0.16–0.55)	0.29 (0.10–0.48)	0.35 (0.06–0.64)	0.69 (0.26–1.13)	0.47 (0.19–0.85)	0.26 (0.08–0.43)	0.48 (0.06–0.90)	0.11 (−0.11 to 0.34)	0.18 (−0.19 to 0.55)	0.23 (−0.23 to 0.68)
Exercise duration										
>12 weeks	0.39 (0.12–0.65)	0.33 (0.02–0.65)	0.77 (0.11–1.44)	–	0.38 (0.02–0.75)	0.25 (−0.04 to 0.54)	0.28 (−0.01 to 0.58)	0.19 (−0.20 to 0.57)	0.18 (−0.19 to 0.55)	0.18 (−0.27 to 0.62)
≤12 weeks	0.27 (0.06–0.47)	0.32 (0.11–0.53)	0.44 (0.19–0.68)	0.74 (0.48–1.00)	0.63 (0.35–0.92)	0.34 (0.11–0.57)	0.43(0.08–0.79)	0.08 (−0.21 to 0.36)	0.24 (−0.18 to 0.65)	0.34 (−0.17 to 0.86)
Session time										
≤45min	0.14 (−0.09 to 0.37)	0.31 (−0.07 to 0.68)	0.44 (0.19–0.68)	0.66 (0.25–1.06)	0.55 (0.15–0.96)	0.35 (0.05–0.64)	0.29 (−0.01 to 0.59)		0.12 (−0.37 to 0.61)	0.07 (−0.31 to 0.46)
>45min	0.41 (0.19–0.65)	0.34 (0.12–0.56)	0.77 (0.11–1.44)	0.82 (0.44–1.19)	0.62 (0.33–0.92)	0.30 (0.07–0.53)	0.42 (0.04–0.79)	0.11 (−0.11 to 0.34)	0.24 (−0.09 to 0.58)	0.43 (−0.04 to 0.90)
Exercise intensity										
Light	0.22 (−0.01 to 0.45	0.27 (−0.08 to 0.61)	0.58 (0.03–1.20)	–	0.24 (−0.11 to 0.59)	0.31 (0.02–0.60)	0.29 (−0.20 to 0.79)	–	–	0.06 (−0.59 to 0.71)

(Continued)

TABLE 4 | Continued

Variables	Muscle Strength			Physical Performance		Body Composition				
	Grip Strength	Knee Extension	Chair and Stand	TUG	Gait Speed	ASM	SMI	Muscle Mass	Lean Mass	BODY FAT
	SMD (95% CI)	SMD (95% CI)	SMD (95% CI)	SMD (95% CI)	SMD (95% CI)	SMD (95% CI)	SMD (95% CI)	SMD (95% CI)	SMD (95% CI)	SMD (95% CI)
Moderate-vigorous	0.35 (0.09–0.61)	0.38 (0.13–0.62)	0.58 (0.26–0.90)	0.81 (0.57–1.05)	0.82 (0.48–1.16)*	0.32 (0.06–0.59)	0.30 (0.03–0.56)*	0.11 (−0.11 to 0.34)	0.18 (−0.189 to 0.552)	0.16 (−0.22 to 0.54)
Vigorous	0.50 (−0.37 to 1.37)	0.43 (−0.35 to 1.20)	0.33 (−0.16 to 0.82)	0.23 (−0.26 to 0.71)	0.44 (0.01 to 0.87)	0.28 (−0.21 to 0.77)	0.56 (−0.23 to 1.35)	–	0.24 (−0.18 to 0.65)	0.55 (−0.26 to 1.37)
Control group										
Active	0.30 (0.08–0.53)	0.28 (0.01–0.54)	0.31 (0.001–0.61)	0.70 (0.41–1.00)	0.76 (0.38–1.15)	0.23 (0.04–0.41)	0.48 (0.13–0.83)	0.14 (−0.14 to 0.42)	0.22 (−0.09 to 0.53)	0.48 (−0.41 to 1.38)
Passive	0.30 (0.07–0.53)	0.38 (0.13–0.63)	0.74 (0.41–1.06)	0.85 (0.24–1.46)	0.34 (0.12–0.56)	0.61 (0.03–1.20)	0.21 (−0.10 to 0.52)	–	0.15 (−0.46 to 0.77)	0.17 (−0.20 to 0.55)

*$p < 0.05$.

AE, aerobic exercise; ASM, appendicular skeletal muscle; AWGS, Asia Working Group for Sarcopenia; EWGSOP, European Working Group on Sarcopenia in Older People; RT, resistance training; TUG, timed up and go; WBV, whole-body vibration training.

percent of female participants, exercise times per week, exercise duration, and dose of exercise intervention. Results of meta-regression are shown in **Table 5**.

Publication Bias

Publication bias was evaluated using Egger's test (in **Table 3**) and Funnel plot (in **Supplementary Figures**). Of which, although the asymmetrical Funnel plot and Egger's test (Egger's regression intercept = 6.13, $p < 0.05$), the Duval and Tweedie's trim and fill showed that five studies were missing on the left side of the mean effect. The adjusted value was SMD = 0.35, 95% CI (0.08, 0.61), which was substantially lower than our estimation (SMD = 0.59). There seems to be evidence for publication bias in this meta-analysis since studies with smaller effect sizes are not provided.

DISCUSSION

The present systematic review and meta-analysis consisting of 17 RCTs (985 individual participants, 726 female, with sarcopenia) investigated the effects of exercises on muscle strength, physical performance, and body composition. The main findings of this systematic review with meta-analysis showed that exercises had significant benefits on muscle strength (grip strength, knee extension, and chair-stand), physical performance (timed up and go, and gait speed), and body composition (skeletal muscle mass index and appendicular skeletal muscle) compared with the control group in older adults with sarcopenia. The effects of exercise on gait speed and SMI were moderated by sex in the study and exercise intensity. These results may be important for implementing exercise interventions for sarcopenic older adults in clinic.

Since the differences in diagnostic criteria for sarcopenia, according to different organizations, the EWGSOP updated the definition and diagnostic criteria in 2008. This definition highlights that muscle strength is a principal element in sarcopenia diagnosis and is a useful predictor of adverse outcomes in people with sarcopenia (2). The EWGSOP and AWGS recommend that handgrip strength and chair-stand test are suitable measures of muscle strength. In our study, muscle strength was measured using the handgrip strength, chair stand test, and knee extension strength. The findings from this meta-analysis demonstrated that after exercise, older adults with sarcopenia demonstrated significant improvements in muscle strength. More specifically, exercises had small effects for grip strength (15 trials, ES = 0.31) and knee extension strength (11 trails, ES = 0.36) and moderate effect for chair and stand (eight trials, ES = 0.56) compared with the control groups, respectively. Consistent with previous meta-analysis and systematic reviews (49, 50), exercise has significant effects on muscle strength in older adults. Increased muscle strength may be associated with the neuronal adaptations, such as increases in muscle fiber tissue or synchronization of muscle contractions (51). During exercise training, muscle fiber are re-structured, leading to an increase in neuronal activity that stimulates an increase in muscle strength (52).

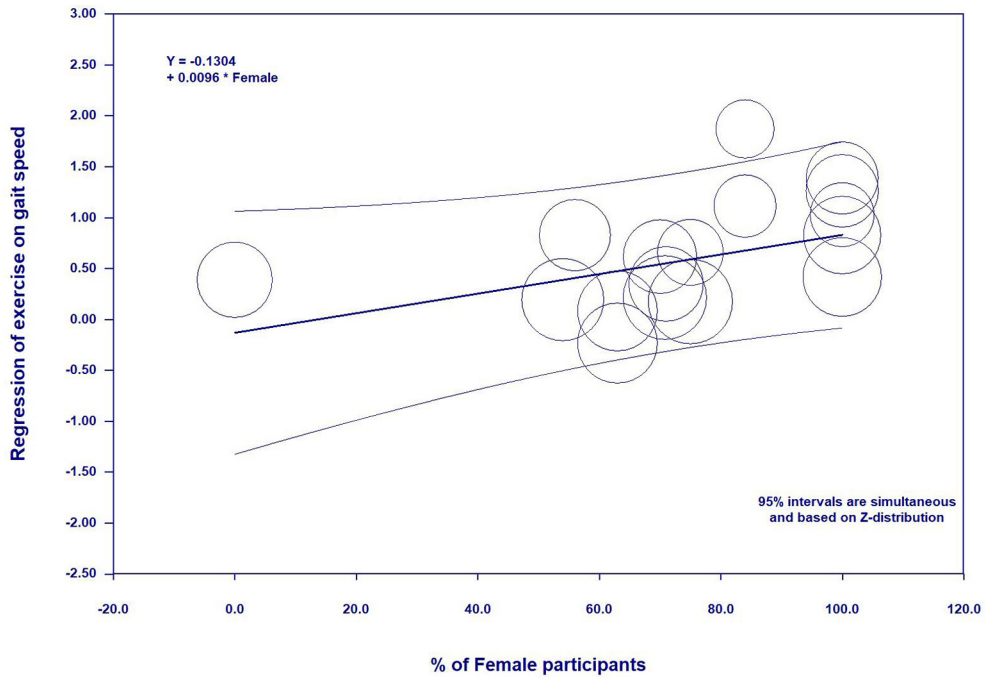


FIGURE 5 | Effect sizes by percent of female participants in meta-regression for gait speed.

In regard to physical performance, the common testing tools include gait speed and TUG. Previous studies have demonstrated that poor physical performance, similar to low muscle strength, is associated with a higher risk of death in older adults (53, 54). The latest EWGSOP consensus recommends using physical performance to assess the severity of sarcopenia. Herein, gait speed and TUG were used to measure the physical performance in this review study. Our meta-analysis found that exercise's benefit is improving gait speed and TUG, and the positive effects can be supported by a previous review study targeting older adults (55). These meaningful results are of great importance because there is a close relationship between muscle strength and physical performance (56). Consistent with another similar study, the study of Capodaglio et al. on older adults over 75 years found that significant improvements in walking ability and TUG were attributed to the improved lower limb strength after exercise training (57). Thus, our findings reinforce the important role of exercise in physical performance in older adults with sarcopenia.

With reference to the body composition, in particular, the use of DXA or BIA to measure skeletal muscle mass and appendicular skeletal muscle mass has been considered as an important approach to assess the muscle quantity or quality to identify sarcopenia in the latest consensus (2). On this basis, our meta-analysis study indicated that the SMI and ASM have been significantly improved after exercise in sarcopenic older adults, which was inconsistent with previous systematic reviews (22, 58). The possible reason is that the improved muscle mass indicates an anabolic potential of exercise, inducing muscle hypertrophy via resistance exercise or aerobic exercise such as cycling and walking among all of ages (59). More importantly, improved skeletal muscle mass might be attributed to the increase in size of slow muscle fibers (60) and the increase in fast-twitch fiber sizes (61). Moreover, the statistical power in our study was augmented through including more eligible studies than previous meta-analysis studies (22, 58). Thus, it is believed that older adults with sarcopenic can improve their muscle mass through appropriate exercise.

In addition, the moderator analyses revealed that moderate to vigorous intensity exercise (ES = 0.81) could produce greater effects on TUG than did vigorous intensity exercise (ES = 0.23). This result may be inconclusive due to the small number of included studies investigating vigorous intensity exercise and the different methods on coding intensity exercise in the subgroup. Actually, a recent systematic review study has documented that both moderate and vigorous intensity exercises can improve functional ability in frail older adults (55). Future research is warranted to determine the effect of exercise at different intensities on physical performance. As for SMI, after practicing exercise at moderate and vigorous intensity, sarcopenic adults had significant improvement in their SMI compared with those practiced exercise at low intensity. This finding is similar to a previous study by Csapo et al., in which they found that high-intensity exercise had more advantage on increasing skeletal muscle mass than low-intensity exercise in older adults (19). Indeed, moderate to high-intensity exercise enhances the skeletal muscle mass via stimulating protein synthesis (62). On the

TABLE 5 | Meta-regression for continuous variables to predict exercise effects on measurement outcomes.

Variables	Muscle strength			Physical performance		Body composition				
	Grip strength β (95% CI)	**Knee extension β (95% CI)**	**Chair stand test β (95% CI)**	**TUG β (95% CI)**	**Gait speed β (95% CI)**	**ASM β (95% CI)**	**SMI β (95% CI)**	**Muscle mass β (95% CI)**	**Lean mass β (95% CI)**	**Body fat β (95% CI)**
Age	−0.0089 (−0.0364 to 0.0186)	−0.0110 (−0.0474 to 0.0254)	−0.0255 (−0.0765 to 0.0255)	0.0069 (−0.0618 to 0.0759)	−0.0252 (−0.0758 to 0.0254)	−0.0134 (−0.0443 to 0.0174)	0.0117 (−0.0249 to 0.0483)	−0.0210 (−0.0726 to 0.0306)	0.0007 (−0.0438 to 0.0452)	0.0023 (−0.0100 to 0.0146)
Percent of female participants	−0.0021 (−0.0087 to 0.0045)	0.0025 (−0.0078 to 0.0128)	0.0018 (−0.0072 to 0.0438)	−0.0012 (−0.0094 to 0.0071)	0.0096 (0.0006 to 0.0186) *	−0.0051 (−0.0107 to 0.0004)	−0.0092 (−0.0162 to −0.0021) *	0.0144 (−0.0661 to 0.0949)	0.0036 (−0.0098 to 0.0170)	0.0096 (−0.0048 to 0.0240)
Exercise time per week in minutes	0.0021 (−0.0014 to 0.0056)	0.0021 (−0.0018 to 0.0060)	−0.0004 (−0.0083 to 0.0075)	0.0016 (−0.0041 to 0.0072)	0.0046 (−0.0009 to 0.0101)	0.0024 (−0.0033 to 0.0082)	−0.0055 (−0.0124 to 0.0014)	—	−0.0011 (−0.0398 to 0.0179)	−0.0010 (−0.0110 to 0.0089)
Exercise duration	0.0063 (−0.0129 to 0.0255)	0.0011 (−0.0305 to 0.0328)	−0.0141 (−0.0657 to 0.0378)	−0.0292 (−0.2068 to 0.1485)	−0.0172 (−0.0705 to 0.0362)	−0.0037 (−0.0255 to 0.0182)	−0.031 (−0.0275 to 0.0213)	0.0073 (−0.0150 to 0.0297)	−0.0012 (−0.0255 to 0.0231)	−0.0049 (−0.0522 to 0.0425)
Dose of exercise intervention	0.00000 (−0.0001 to 0.0001)	0.0001 (−0.0001 to 0.0002)	0.0001 (−0.0002 to 0.0003)	0.0004 (−0.0005 to 0.0014)	0.0001 (−0.0002 to 0.0003)	−0.0001 (−0.0002 to 0.0002)	−0.0001 (−0.0002 to 0.0001)	0.0001 (−0.0001 to 0.0002)	−0.00001 (−0.0002 to 0.0002)	−0.00001 (−0.0003 to 0.0002)

*$p < 0.05$.

ASM, appendicular skeletal muscle; SMI, skeletal muscle mass index; TUG, timed up and go; –, the continuous variable in each study is equivalent.

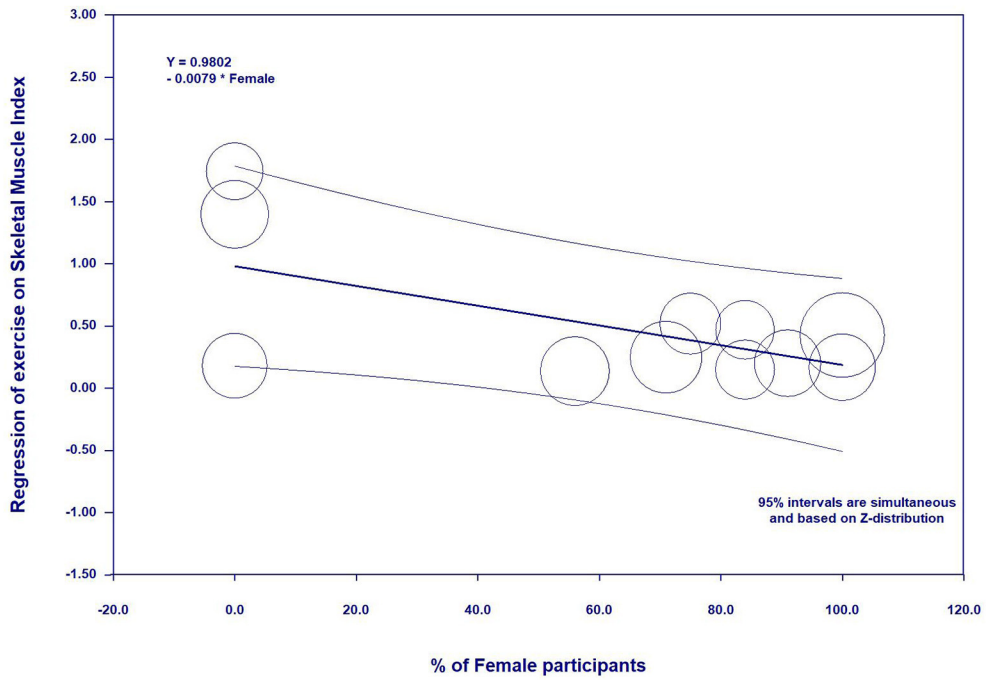


FIGURE 6 | Effect sizes by percent of female participants in meta-regression for skeletal muscle index.

contrary, lack of stimulation of the protein synthesis in muscle is related to low-intensity exercise, and it is recommended to increase skeletal muscle mass by compensating for more repetitions and velocity of motion (63). Despite this, it is recommended to explore the underlying mechanism of effects of exercise at different intensities

Additionally, the meta-regression revealed gender-specific effects on exercise-related changing in gait speed and SMI, implying a tendency that female participants had more improvements in gait speed and SMI than male participants after practicing exercise. The explanations for this findings may be attributed to external confounding (e.g., completed quality and motivation of the participants) that might affect the results (36). Based on this hypothesis, gender-specific effects did contribute to significant differences on other outcomes, such as grip strength, chair and stand, TUG, etc. Further studies are warranted to investigate the gender difference on the effects of exercise on physical performance and skeletal muscle mass.

Our systematic review and meta-analysis have some strengths that should be noted. All studies included in this meta-analysis were RCTs, which provided the empirical data for understanding the evidence of a treatment's efficacy. Furthermore, participants in this present study were only sarcopenic older adults without other physical conditions, like not being obese; so our research findings can be applied to the prevention or treatment in this sarcopenia population. Additionally, other potential confounders were examined to find whether they had any influence on the effects of exercise. This novelty could provide more information for future research to look at the influences of these confounders.

There are, however, several limitations in our study. First, as there were no consistent assessment criteria for sarcopenia, participants who met the initial sarcopenia defined by the EWGSOP and AWGS were included in our study. It may result in publication bias. Herein, according to the latest operational definition of sarcopenia (e.g., EWGSOP, AWGS), uniform cutoff points are expected to diagnose the subject and measure the outcomes in the future study. Second, the included studies used different instruments to measure the interested outcomes such as body composition (e.g., BIA, DEXA), which will contribute to the effect size of outcomes. While both of them used to examine the sarcopenia in clinical research, which is suggested by EWGSOP and AWGS, the multifrequency BIA equivalent to the DEXA measurements could be used in future research so as to ensure the accuracy of the diagnosis. Moreover, confirming the effect of exercise on interested outcomes by analyzing different instruments used to measure muscle mass separately is warranted. Third, studies using a sole exercise intervention to treat sarcopenia were included, excluding studies combing exercise intervention and nutrition. As a source of muscle synthesis, nutrient intake methods are important for the prevention and treatment of sarcopenia. There is a need for further research that examines the effect of combined exercise and nutrition intervention on sarcopenia. Four, the percentage of the female participants (female 74%) was considerably high compared with male participants, and the findings may not generalize all populations. As a result, further study may benefit from investigating the effects of exercise on sarcopenia in males and females separately due to physical difference in gender.

CONCLUSION

These meta-analysis results suggest that exercise interventions have positive effects on muscle strength, physical performance, and skeletal muscle mass for sarcopenic elderly, but no effect is found in body composition (e.g., fat mass, lean mass, and fat-free mass). Further researches need to use the latest consensus criteria proposed by EWGSOP or AWGS to identify the sarcopenia, and a larger number of studies are recommended to confirm our findings. Meanwhile, the effective exercise protocol should be designed as promoting strategies in treating sarcopenia.

DATA AVAILABILITY STATEMENT

The original contributions generated for the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

YZ and WS conceptualized the study. YZ, LZ, JB, and XL handled the methodology. YZ, S-TC, DK, and XL were in charge of the software. DK, XL, and WS did the validation. YZ, LZ, and S-TC performed the formal analysis. YZ, LZ, S-TC, and JB conducted the investigation. YZ and XL were in charge of the resources. YZ, JB, and XL did the data curation. YZ, LZ, and XL prepared and wrote the original draft. LZ and WS reviewed, edited, and wrote the manuscript. YZ, S-TC, and DK did the visualization. WS was in charge of the supervision and project administration. All authors have read and agreed to the published version of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.649748/full#supplementary-material

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REVIEW
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Musculoskeletal Changes Across the Lifespan: Nutrition and the Life-Course Approach to Prevention

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Aging is characterized by the progressive decline of muscle mass and function, the so-called sarcopenia. Also bone loss is widespread among older people. Sarcopenia and osteopenia/osteoporosis are associated with several adverse outcomes including falls, risk of fractures, functional decline, frailty, and mortality. Recently, the life-course approach to prevent or delay functional decline has become very popular. Regarding musculoskeletal health, there is suggestive evidence that acting during critical or sensitive periods of life in which each person build-up its biological reserves may influence the rate of functional decline in the later stages of life. A life-course approach to musculoskeletal health should take place during early life when plasticity allows more easily the attainment of the peak of the musculoskeletal system driven by environmental stimuli. The rate of the subsequent decline will depend on the peak previously reached. Nutrition and physical exercise are important environmental factors that can influence musculoskeletal development by favoring and maintaining peak bone and muscle mass and strength. Here we provide an overview of body composition changes occurring across the lifespan and strategies based on nutrition and physical exercise to support musculoskeletal health as well as minimizing losses during older life.

Keywords: aging, sarcopenia, bone, obesity, frailty, inflammation, early life, exercise

HIGHLIGHTS

- Geriatrics and Pediatrics are commonly seen in antithesis as they occupies the two extremes of life
- During early life each person rapidly accumulates his/her functional capacities in body functions or structures to reach a peak or a plateau at maturity
- Maintaining musculoskeletal health and preventing early losses is pivotal during adult life
- In older life, minimizing losses is crucial
- Implementing a holistic approach, based on nutrition and physical exercise, that people can apply during the life course may optimize the functional ability during aging.

INTRODUCTION

People are living longer but only a few years are still lived without disability (1). The traditional models of care, which were built and remain centered on single disease treatment, are unprepared to manage the complexity of older individuals characterized by chronic comorbidities and mutually interacting syndromes (2, 3). Indeed, there is a need for a more comprehensive and appropriate assessment of the aging population. Advancing age is accompanied by a progressive decline in many functions which cannot be explained by chronological age per se. Sarcopenia, defined as the progressive loss of muscle mass and strength (4), is one of the most serious health concerns in older people. However, sarcopenia can also occur earlier in life in combination with a variety of health conditions. Furthermore, genetic and environmental factors acting during the life-course may influence the decline of muscle mass and strength commonly seen with aging (5).

Phenotypic changes occur very quickly during the first years of life, then stabilize during young adulthood, and accelerate once again with aging (6). During early life, each person accumulates his/her biological reserves which influence the degree of functional ability during older adulthood (7). In the last decade, the life-course approach to prevent or delay functional decline has become very popular (1). The life course approach encompasses both biological and environmental factors acting during gestation, childhood, adolescence and adulthood and their influence in health status, functions and diseases during older life (8). Implementing a holistic approach to prevention that people can apply during their lifetime may optimize functional ability trajectory during aging (9). Recently, the World Health Organization (WHO) introduced the concept of intrinsic capacity which is defined as the composite of all physical and mental capacities that an individual can draw upon the lifetime (10). This new construct may potentially change the current conduction of clinical practice, shifting from a disease-centered toward a function-centered approach (11). In the context of intrinsic capacity, vitality represents the biological background of every individual encompassing complex and dynamic biologic systems which sustain life and functioning. The capacity of any individual expressed by cognitive, locomotor, sensory, psychological domains, is the phenotypical and functional manifestation of this biological background. Based on this concept, designing trajectories of capacity could ideally allow intercepting early influences on late life, and, consequently, implement a personalized plan of intervention (12).

Nutrition, an important contributor to the vitality domain, is a key determinant of health in all age groups, beginning from pregnancy and early childhood and extending throughout the lifespan (6). The quality of the diet over the life-course has been closely related to the incidence of sarcopenia (13). Indeed, (early) nutritional interventions may be able to reduce the incidence of sarcopenia or revert it, potentially improving the individual's intrinsic capacity (11, 13). In other words, it has been repeatedly proposed that inadequate early nutrition may lead to the impaired development of repair systems, suggesting that rates of aging may be determined at the very earliest stages of the life (14).

Geriatric and pediatric specialties occupy the two extremes of life, without formal connections (15). However, both pediatricians and geriatricians look at the person's health in a multidimensional way. As early as 1914, Ignatz Nascher defined senility as a "second childhood". Nascher stated that no function, organ, or tissue looks exactly within these two periods of life. Indeed, aging is not a regressive process but a progressive one. However, older people show frequently reliance on others (especially those who are frail or institutionalized) as well as pediatric ones. This review article is intended to close the gaps between the two specialties by providing an overview of changes in body composition occurring during the lifetime with a special focus on specific nutrition and physical activity intervention strategies throughout the lifetime, aimed at preventing and delaying the functional decline in musculoskeletal system seen with the aging process.

MUSCULOSKELETAL CHANGES

Both muscle and bone are highly malleable tissues responding to the environment during the life-course. The two tissues that develop during adolescence, reach a peak in density around the third decade of life, which is maintained in midlife and then declines with aging (16, 17). With aging, there is a progressive decline in muscle mass, strength, and functionality, the so-called "sarcopenia". In fact, after the fourth decade of life, there is a progressive decline in muscle mass (i.e., 1–2% per year) and strength (i.e., 1.5% per year) (18). However, it has been suggested that muscle mass and strength in older people does not reflect only the rate of loss but also the peak reached during early life (19). In particular, adolescence represents a window of opportunity for musculoskeletal health since this period is characterized by profound changes in body composition resulting in the rapid accretion of both bone and muscle mass. These changes are largely driven by hormonal factors and differ between genders. Indeed, in males the highest levels of testosterone and IGF-1 determine a largest increase in both muscle mass and strength compared to females (20). Despite the timing of pubertal events varies widely among individuals, in females the largest increase in fat-free mass is observed nearly at the age of 15, while in men between 12 and 15 years of age. In both genders, a rapid increase in total body fat is seen but in males is less marked given the concomitant fastest accretion in fat-free mass (21).

There are several mechanisms that concur to the development of sarcopenia. These include malnutrition, physical inactivity, hormonal changes, inflammation, increased catabolism, and anabolic resistance, myocyte's loss, reduced satellite cell number and function, loss of α-motor neurons, mitochondrial dysfunction, and insulin resistance (22, 23). Particularly, insulin resistance through reducing the ability to use the available proteins may result in metabolic alterations associated with type 2 diabetes further exacerbated by sarcopenia (23–25). Interestingly, it has been reported a positive association between

birth weight and both muscle mass and strength, which is even maintained during the lifespan (26, 27). Additionally, low birth weight has been consistently associated with type 2 diabetes later in life (28). Indeed, these findings could provide an additional explanation for the association between low birth weight and the incidence of sarcopenia during aging probably through the mediation of insulin resistance. Also genetic and other early life factors (i.e., early growth, longer duration of breastfeeding) have been associated with muscle mass and strength (29). Other than birth weight, it has been reported that also prepubertal and pubertal growth may influence both muscle strength and physical performance later in life (i.e., midlife) (30, 31).

In recent years, above all, inflammation and mitochondrial dysfunction received particular attention as a major determinant of sarcopenia (32, 33). The detrimental effects of persistent inflammation and mitochondrial damage are seen in a variety of pathological conditions characterized by metabolic alterations including diabetes, insulin resistance, and cardiovascular diseases (32). The accumulation of mitochondrial damage and a chronic inflammatory state along with oxidative stress during the lifespan may be the precursors of a variety of age-related metabolic diseases. Indeed, inflammatory status could be regarded as a function of an individual, an early determinant of the aging process which is impacted by diet (6).

On the other hand, bone mass steadily increases during childhood, then rapidly accelerates during adolescence to reach a peak at around 20 years of age (34, 35). However, given the increased levels of estrogens, adolescent females experience a more rapid increase in bone mass than males (20). After the age of 60, a progressive decline in bone mineral density (BMD) of nearly 1–1.5%/year is seen (36). By the age of 70, bone mass is reduced by nearly 30–40% (37, 38). In midlife women, the most important risk factor for bone loss is menopause, since after that the normal bone turnover cycle is impaired by estrogen deficiency, which explains the more pronounced bone loss in the female gender compared to males (20). In particular, across the lifespan women experience a loss of about 50 and 30% of trabecular and cortical bone respectively. Nearly half of the overall bone loss in women is experienced during the first 10 years after menopause (38, 39). According to the WHO criteria, bone loss is defined by the so-called "T-score", a standardized measure that compares BMD to the average values of young healthy women. Indeed, osteopenia is defined by a T-score between −1 and −2.5 while osteoporosis by a T-score $\leq$-2.5 (40). Osteopenia and osteoporosis are also too prevalent conditions during aging (16). Not surprisingly, osteoporosis and sarcopenia frequently occur simultaneously, even leading to the creation of a so-called "osteosarcopenia" condition. Like every other age-related condition, osteoporosis and sarcopenia show a common background in the biology of aging (16). To date, physical inactivity, as well as nutritional deficiencies, may lead to a decline of both tissues (36). Additionally, inflammatory states, endocrine alterations, fat infiltration, metabolic derangements, vitamin D deficiency, comorbidities, and genetic factors are all involved in the pathogenesis of both conditions (i.e., muscle and bone loss) (41). Interestingly, it has been reported that genetic traits determining the peak of bone and muscle mass during early life, may influence the trajectory of both tissues late in life. Across the lifespan, hormonal dysfunctions (i.e., low levels of testosterone in men and estrogen in women) are also known to negatively affect both muscle and bone (16, 42).

ADIPOSE TISSUE CHANGES

Adipose tissue is a fundamental component of body composition and not only an inert body fat storage. In fact, adipose tissue is today recognized as an active endocrine organ mediating several metabolic processes and secreting a variety of adipokines and cytokines regulating systemic inflammation (43). As a consequence, adipose tissue abnormalities may have long-term negative effects on musculoskeletal health probably through the mediation of inflammatory processes, metabolic dysregulation, and altered insulin sensitivity (44–47). Alterations of adipose tissue composition can occur as early as during fetal life and can persist during adulthood (47). Indeed, there is evidence that high birth weight, the so-called fetal macrosomia, is associated with the development of alterations in body composition (i.e., obesity) during adulthood potentially contributing to muscle decline (47, 48). During infancy and early childhood, particular attention should be paid to the growth acceleration. Regarding adipose tissue, it is important to monitor the BMI growth curve which typically is described as *U*-shaped. Infant's BMI tends to reach a peak at around 6–9 months of age and then progressively decreases until 5–7 years of age, from then the BMI curve gradually increases once again delineating the so-called "adiposity rebound" (49, 50). Over time, several studies reported an association between an earlier adiposity rebound and an increased risk of being obese during adulthood as well as a close relationship with non-communicable diseases (49, 51, 52). The complex relationship between body composition alterations during early life and the long-term health effects can be explained by the so-called "thrifty phenotype hypothesis" (**Figure 1**).

Accordingly, poor nutrition during early life may results in a relatively down-expression of the functional units within splanchnic organs (in particular, pancreas and liver). Therefore, it has been associated with endocrine and metabolic adaptations of the fetus to survive (e.g., low vs. high glucose and energy supply). These adaptations, matched with a higher than programmed energy intake and unfavorable lifestyles in the later phase of life, may further accentuate negative processes, including fat accumulation in organs (i.e., liver) and lean tissue (i.e., muscles). Altogether, these phenomena lead to a consequent decrease in insulin sensitivity and glucose tolerance and reduced muscle mass (46, 54, 55). Adiposity trajectories of z scores (weight-for-height and BMI) have been significantly associated with higher fasting insulin and homeostasis model assessment of insulin resistance (i.e., HOMA-IR). In particular, higher insulin resistance at 14 years of age have been reported in those subjects in which adiposity remained high (56). Lawlor et al. (57) reported that low birth weight, low offspring birth weight, short leg length, high adult BMI, and greater adult waist-to-hip ratio were all independently associated with adult insulin resistance. On contrary, another study has not found associations between birth

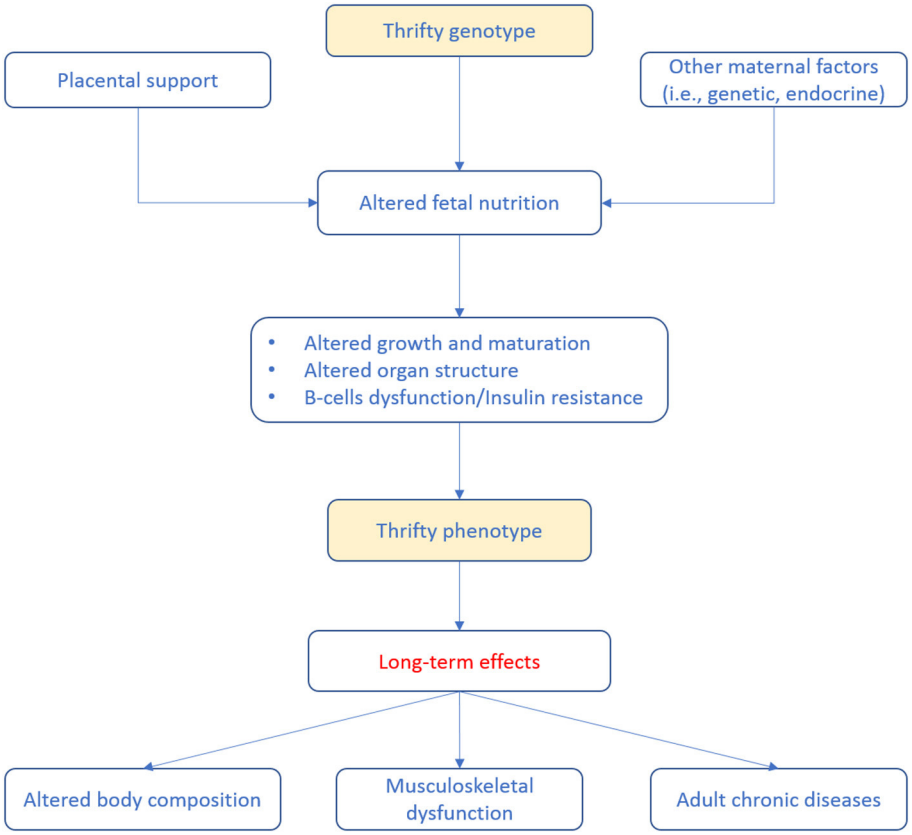

FIGURE 1 | Life-course events predisposing to adult diseases according to the so-called thrifty phenotype hypothesis (53). Poor infant growth, as a consequence of in utero undernutrition, may lead to alterations in glucose-insulin metabolism that, coupled to the effects of obesity, aging and physical inactivity, promotes the development of adult diseases.

weight and HOMA-IR, while reported that adult lifestyle and body composition were associated with larger variances in insulin secretion and HOMA-IR (58). It has been widely reported that overweight and obese children are more likely to have these conditions during adulthood, with early development of chronic diseases (i.e., type 2 diabetes and cardiovascular diseases) (59–61) and a negative impact on musculoskeletal health (47).

Regarding older life, concomitantly to muscle mass decline, there is also a progressive increase in adipose tissue. Body fat distribution changes too, with an increase in visceral abdominal fat compared to the subcutaneous abdominal fat (62). Additionally, aging is also associated with fat infiltration of the muscle and bone marrow inducing apoptosis of the myocytes and osteocytes (36). Intramuscular fat infiltration, given its lipotoxic effects, can exert detrimental effects on muscle strength and quality also affecting mobility function (63, 64). Chronic low-grade systemic inflammation, which represents a hallmark of aging, has been indicated as one of the main factors responsible for muscle decline in older people (65). Indeed, the abnormal secretion of these inflammatory mediators by the adipose tissue may further exacerbate the muscle decline in those individuals with obesity. Interestingly, it has been suggested that pro-inflammatory processes occurring during the life-course may determine the inflammatory trajectory later in life (66), thus potentially influencing musculoskeletal health in older life. Therefore, obesity and chronic inflammation should be managed with earlier interventions aimed at targeting early modifiable factors given their negative effects on musculoskeletal health later in life.

INTERVENTIONS

There is suggestive evidence that acting during critical or sensitive periods of life in which each person build-up its biological reserves may influence the rate of functional decline in the later stages of life. The life-course approach to musculoskeletal health should begin during early life when plasticity allows more easily the attainment of the peak of the musculoskeletal system driven by environmental stimuli. However, some lifestyle factors during adulthood also play an active role in maintaining musculoskeletal health and minimizing musculoskeletal decline. Indeed, the rate of the subsequent decline will depend on the peak previously reached,

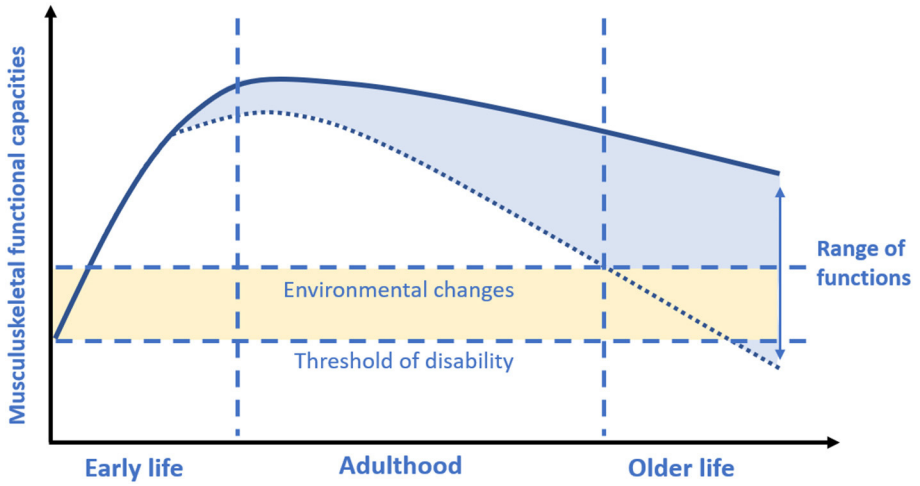

FIGURE 2 | Musculoskeletal functional capacities across the lifespan. Based on concepts and findings by Kuh (7), Sayer et al. (19), and Cruz-Jentoft et al. (17). During early life each person rapidly accumulates his/her functional capacities in body functions (i.e., muscle) or structures (i.e., bone mass) to reach a peak or a plateau at maturity (i.e., nearly at the end of adolescence period). Afterwards, gradually starts a decline with age. The greater the peak, the slower the consequent decline. However, it should be considered that the rate of decline may be also largely driven by environmental factors during adult life.

but also on strategies promoting muscle and bone health later in life (67) (**Figure 2**).

Among various interventions that can be implemented, nutrition and physical exercise seem to be the most promising (68). The promotion of physical exercise and adequate intake of certain nutrients during physical development may maximize the chances to achieve a higher peak of musculoskeletal mass and strength, controlling the rise of fat within muscle fibers, with a consequent less pronounced decline later in life. During childhood and adolescence, healthy habits are more easily acquired than at later ages. However, if, on the one hand, it is crucial maximizing the peak of muscle mass and strength during early life, maintaining the muscle and bone in adult life and minimizing losses during aging is also pivotal.

Nutritional Interventions

Nutrition is a key determinant of health in all age groups. Growing evidence suggests that environmental stimuli, such as diet, particularly during pregnancy and early life, and later in life, can act as a determinant of health-related outcomes during aging (69). Both under and over nutrition must be prevented, and particular attention should be paid to micronutrient deficiencies. It is important to note that nutritional interventions can occur at two different levels, with either a preventive or therapeutical approach. The preventive strategy is directed to anticipate possible macro- or micronutrient deficiencies during a defined moment in life. Other than this, therapeutical strategies are aimed to correct a manifested deficit.

Pregnancy and Early Life

Early nutritional interventions aimed at setting the basis for a lifelong healthy life can start before conception by favoring the achievement of healthy weight in women. Nutritional intervention during pregnancy should focus on favoring balanced nutrition and food rich in critical nutrients. It is interesting to note that during pregnancy, micronutrient requirements increase more than energy requirements as they mediate important developmental functions for the fetus (70). The WHO recommends the supplementation of both iron (30–60 mg/day) and folic acid (400 mcg/day) during pregnancy for the prevention of maternal anemia, preterm birth, low birth weight, and sepsis (71). Folate supplementation is also recommended before conceiving to promote neurodevelopment (72). Regarding iron supplementation, it has been pointed out that daily supplementation may be limited by the lack of compliance and safety concerns in those with an adequate intake. For this reason, intermittent regimens for iron supplementation have been proposed as a more acceptable strategy (73). Other nutritional recommendations include eating ocean fish twice a week or supplementation with long-chain ω-3 polyunsaturated fatty acids, such as DHA (300 mg/day), as it may help reduce the risk of preterm birth (70). The supplementation of other micronutrients is not recommended, nonetheless, it is important to strictly monitor and correct eventual deficiencies before the deficit becomes clinically evident. For instance, vitamin B12 deficit may negatively impact neurodevelopment and fetal growth and should not be overlooked. The role of vitamin D has also been the object of many studies. It represents the principal mediator of maternal calcium homeostasis and therefore influences the bone development of the fetus. Vitamin D deficiency during pregnancy was linked to osteopenia in newborns and reduced bone density in childhood. Therefore, particular attention should be paid to vitamin D status during pregnancy (74, 75). After birth, it is important to promote a balanced diet and the loss of excessive weight gain in women. Nutrition in infants and young children should aim to achieve the

correct weight gain according to the age growth standard. Over time, several studies reported a difference in body composition among breastfed (BF) infants and formula-fed (FF) infants. Gale et al. (76), in a systematic review and meta-analysis, showed that fat-free mass in FF infants was higher in the first year of life while fat mass was lower at 3 and 6 months compared to BF infants. On contrary, at 12 months they found a higher fat mass in FF children. Recently, Rodríguez-Cano et al. (77) documented that exclusive or predominant breastfeeding resulted in an increased fat mass at 6 months compared to those who were not exclusively BF. However, a longer duration of breastfeeding has been associated with subcutaneous fat and not with visceral fat distribution (78, 79). It could be assumed that the higher fat mass observed in BF infants during the first months of life may represent a protective factor for the subsequent weaning period (76). The higher fat mass in BF infants may thus reflect an optimal phenotype resulting in the protection from obesity occurrence in late life (80, 81). Furthermore, a more rapid weight gain has been observed in FF infants compared to BF infants at 3 and 6 months of age in both genders and between 6 and 9 months in girls only (82). Growth acceleration/rapid weight gain is to be prevented as it is associated with lifetime risk. Victora et al. (83) reported an association between rapid growth and greater fat mass at 18 years of age, regardless of the age in which rapid growth occurs. The WHO recommends exclusive breastfeeding for 4–6 months as the preferred method of infant feeding. Interestingly, Robinson et al. (84) reported an association between greater exposure to breastfeeding and higher grip strength in older life. If lactation is not possible for the mother, infant formula with a low content of protein is to be preferred as formula with high protein content are linked to a (mild) higher risk of rapid weight gain and risk of overweight (85). Regular animal milk is not recommended for the first year of life given its high amount of proteins. As for complementary foods, it should be initiated not before 17 weeks and not later than 26 weeks of age (70). A greater variety of foods should be offered immediately to infants for the health advantages of diet diversity in the medium and long term (86). Finally, in the first year of life and early childhood, the intake of simple sugars and salt should be limited (87).

During childhood and later in adolescence nutritional interventions should promote balanced nutrition and the quality of diet. Both children and adolescents are considered at risk of malnutrition given the increased energy and nutrients demand of the body for its development. Indeed, an adequate amount of energy and nutrients is required to sustain the growth spurt (88, 89). Particular attention should be paid to proteins, calcium, and vitamin D, which are essential to maximizing both peak bone mass and muscle mass and strength peak (90). Vitamin D deficiency is widespread among children and adolescents (91). For this reason, in many developed countries and especially in those in which sunshine exposure is poor, vitamin D is added to many food products (e.g., milk, breakfast cereal, flour) (92). Ward et al. (93) and Foo et al. (94) found an association between low vitamin D levels and lower grip strength and muscle power in adolescents. However, the results of randomized controlled trials in which vitamin D was supplemented in adolescents are controversial. El-Hajj Fuleihan et al. (95) reported a significant increase in lean mass after vitamin D supplementation in premenarcheal girls, while no significant changes in grip strength were found. On contrary, vitamin D supplementation in postmenarcheal girls and adolescent boys has not proven effective in increasing lean mass and muscle strength (95, 96). Dietary proteins beyond muscle accretion play important functions in bone health during childhood and adolescence. Proteins are a source of amino acids, which are important in the formation of the bone matrix and intervene in the stimulation of IGF-1 that promotes bone formation (90). However, excess protein intake has been associated with childhood obesity and therefore it should be strictly monitored (97). According to the US Institute of Medicine, the recommended intake for female and male adolescents should be 1,300 mg/day for calcium, 600 IU/day for vitamin D, and is 0.85 g/kg body weight/day for protein (98). Also, iron requirements are increased during adolescence to support the high amount of muscle and higher hemoglobin levels in both genders, as well as to replace menstrual losses in females (89). However, the indications in females of reproductive age are difficult due to the wide distribution of women with higher menstrual losses.

Overweight and obesity are widespread conditions among children and adolescents who are more prone to being overweight and obese as adults (99). During the adolescence period, there is a change of eating behaviors through a net shift toward convenience foods that are rich in saturated fatty acids and sodium and less consumption of healthy food (i.e., fruits, vegetables, dairy whole grains) (89). Such unhealthy behavior is associated with the risk of developing overweight and obesity. Indeed, given the deleterious effects of obesity (i.e., inflammation and early development of chronic diseases) which negatively affects also muscle health and are likely to persist into adulthood, weight management is pivotal during this delicate period. Primary care-based interventions, if properly addressed, can positively contribute to the prevention of unhealthy habits as well as obesity in children and adolescents. Also, school-based interventions may be very useful since usually a high amount of time is spent in the school environment (100).

Adult Life

The continuity of a life-course approach can be pursued also during adult life since this period is characterized by the major occurrence of chronic diseases. The adult phase of life can be seen as a critical period in which both preventive strategies and treatment of manifested pathologies can be implemented. In other words, addressing adult risk factors (i.e., under- and over-nutrition, physical inactivity) may be a complementary strategy in the prevention and treatment of chronic conditions reducing both morbidity and mortality (101). Evidence for the role of adult nutrition on the musculoskeletal decline at older ages is still limited. Sabia et al. (102) found an association between unhealthy behaviors during midlife (i.e., low consumption of fruit and vegetables, physical inactivity, smoking, and unmoderated alcohol consumption) and slower gait speed 17 years later. Stenholm et al. (103) documented that excess body weight in midlife is a predictor of muscle strength decline in old age (i.e., after 22 years of follow-up). They also reported an

association between marked weight loss and accelerated decline in grip strength. Of note, adherence to the Mediterranean diet has been associated with a slower decline in physical function (104, 105).

Older Life

The implementation of early preventive strategies is of particular interest. However, nutritional targets need to be constantly pursued during older life in order to preserve muscle and bone and to delay the functional decline. It is well recognized that older people need more protein to counteract muscle decline than young and adult individuals, mainly because of a declined anabolic response and increased catabolism (23). It is widely acknowledged that the traditional recommended dietary allowance for protein intake (i.e., 0.8 g/kg body weight/day) for all adults is not adequate for older people (23, 106). Indeed, it is recommended a protein intake of at least 1.0 g/kg body weight/day to maintain muscle mass in older people. In presence of acute or chronic illnesses, it is recommended that the protein intake should be increased up to 1.2–1.5 g/kg of body weight/day, while in presence of highly catabolic conditions it may be increased up to 2.0 g/kg of body weight/day (23, 106). Regarding protein source, animal-based proteins are suggested to induce a higher anabolic response than those plant-based proteins, because their higher content of leucine and a greater digestibility (22, 107). Whey proteins (i.e., fast digested proteins) seem to greater stimulate muscle protein accretion than casein (slow digested protein) and soy proteins (23). It is also pivotal an adequate amount of energy since if caloric intake is not sufficient, body fat and muscle are catabolized to provide energy (13). For what concerns caloric provision, it is therefore recommended a guiding value for energy intake of 30 kcal/kg of body weight/day (108). What is more, both the amount of energy and proteins should be adjusted according to the individual's nutritional status, physical activity level, clinical conditions, and preferences (108). It has been also suggested that a high amount of protein per meal (i.e., 25–30 g per meal containing at least 2.5 g of leucine) is required for anabolic response in older individuals (23). Vitamin D deficiency is very common in older individuals and it has been associated with reduced muscle mass and strength; the correction of deficiencies should thus be actively pursued (109, 110). Furthermore, supplementation of Vitamin D and calcium (i.e., at least 1,000 IU/day of vitamin D and 1,000–1,200 mg/day of calcium) is generally recommended in case of deficiency to preserve bone mass and to prevent osteoporotic fractures (111, 112). Protein intake plays a key role also for bone health through the life-course. Physiologically, there is a steady turnover and remodeling of the bone protein matrix which account for nearly a half of bone volume and one third of its mass. Indeed, an adequate amount of proteins is required to support both the formation and maintenance of bone mass (113). A recent systematic review (114) suggested that a protein intake higher than the current RDA may help in reducing the risk of hip fracture as well as may promote BMD maintenance in older people. Finally, in recent years calorie restriction has received growing interest. In particular, calorie restriction without malnutrition seems to have strong anti-inflammatory properties (115), reduced oxidative stress, health span improvement and lifespan extension (116). However further (especially human) studies are needed to elucidate the mechanisms and efficacy as well safety and feasibility of calorie restriction.

Physical Exercise Interventions

The promotion of habitual physical activity is essential from early life, as it benefits musculoskeletal tissue development and helps to maintain a healthy body weight throughout life. What is more, during adolescence physical activity has a significant influence on the growth of the fat-free mass, with early prevention of fat accumulation within muscles that unfavorably affect the glucose/insulin axis and homeostasis. Several hormonal factors like testosterone, growth hormone, and IGF-1, which are stimulated by physical activity, in turn, promote muscle mass accretion during adolescence (117). Recently, Hao et al. (118) reported an association between moderate and vigorous physical activity with greater skeletal muscle mass in adolescents. On the contrary, they found that a diet rich in saturated fatty acids and sweetened soft drinks was associated with a lower muscle mass, also suggesting an attenuation of the beneficial effects of physical activity on muscle mass accretion during adolescence. Sedentary behaviors are generally accompanied by the consumption of processed foods, which are rich in energy and saturated fats and may negatively influence musculoskeletal health (119). Adolescence is recognized as the period when the bone has the highest responsivity to exercise load, which positively influences skeletal development (120). Physical exercise during bone mass development stimulates bone accretion and appears to delay the onset of osteoporosis during older life. The consequent increase in muscle mass and strength and muscle contraction resulting from physical exercise also determines an increase of bone load and stimulates bone formation (20). Furthermore, longitudinal studies documented that active children had a greater BMD (i.e., +8–10%) in their adulthood compared to the sedentary ones (121). The WHO recommends a minimum of 60 min of moderate to vigorous-intensity physical activity per day in children and adolescents (122). Regarding adult life, it has been suggested that physical activity across adulthood promotes physical performance in midlife and later life. For instance, Cooper et al. (123) reported a cumulative positive effect of physical activity performed in adult life on physical performance later in midlife. Patel et al. (124) found that people with a higher level of physical activity during midlife showed greater physical performance in old age than less active individuals. On the contrary, physically strenuous work in midlife was reported to be a predictor of muscle strength decline after 22 years of follow-up, whereas becoming physically inactive has been associated with an accelerated loss of grip strength (103). Interestingly, the "Dallas Bed Rest and Training" study (125), conducted in 1966 and enrolling 5 healthy 20-year-old male subjects with a 30-year follow-up, found that 3 weeks of bed rest at 20 years of age was detrimental as well as 30 years of aging. In particular, the authors found a significant increase in body fat while fat-free mass did not change. However, they noted that techniques they used at the middle-age assessment may not be able to adequately capture

the loss of muscle mass. They also found that the period of bed rest at baseline had a more profound impact on cardiovascular capacity than what was observed at the 30-years of follow-up, with physical inactivity accounting for a greater extent to the decline in aerobic power, although the effect was confounded by the marked increase in body fat. On contrary, the authors demonstrated the beneficial effects of endurance training. This study has immediate clinical implications since it changed clinical practice by minimizing sedentary time when caring for acute and chronic medical conditions (126).

In older adults, it is widely agreed that muscle loss can be counteracted by exercise training. Practice guidelines provide strong recommendations for physical activity as the primary treatment of sarcopenia (127). For older people, structured exercises are recommended to target health-associated physical benefits (5, 23). In particular, resistance training has been proved to reduce insulin resistance and, consequently, promote protein synthesis, increasing muscle mass, strength, and performance (128). Regarding bone health, the most effective type of physical activity is progressive resistance training (weight-lifting and/or resistance bands and cables) and high-impact activity (hopping, skipping, jumping) which help to maintain and increasing BMD in older adults (129). According to the WHO "Global Recommendations on Physical Activity for Health" (122), regular exercise produces benefits both in adults aged 18–64 and in older adults aged 65 and above (with even more benefits in the latter group). Moderate- and vigorous-intensity exercises appear to provide similar health benefits in both groups. Since sarcopenia is defined as a generalized skeletal muscle disorder, it has been recently recommended to perform holistic training involving all muscle groups (130). The WHO recommends to adults aged 65 years and above to perform at least 150 min/week of moderate-intensity physical activity or at least 75 min/week of vigorous-intensity physical activity or an equivalent combination of the two (122). An additional benefit can be obtained by increasing the amount of moderate-intensity physical activity to 300 min/week or to 150 min/week of vigorous-intensity physical activity, and by performing strengthening activities involving the major muscle groups on 2 or more days a week (122). Additionally, an exercise frequency of 2 or more non-consecutive days per week, for at least 3 months has been recommended to significantly improve muscle mass and function. In healthy older adults, an exercise duration of 10 to 15 min per session with eight repetitions for each muscle group has been considered to be sufficient to counteract muscle decline (23, 131). For people with poor mobility, it is suggested to do exercises to enhance balance and prevent falls on 3 or more days per week (122). Exercise training is considered to be safe in older people. However, it has been recommended that it should be supervised in those who are frail or sarcopenic (131). A recent meta-analysis of randomized controlled trials found that long-term exercise training does not influence the risk of dropouts due to health issues or mortality in older adults. On contrary, exercise training results in a reduced mortality risk, decreasing the number of falls and fall-associated injuries and improving physical function (132).

CONCLUSION

The age-related musculoskeletal decline (and its adverse consequences) poses an essential burden to individuals and healthcare systems. To date, nutrition and physical exercise remain a mainstay of prevention and intervention for both sarcopenia and osteoporosis, as they are for many other conditions (i.e., ischemic heart disease, diabetes, COPD). Furthermore, there are no formally approved pharmacological agents to prevent or treat sarcopenia. On the other hand, although several drugs exist for the treatment of osteoporosis, they should only be reserved for selected individuals. Implementing preventive strategies even from early life is an emerging area of interest to timely address both the muscle and skeletal decline seen with aging, also associated with early accumulation of fat within muscle mass and the related endocrine-metabolic adaptations. Since early life may represent a window of opportunity in which each person builds up its functional capacities, education toward a healthier lifestyle at a population level may have favorable cascade-like effects, particularly in those living in low socioeconomic conditions. In this period of life, both muscle and bone reach their peak in mass and strength. Maximizing the musculoskeletal peak through adequate nutrition and physical activity at a young age and maintaining the peak in adulthood, is a strategy to counteract the consequent rate of decline seen in older life. Furthermore, preventing the excess of body fat throughout the lifespan is also pivotal, given the negative effects on musculoskeletal health and, more generally, preventing the onset of some chronic conditions later in life. Indeed, implementing a holistic approach to prevention may pave the way to better understand and modify the health trajectories of the individual.

AUTHOR CONTRIBUTIONS

DA and GS equally contributed to conceptualizing and writing the manuscript. ES, CL, CA, and MC edited and revised the manuscript. DA, GS, ES, CL, CA, and MC approved the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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A Multi-Institutional Randomized Controlled Trial to Investigate Whether Zoledronate Prevents Bone Loss After Discontinuation of Denosumab: The Study Protocol of Denosumab Sequential Therapy (DST) Trial

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Background: Though denosumab is an effective treatment for osteoporosis, the rebound effect after discontinuation has drawn investigators' attention. It includes a dramatic loss of gained bone mineral density (BMD) and an increased risk of vertebral fractures. This prospective multi-institutional randomized controlled trial aims to investigate whether zoledronate prevents loss of BMD after discontinuation of denosumab. The trial was registered as Denosumab Sequential Therapy (DST) trial in March 2019 at clinicaltrials.gov, with the identifier NCT03868033.

Methods: The study is conducted at National Taiwan University Hospital and its branches. Patients who have continuously received denosumab treatment for two or more years are surveyed for eligibility. Baseline characteristics and questionnaires of life quality are recorded after recruitment. BMD, circulating levels of bone turnover markers (BTMs), including serum N-terminal propeptide of type 1 collagen (P1NP) and C-terminal telopeptide (CTX), are checked before the stratified randomization to 4 groups. Biological sex and the T-scores are used to create 4 strata. The participants in group 1 adhere to regular denosumab therapy for another 2 years. All the other patients receive on-time zoledronate treatment in the first year. The participants in group 2, 3, and 4 have on-time denosumab, on-time zoledronate and drug holiday in the second year, respectively. BMDs are checked annually. Pre-scheduled checkpoints of BTMs are also arranged. For patient safety, rescue treatment with another injection of zoledronate will be applied to

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the patients on drug holiday if the CTX levels raise above the pre-specified threshold, 0.573 ng/mL for women and 0.584 ng/mL for men. The primary outcomes are the percentage changes of BMDs in lumbar spine, total hip and femoral neck. The secondary outcomes include the changes of serum level of the BTMs, new osteoporotic fractures, extra zoledronate injections needed in group 4 and the differences of quality of life.

Discussion: We aim to provide evidence whether zoledronate prevents bone loss after denosumab cessation. To our knowledge, the study has the largest sample size. No other randomized controlled study included all the three different treatment strategies and a positive control. It is also the first associated randomized controlled trial outside Europe.

Keywords: denosumab, rebound effect, osteoporosis, zoledronate, bone loss, bone mineral density

INTRODUCTION

Denosumab (Dmab), a monoclonal antibody against the receptor activator of nuclear factor kappa-light-chain-enhancer of activated B cells ligand (RANKL), is an effective anti-resorptive agent to treat patients with osteoporosis (1, 2). The rebound effect after discontinuation of Dmab treatment has drawn investigators' attention in recent years. The rebound effect includes a complete or near-complete loss of gained bone mineral density (BMD), and an increased risk of vertebral fractures (3–6). After cessation of Dmab treatment, the serum levels of bone turnover markers (BTM) raise rapidly in 3 months and return to baseline about 24 months later (7). The BMD loss may occur with the increased rate of bone turnover. Bone et al. reported total hip BMD would lose about 4% within 1 year after the withdrawal from 2-year Dmab treatment (7). For the patients who were treated with 1-year zoledronate (ZOL) and discontinued the treatment in the second year, the total hip BMD loss would be about 1.7% (8).

Meanwhile, vertebral fractures after discontinuation of Dmab were observed in patients receiving two or more doses of Dmab. The vertebral fractures tended to be multi-level around the thoracolumbar junction (4, 6). Ferrari reported 1–10% of the patients with Dmab cessation may have vertebral fractures (9). Compared with patients who received on-time Dmab injection therapy, those delayed a dose by more than 16 weeks were associated with increased risks for vertebral fractures (10). Our nationwide population-based cohort study also showed discontinuation of Dmab resulted in an increased risk of major osteoporotic and vertebral fractures. The increased risk tended to reveal within 1 year after discontinuation and the risk was greater among the patients with longer duration of Dmab treatment (11). In addition to vertebral fractures, higher incidences of major osteoporotic fractures and hip fractures were also observed in the following years of Dmab withdrawal (12).

The open-label multi-institutional randomized controlled trial aims to investigate whether ZOL treatment at 6 months after previous Dmab administration prevents bone loss in patients who have received Dmab for two or more years. Moreover, three different treatment strategies over 2 years for BMD preservation are also investigated with a positive control group adherent to continuous Dmab treatment every 6 months.

TABLE 1 | Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Post-menopausal women or men ≥ 50 years old, regularly received Dmab for at least 2 years	1. Patients had ever used antiosteoporosis medications other than Dmab 2. Estimated glomerular filtration rate <35 ml/min. 3. Malignancy 4. Continuous steroid treatment, hormone therapy or other medical treatment affecting bone metabolism 5. Secondary osteoporosis 6. Metabolic bone diseases 7. Contraindications to ZOL 8. Patients older than 80 years old 9. Hypocalcemia

Dmab, denosumab; ZOL, zoledronate.

METHODS AND ANALYSIS

Study Subjects and Sample Size Calculation

Post-menopausal women and men aged 50 years or older, regularly treated with Dmab every 6 months for two or more years, are evaluated for eligibility. The criteria are listed in **Table 1**. The patients are recruited at NTUH, NTUH Hsin-Chu Branch, and NTUH Yunlin Branch. Under the condition of 90% power and a two-sided error α probability of 0.05 with a 3.27% standard deviation (SD) (8), at least 19 patients are considered necessary in each group. Take the potential dropouts into account, the estimated sample size is around 25 in each group. Totally 100 participants are estimated to be adequate to complete the study.

Data Collection and the Stratified Randomization

After the acquirement of written informed consents, the baseline demographic characteristics of the recruited participants are recorded, including age, sex, body height, body weight, body mass index (BMI), history of previous doses of Dmab administration, adverse effects of Dmab, past histories of fractures, comorbidities, fracture risk assessed by Fracture Risk

TABLE 2 | The results of randomization to the four groups from the four Strata.

Stratification by Sex	Stratification by T-score*	Group 1	Group 2	Group 3	Group 4	Case numbers in each Stratum
Female	T-score> −2.5	10	10	11	10	41
	T-score≤ −2.5	13	13	14	14	54
Male	T-score> −2.5	1	1	0	1	3
	T-score≤ −2.5	1	1	0	1	3
	Case numbers in each group	25	25	25	26	Total case numbers = 101

**The representative T-score is the lowest value measured in lumbar spine, femoral neck, or total hip region of each participant.*

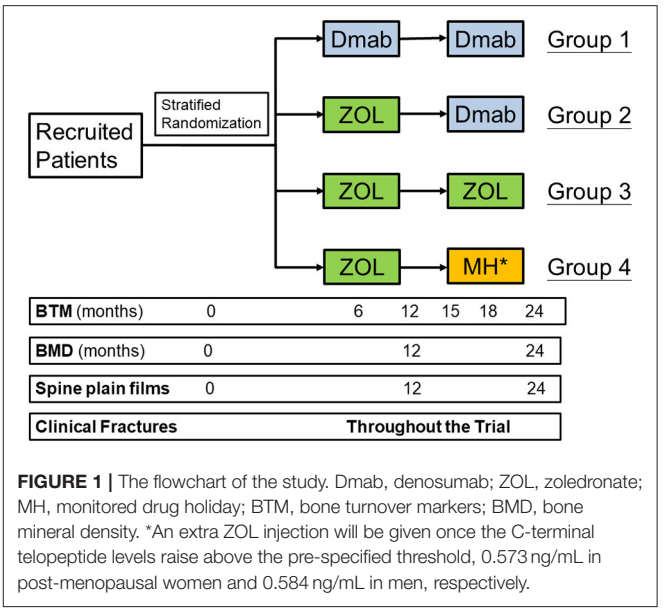

FIGURE 1 | The flowchart of the study. Dmab, denosumab; ZOL, zoledronate; MH, monitored drug holiday; BTM, bone turnover markers; BMD, bone mineral density. *An extra ZOL injection will be given once the C-terminal telopeptide levels raise above the pre-specified threshold, 0.573 ng/mL in post-menopausal women and 0.584 ng/mL in men, respectively.

Assessment Tool (FRAX), histories of falls and dental conditions. Baseline BMD in spine, total hip and femoral neck regions are checked as well as baseline laboratory tests, including serum level of creatinine, serum N-terminal propeptide of type 1 collagen (P1NP), C-terminal telopeptide (CTX). The participants are also interviewed for baseline health-related quality of life through the 5-level EQ-5D version (EQ-5D-5L) (13) and World Health Organization Quality of Life–BREF (WHOQOL-BREF) questionnaires (14, 15). Study data are collected and managed using the Research Electronic Data Capture (REDCap) tools hosted at National Taiwan University Hospital and its branches (16). The participants are stratified by biological sex and the lowest T-score in total hip, femoral neck and spine region, into 4 strata. Then the stratified participants are randomly allocated via a computer-generated sequence hidden from investigators. The distribution of the enrolled cases to the four groups from the four strata are shown in **Table 2**. The accesses to the data recorded on the Redcap tools are allowed only for groups members in charge of data analysis.

Study Design and Intervention Methods

It is a 2-year prospective, multi-institutional, randomized controlled clinical trial. The study flowchart is shown in **Figure 1**. During the 2-year study period, the patients in group 1 continuously receive Dmab treatment once every 6 months for 2 years. Group 1 is regarded as the positive control group. The patients in the other three groups receive on-time ZOL, 6 months after last Dmab treatment, at the 1st year. At the 2nd year of the study, patients in group 2 switch back to have on-time Dmab treatment once every 6 months, 1 year after previous ZOL treatment. Patients in group 3 have on-time ZOL therapy in the 2nd year, while the patients in group 4 start to have drug holiday in the 2nd year. Spine, total hip and femoral neck BMDs are checked annually. Serum levels of P1NP and CTX are checked at baseline, 6, 12, 15, 18, and 24 months after the randomized allocation. Once the CTX level elevates above the pre-defined level in group 4 patients, an extra dose of ZOL will be given. For the safety of the participants, we use relatively strict and low threshold level of CTX, 0.573 ng/mL for post-menopausal women and 0.584 ng/mL in men, respectively (17–23). The events of morphologic vertebral fractures, clinical vertebral fractures and other osteoporotic fractures are confirmed by radiograph annually and whenever necessary by physician's decision. The adverse drug reactions, observed by research members or reported by the patients, are recorded. Life quality questionnaires are acquired every 6 months. We provide instruction for all participants to acquire at least 800 international unit of vitamin D3 and 1,000 mg of calcium daily.

Primary and Secondary Outcomes

The primary outcomes are the percentage changes of BMDs in lumbar spine (LS), total hip (TH) and femoral neck (FN) among the study groups. The secondary outcomes include morphological and clinical osteoporotic vertebral fractures, other osteoporotic fractures, differences of the BTMs, extra zoledronate injections needed in group 4 and the longitudinal changes of the questionnaires-based life quality.

In the first year, we try to explore the extent of bone loss after drug switch. The percentage changes of the BMDs of the participants in group 1 are compared with those of the participants in the other groups who are treatment with ZOL in the first year. We will also investigate the factors related to significant bone loss after transition from Dmab to ZOL.

After final follow-up of the second year, we will compare the percentage changes of BMDs in Group 4 with historical negative control. Furthermore, the comparison of percentage changes of the BMDs among these four groups will be completed. The differences of circulating BTM changes among the four groups and the changes of life quality will also be investigated.

Data Analysis

Intention-to-treat analysis will be performed. For the primary outcomes, Shapiro-Wilk test will be used to exam the normality. Normally distributed continuous data will be evaluated via one-way analysis of variance (ANOVA). Otherwise, the Kruskal-Wallis test will be applied. To detect factors related to significant

bone loss after drug switch, we define significant bone loss as more than 5 % BMD loss in LS or more than 4% BMD loss in TH region according to the literature (24). We will also evaluate the associations between significant bone loss and potentially important prognostic factors, including age, sex, BMI, previous fracture history, FRAX, Dmab duration, baseline CTX level, baseline P1NP level, institution, baseline BMD in LS, FN and TH regions by univariate logistic analysis. Relevant covariates will be further included into the multivariate logistic regression analysis to identify the factors accounting for significant bone loss.

For the secondary outcomes, Fisher's exact test and chi-squared test are used to determine whether categorical data from different groups are independent. Depending on normality, one-way ANOVA or Kruskal-Wallis test will be applied for numerical data. Events of osteoporotic fractures, vertebral fractures and adverse reactions will be reported.

DISCUSSION

Real-world data showed that the compliance of continuous use, or the "persistence," of Dmab ranged from 65.8 to 88% in the first year and decreased to be around 41.2–75% in the second year (25–28). During the era of COVID-19 pandemic, the persistence may drop further. Solid evidence for effective sequential therapy of osteoporosis to prevent bone loss after Dmab discontinuation is required.

Bisphoshonates (BPs) may, at least partially, preserve the gained bone mass and decrease the risk of vertebral fractures (29). There were two associated single-institutional randomized controlled trials. The Greek study group compared the treatment effect of single dose of zoledronic acid (ZOL) with two doses of Dmab, followed by direct drug holiday in women who reached non-osteoporotic BMD level. A single dose of ZOL was effective to prevent bone loss in most patients with low vertebral fracture risk at 2 years following drug switch. But three out of 27 participants still experienced BMD decrease greater than the least significant change. The bone loss was deemed to be caused by not-yet-defined intrinsic factors (30). The BTM levels elevated within 1 year after drug switch, suggesting that further cautious survey was necessary since further bone loss was possible (31). The randomized trial by the Danish group showed inevitable BMD loss in post-menopausal women and men above 50 years with osteopenia after ZOL treatment following Dmab cessation from long-term denosumab treatment for 4.6 $\pm$ 1.6 years. The bone loss corresponded to 0.25 to 0.5 standard deviation of gained bone mass, irrespective of the 6-, 9-month, or observational treatment strategy. On-time treatment with ZOL seemed to be the most attractive strategy among the investigated options in the study (32). Although a single dose of ZOL may be helpful, the individual setting for sequential therapy may vary widely regarding the baseline fracture risk, bone turnover rate, duration of Dmab treatment and other factors. Further randomized controlled trial was deemed to be particularly necessary (9).

Strengths

To the best of our knowledge, this is the first "multi-institutional" study among the randomized controlled trials about subsequent treatment after Dmab discontinuation. The current trial may also include the largest sample size among the randomized controlled trials. The other strengths of the study are as the following. Firstly, we include both men and women with osteoporosis or osteopenia to evaluate therapeutic effects in different disease status. By these means we may improve the external validity of the study. Through stratified randomization, the biological characteristics, and the severity of osteoporosis along with possible confounding factors are expectantly to be equally distributed among four groups.

Secondly, we have four study groups with different treatment strategies. Group 1 stands as the positive control. In the first year, we may illuminate the extent of bone loss in LS, TH and FN regions after drug switch by comparing the percentage changes of the BMDs between the patients treated with Dmab and those with ZOL. The factors associated with significant bone loss after drug switch may provide important clinical implications. Group 2 will show the percentage changes of BMD after double drug switch, which has not yet been investigated previously. Group 3 will exhibit the effect of two consecutive ZOL injection on BMD and BTM levels. We will assess BMD and BTM levels changes after 1-year drug holiday following drug switch in group 4 participants. Comparison between group 3 and 4 may provide crucial information. Presumably two injections of ZOL may preserve more bone than one injection. The changes of BTM levels 1 year after drug transition and how it responds to the second injection of ZOL, will be observed. The percentage changes of BMDs in Group 4 will be compared with historical negative control due to ethical concerns. Thirdly, we have regular BTM checkpoints to show the chronological changes with different treatment strategies. Finally, we are the first Asian RCT study concerning Dmab sequential therapy.

Limitations

To begin with, we will not be able to evaluate the therapeutic responses of patients in different timelines of ZOL treatment, as done by the Danish group. However, according to Sølling et al., on-time treatment may be the most effective and attractive option (32). Secondly, according to the database survey by the investigators, we have fewer male patients having long-term Dmab treatment. The male population in the recruited participants may drop even further, as shown in **Table 2**. This corresponds to the real-world situation in osteoporosis treatment (33). As mentioned above, the potential confounding factors may be reduced by the stratified randomization. Furthermore, due to ethical concerns, we do not design a group with direct drug holiday after Dmab cessation as the negative control. Historical control is applied instead. Thirdly, the dual-energy x-ray absorptiometry (DXA) devices are not unified among the institutions. This is commonly seen among the multi-institutional studies like, for example, the FREEDOM trial (34). We use General Electric Lunar Prodigy (General Electric Healthcare), Stratos DR (Diagnostic Medical Systems-Imaging)

in NTUH, Stratos DR in NTUH Hsin-Chu Branch and Hologic (Hologic Inc.) in NTUH Yunlin Branch, respectively. Each participant is evaluated by only one specific type of device throughout the study. We use percentage changes of the BMDs as the outcome measures to eliminate the potential bias from the absolute values of the BMDs generated from different devices.

In summary, we aim to provide evidence to determine whether ZOL treatment prevents bone loss after Dmab cessation. We also try to determine the effectiveness of three sequential therapeutic strategies. The potential for extension of the study is preserved.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by National Taiwan University Hospital Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

S-HF designed the study with the help from C-YL and C-YW. C-CL, S-HF, and T-HW are the project instructor in NTUH, NTUH Yun-lin Branch, and NTUH Hsin-Chu Branch, respectively. S-HF, C-CL, and H-YC handled the research ethics. C-CL, Chi-CH, Chu-CH, H-YC, Y-LC, T-MW, W-JT, and S-HF contributed to the execution of the study. C-CL wrote this manuscript as checked by C-YW and S-HF. Supervision is provided by C-YW, C-YL, T-MW, R-SY, T-HW, and S-HF. Statistics are managed by C-YL, C-YW, and S-HF. All authors have given their final approval of the version to be published and agree to be accountable for all aspects of the work.

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Association of Obesity, Sarcopenia, and Sarcopenic Obesity With Hypertension in Adults: A Cross-Sectional Study From Ravansar, Iran During 2014–2017

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Background and Aims: Hypertension may lead to disability and death by increasing the risk of cardiovascular disease, kidney failure, and dementia. This study aimed to determine the association between obesity, sarcopenia and sarcopenic obesity, and hypertension in adults resident in Ravansar, a city in the west of Iran.

Methods: This cross-sectional study was conducted on 4,021 subjects from the baseline data of the Ravansar Non-Communicable Disease (RaNCD) cohort study, in the west region of Iran, from October 2014 up to February 2017. Body composition was categorized into obese, sarcopenia, sarcopenic obese, and normal based on measurements of muscle strength, skeletal muscle mass, and waist circumference. Univariate and multiple logistic regression models were used to examine the relationships, using the STATA 15 software.

Results: The mean age of the participant was 47.9 years (SD: 8.4), the body mass index (BMI) was 26.84 kg/m^2 (SD: 4.44), and the prevalence of hypertension was 15.12%. The prevalence of obesity, sarcopenia, and sarcopenic obesity were 24.37, 22.01, and 6.91%, respectively. Body composition groups had significant differences in age, total calorie intake, BMI, skeletal muscle mass, and muscle strength (P-value $\leq$ 0.001). In crude model, the obese (OR = 2.64; 95% CI: 2.11–3.30), sarcopenic (OR = 2.45; 95% CI: 1.94–3.08), and sarcopenic obese (OR = 3.83; 95% CI: 2.81–5.22) groups had a higher odds of hypertension. However, in adjusted models, only the obese group had a higher likelihood of hypertension (OR = 2.18; 95% CI: 1.70–2.80).

Conclusion: This study showed that obesity was associated with hypertension, whereas sarcopenia and sarcopenic obesity had no significant relationship with hypertension.

Keywords: sarcopenia, obesity, sarcopenic obesity, body composition, hypertension, blood pressure

INTRODUCTION

Hypertension is the main cause of death or disability in the world (1). In comparison to developed countries, the risk of deaths from hypertension is more than doubled in low and middle-income countries for all ages (2, 3). A systematic review showed that the prevalence of hypertension in the Iranian population was 22.1% (4). Alcohol consumption, physical inactivity or unhealthy diet, body size, or body composition might be risk factors for hypertension (5, 6).

Muscle performance and skeletal muscle mass continuously decrease during aging. Sarcopenia refers to a condition that the decline in muscle mass and muscle function is more than regular age-dependent progress (7, 8). Sarcopenia is also known as an important component of fragility that is associated with a physical disability, the tendency to fall, mortality, inflammation, and insulin resistance (9–13). Despite cross-sectional studies showing that sarcopenia was significantly associated with odds of hypertension (14, 15), a prospective cohort study did not confirm such a relationship for cardiovascular diseases (16).

Aging, which is accompanied by a decrease in physical activity, is not only related to reductions in muscle mass but also could increase the fat mass (12). As age increases, fat distribution changes in the body, which is associated with increased visceral fat, as well as fat depositions that happen in the liver, heart, skeletal muscle, and pancreas (17). Obesity, especially the fat stored in visceral tissue, produces extra pro-inflammatory adipokines, which leads to a low-grade inflammatory state (18). This low-grade inflammatory disease can lead to a loss of skeletal muscle mass, cognitive decline, a decrease in immune function, increased insulin resistance, and atherosclerosis (19–21). Moreover, studies revealed that the prevalence of hypertension was significantly higher in people with obesity than non-obese subjects (22).

Sarcopenic obesity represents a combination of sarcopenia and obesity, which means unusual muscle loss, coinciding with fat accumulation (23). Studies suggest that when obesity and muscle loss co-exist, they can synergistically increase the risk of several diseases (23, 24). According to cohort studies conducted in Korea (14, 25) and the United States (26), sarcopenic obesity was related to increasing the risk of hypertension. However, dos Santos et al. found that sarcopenia and sarcopenic obesity were not associated with cardiometabolic impairments (27). Due to the heterogeneity between studies and limited evidence on the relationship between sarcopenic obesity and hypertension in different societies, especially in Iran, the main purpose of this study was to examine which body composition indices including obesity, sarcopenia, and sarcopenic obesity were associated with the odds of hypertension according to an assessment of both muscle strength and muscle mass in adults resident in Ravansar, a city in the west of Iran.

MATERIALS AND METHODS

Study Population

The study was carried out as a cross-sectional analysis of the baseline information from the Ravansar Non-Communicable Diseases (RaNCD). The comprehensive information on the setting, location, data collection, and sampling method procedure have been published previously (28, 29). In total, the RaNCD cohort was a population-based study with aim of investigating the non-communicable diseases in Kurdish participants in Ravansar city, Kermanshah Province, west of Iran. Ravansar is a district with urban and rural areas, located in the west of Iran in the province of Kermanshah with a population of about 50,000 people, all of the Iranian Kurdish ethnicity. This cohort was one of the ten centers of the Prospective Epidemiological Research Studies in Iran (PERSIAN) mega cohort study that is approved by the ethics committees at the Ministry of Health and Medical Education, Tehran University of Medical Sciences, Iran. Baseline data were collected from October 2014 up to February 2017, and 10,000 adults between the ages of 35 and 65 (both men and women), who were registered as permanent residents of Ravansar were included in this cohort (28). In the present study, all participants in the baseline phase of the RaNCD cohort study were included in the study.

The inclusion criteria for the participants in the RaNCD cohort study were (A) participants were permanent residents of Ravansar; (B) within the age range of 35–65 y; (C) inclination to participate in the study along with the possibility of staying in Ravansar for the upcoming future; (D) provided written informed consent. In the RaNCD study, the subjects that were reluctant to participate in the study lived in Ravansar for less than one year and were unable to come to the cohort center or to communicate with interviewers (due to mental or physical disability, blindness, deafness, unable to speak, and affected by any acute psychological disorder) were not included. In the current cross-sectional study, participants were excluded according to the following exclusion criteria: 5,396 subjects without muscle strength measures, 133 pregnant women, 93 with cancer, 25 with hormonal medications, and 332 with thyroid abnormalities. Finally, 4,021 participants met the inclusion criteria and were included in the study (**Figure 1**).

Data Collection

All the individuals who participated in the study were examined through telephone and face-to-face interviews and clinical examinations. The data collection and management were carried out by using database applications. For example, all questionnaires are filled out through an online survey and regularly supervised by internal and external evaluation teams. Questionnaire information was collected by well-trained staff through face-to-face interviews. Information about age, sex, marital status, education, economic status, physical activity, history of smoking, alcohol consumption, and history of chronic diseases was recorded online in an electronic questionnaire form. Dietary data were collected through 125-item food frequency questioners (28). Weight, height, waist circumference (WC), and hip circumference were measured by trained researchers. The PERSIAN Cohort standard physical activity questionnaire was used to assess participants' physical activity. The questionnaire consisted of 22 items about the different activities of the participants during the day. Then, physical activity was categorized into three groups (light, moderate, and

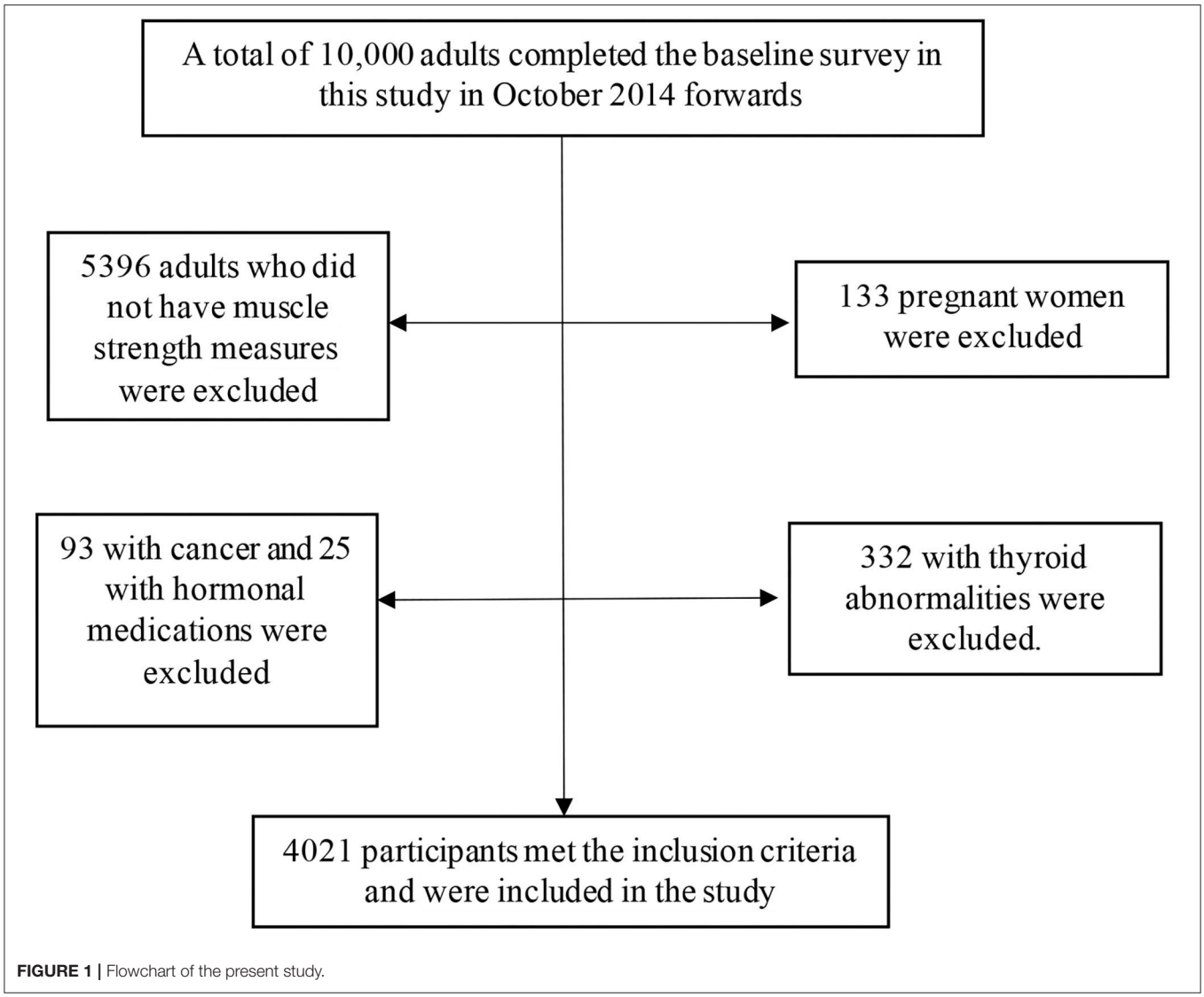

FIGURE 1 | Flowchart of the present study.

high) based on activity intensity. The details of the standard protocols of measurements have been published in the study of the RaNCD cohort profile (28).

Body Composition

All contributors were asked to remove their heavy clothes, shoes, and accessories. Then, body composition including body weight, body mass index (BMI), and skeletal muscle mass (SMM) were measured using an automated Bio-Impedance Analyzer BIA (Inbody 770, Inbody Co, Seoul, Korea) with a precision of 0.5 kg (28, 30). Height was measured by an automatic BSM 370 (Biospace Co., Seoul, Korea) with a precision of 0.1 cm. All tools and devices in the RaNCD cohort center were calibrated before the study began (28).

To measure abdominal obesity, WC was selected as an indicator of obesity, because abdominal obesity is a strong predictor of risk factors for cardiovascular disease and hypertension (31). WC was measured by non-stretched and flexible tape in the narrowest area, at the distance between the last ribs and the top of the iliac crest when the subjects were in the expiratory state. Studies indicated that WC has a high correlation with total, abdominal, and visceral fat (32).

Handgrip Strength

To measure muscle strength, handgrip strength was measured, using a digital dynamometer (Seahan, model SH5003, Seahan Co, South Korea). Muscle strength was measured based on the Southampton protocol. According to this protocol, the participants performed the test using the dominant hand in a sitting position on a chair, with their elbow extended to 90° along the vertical axis and their wrists in slight extension. This test was repeated 3 times with 15 s between trials, and the mean value was recorded in kilogram. The calibration of this dynamometer was conducted based on the manufacturers' manual. The calibration for the device was performed at the factory by loading it at the center with weights and making

appropriate adjustments in the gauge. This process for the calibration should be done once a year. If there was an error in the calibration, the device should be returned to SAEHAN Corporation for recalibration. The validity and reliability of the dynamometer were confirmed previously (33). Grip strength was chosen as an indicator of overall muscle strength, because of its excellent reproducibility. There is also evidence that grip strength is highly correlated with the strength of other muscle groups (34).

Definitions of Sarcopenia

Sarcopenia was categorized based on skeletal muscle mass and skeletal muscle strength. Initially, individuals were divided into sex-specific tertile (low, moderate, and high), based on WC, muscle strength, and muscle mass. Individuals with low or moderate WC tertiles and moderate or high muscle mass and muscle strength tertile were categorized as having a "normal" body composition. Individuals who were classified as "obese" were in the high WC tertiles and had either moderate or high muscle mass and muscle strength tertiles. Individuals were classified as "sarcopenic" if they had either the low or moderate WC tertile and the low muscle mass and low muscle strength tertile. Lastly, individuals who were categorized as "sarcopenic obese," were in the high tertile of WC and the low tertile of muscle mass and muscle strength (34).

Blood Pressure Measurement

To measure the blood pressure, people were asked to sit on a chair, and blood pressure was measured by a manometer (Rudolf Riester GmbH, Bruckstr, Jungingen, Germany) cuff and stethoscope (Rudolf Riester GmbH, Bruckstr, Jungingen, Germany), in the seated position and from both right and left arm, and it was repeated 10 min later. The blood pressure of all the participants was measured in the morning to minimize the effects of diurnal variation. The mean of the readings was recorded as the final blood pressure. Blood pressure was coded as normal (<120/80 mmHg), pre-hypertensive (120/80–139/89 mmHg), or hypertensive (140/90 mmHg and/or medication use) (25).

Statistical Analysis

Continuous variables are presented as mean ± SD and categorical variables are presented as *n* (%). The normality test was checked using the Kolmogorov–Smirnov test for the continuous variables. ANOVA test was used to compare the mean values among the four groups and the Scheffe *post-hoc* test was also applied to determine the significant difference between the groups. To examine the association between hypertension and sarcopenia, obesity, or sarcopenic obesity, univariate and multiple logistic regression models were used to estimate crude and adjusted odds ratios (ORs), and 95% CIs, respectively. In model 1, the relationship was controlled for age (years) and sex (male/female). In the second model, additional adjusting was applied for alcohol (yes/no), total calorie (kcal/d), carbohydrate (g/d), total fat (g/d), place (rural/urban), quantiles of education, quantiles of wealth, and physical activity (MET-h/wk). Missing was controlled by the imputation method. All of the statistical analyses were analyzed using STATA software version 15(StataCorp, Lakeway Drive College Station, Texas, USA). The significance level was set at a *P*-value <0.05.

TABLE 1 | Characteristics of participants in this study.

Variables	Mean ± SD; *n* (%)*
Age (years)	47.9 ± 8.4
Total calorie (kcal/d)	3,177 (,1100)
Body mass index (kg/m^2)	26.84 ± 4.44
Gender	
Male	2,240 (55.71)
Female	1,781 (44.29)
Quantiles of wealth	
1 (Poorest)	910 (22.63)
2	879 (21.86)
3	843 (20.96)
4	756 (18.80)
5 (Richest)	633 (15.74)
Education years	
Illiterate	1,096 (27.26)
1–5 years	1,438 (35.76)
6–9 years	709 (17.63)
10–12 years	520 (12.93)
>13	258 (6.42)
Physical activity	
High	1,065 (26.49)
Moderate	1,892 (47.05)
Light	1,064 (26.46)
Place	
City	995 (24.75)
Village	3,026 (75.25)
Smoking	
Yes	1,035 (25.74)
No	2,986 (74.26)
Alcohol use	
Yes	303 (7.54)
No	3,718 (92.46)
Hypertension	
Yes	608 (15.12)
No	3,413 (84.88)

**Data are presented as mean ± SD for continuous variables and frequency (%) for categorical variables.*

RESULTS

Out of 10,000 participants in the Ravansar cohort, 4,021 participants met the inclusion criteria. **Table 1** shows the characteristics of participants. The mean age of the participants was 47.9 years (SD: 8.4), the total calorie intake was 3,177 kcal per day (SD: 1,100), and the BMI was 26.84 kg/m^2 (SD: 4.44). In addition, 55.7% of participants were men, 75.2% were living in a village, 25.7% were smoking, 7.5% used alcohol, and 15.1% of them had hypertension. The other characteristics, such as

TABLE 2 | Baseline characteristics of groups according to sarcopenia and obesity classification.

Variables	Normal	Sarcopenia	Obese	Sarcopenic-obese
Number (%)	1,878 (46.7)	885 (22.01)	980 (24.37)	278 (6.91)
Age (year)*	45.871 (7.7)	51.254 (9.01)[abc]	47.637 (7.6)[a]	52.672 (8.2)[ab]
Total calorie (kcal/d)*	3478.2 (1072.8)	2532.4 (885.6)[ab]	3369.3 (1068)	2520.2 (854.3)[ab]
Carbohydrate (g/d)*	402.2 (145.7)	401.4 (4)	411.8 (148.4)[a]	406.5 (151.3)[ab]
Total fat (g/d)*	78.5 (33.8)	79.2 (35.2)	79.3 (32.9)	79.2 (34.1)
Total protein (g/d)*	91.1 (36.6)	90.45 (38.8)[b]	93.3 (36.8)[a]	91.8 (37.8)
BMI (kg/m^2)*	25.007 (3.1)	24.42 (3.3)[abc]	31.376 (3.6)[a]	30.916 (2.89)[a]
Waist circumference (cm)*	93.3 (6.07)	90.9 (7.6)[abc]	109 (5.2)[a]	107.5 (4.3)[ab]
Skeletal muscle mass (kg)*	29.3 (3.8)	19.3 (2.01)[abc]	30.5 (5.2)[a]	20.6 (1.3)[ab]
Muscle strength (kg)*	39.8 (8.9)	20.01 (3.3)[ab]	37.4 (9.6)[a]	19.8 (3.06)[ab]

**Data are presented as mean ± SD.*
[a]P-value <0.001 for sarcopenia, obese, sarcopenic-obese vs. normal group.
[b]P-value <0.01 for sarcopenia and sarcopenic-obese vs. obese group.
[c]P-value <0.001 for sarcopenia vs. sarcopenic-obese group.
BMI, Body Mass Index; kg, kilogram; kcal, kilocalorie; g, gram; d, day.

TABLE 3 | Odds ratios and confidence intervals for hypertension according to sarcopenia and obesity classification.

	Normal	Sarcopenia	Obese	Sarcopenic-obese
Crude	1 (Reference)	2.45 (1.94–3.08)[a]	2.64 (2.11–3.30)[a]	3.83 (2.81–5.22)[a]
Model 1	1 (Reference)	1.01 (0.71–1.45)	2.29 (1.79–2.93)[a]	1.5 (0.98–2.30)
Model 2	1 (Reference)	0.94 (0.65–1.35)	2.15 (1.67–2.77)[a]	1.35 (0.87–2.09)

Model 1, Adjusted for age and sex.
Model 2, Adjusted for age, sex, alcohol, total calorie (kcal), carbohydrate (g), total fat (g), place, education, quantiles of wealth, physical activity.
[a]P-value <0.001.

quantiles of wealth, education levels, and physical activity were shown in **Table 1**.

The baseline characteristics of individuals according to sarcopenia, obesity, and sarcopenic obesity classification are indicated in **Table 2**. Out of the 4,021 included subjects, 1,878 (46.7%) were classified as normal, 885 (22.01%) had sarcopenia, and 980 (24.3%) of them had obesity. Furthermore, 278 (6.9%) of them had sarcopenic obesity. Based on one-way ANOVA, there were significant differences between body composition groups and age, total calorie intake, carbohydrate intake, protein intake, BMI, skeletal muscle mass, and muscle strength (P-value $\leq$ 0.001). The Scheffe *post-hoc* test was conducted to establish the differences between body composition groups (**Table 2**). Accordingly, the normal group was significantly younger, had lower BMI, lower WC, and had higher skeletal muscle mass and muscle strength than the obese, sarcopenia, and sarcopenic obesity groups (P-value $\leq$ 0.001). Also, the obese group was younger (P-value $\leq$ 0.001), had higher calorie intake (P-value $\leq$ 0.001), had higher WC, and had higher skeletal muscle mass and muscle strength (P-value $\leq$ 0.001) than the sarcopenia and sarcopenic obesity groups. Finally, the sarcopenic group was younger, had lower BMI, and had lower WC and skeletal muscle mass than the sarcopenic obesity group (P-value $\leq$ 0.001).

The OR and CI for hypertension, according to sarcopenia, obesity, and sarcopenic obesity classifications are shown in **Table 3**. The crude model shows that sarcopenia (OR: 2.45; 95% CI: 1.94–3.08), obesity (OR: 2.64; 95% CI: 2.11–3.30), and sarcopenic obesity (OR: 3.83; 95% CI: 2.81–5.22) increased the odds of hypertension. Model 1, adjusted for age and sex shows that only the obese group was significantly related to hypertension (OR: 2.29; 95% CI: 1.79–2.93). Whereas, sarcopenia (OR = 1.01; 95% CI: 0.71–1.45) and sarcopenic obese groups (OR = 1.5; 95% CI: 0.98–2.30) were not associated with hypertension. Model 2 adjusted for age, sex, alcohol, total calorie, carbohydrate, total fat, place, education, quantiles of wealth, and physical activity, shows that only the obese group had a higher odds of hypertension (OR = 2.18; 95% CI: 1.70–2.80). However, no significant relationship was observed between sarcopenia (OR = 0.95; 95% CI:0.66–1.36) and sarcopenic obese groups (OR = 1.39; 95% CI:0.90–2.14) and OR of hypertension.

DISCUSSION

The main target of this study was to clarify the relevance of obesity, sarcopenia, and sarcopenic obesity for the odds of hypertension in adult residents in the west of Iran. This study showed that only the obese group was associated with the odds of hypertension after adjusting for main confounders, whereas the sarcopenia and sarcopenic obese groups had no significant relationship with hypertension.

Based on the result, obesity was positively associated with hypertension. In line with our findings, a study on obesity and cardiovascular risk factors including hypertension in Americans showed that people with obesity had a significantly higher

prevalence of hypertension than groups without obesity (35). Moreover, a cross-sectional study in Northwest Ethiopia has demonstrated that the relationship between hypertension and obesity could be different in distinct countries. Accordingly, it showed that in Northwest Ethiopia, the prevalence of hypertension is lower than in Uganda, Mozambique, Eastern Nigeria, and Northern India, and this difference may be due to the higher prevalence of obesity (22). However, we failed to find a significant relationship between sarcopenia and sarcopenic obesity and odds of hypertension. In line with our survey, in a prospective study conducted on 4,252 adult men in England (16), investigators indicated that there was no significant association between sarcopenia and sarcopenic obesity with risk of CVD and CHD events. Similarly, another cohort study conducted on 3,366 older adults in the United States (34), showed that sarcopenic obesity identified based on muscle mass was not significantly related to cardiovascular disease (CVD). Nevertheless, some studies showed that sarcopenia and sarcopenic obesity had a significant relationship with hypertension (14, 15, 25). It seems that obesity is significantly related to hypertension and the conflicting findings on the association between sarcopenic obese subjects and the risk of hypertension, may be due to differences in the study populations, and the lack of a single diagnostic method or different tools of body composition assessment that have been used to diagnose sarcopenic obesity. Therefore, more studies in this regard are suggested.

Obesity can induce hypertension through various mechanisms. First, increasing leptin leads to hypertension *via* increasing the sympathetic nervous system (SNS) (36, 37). Second, low serum levels of adiponectin cause endothelial dysfunction and hypertension through increasing insulin resistance (38, 39). Third, the high level of thromboxane A2 (TXA2), plasminogen activator inhibitor-1 (PAI-1), inflammation factors (IF), free-fatty acids (FFA), and angiotensinogen (AGT) may be related to hypertension (40). It should be noted that central obesity, as well as visceral adipose tissues (VATs), are directly related to hypertension (41). Because in comparison with total adiposity, VATs are associated with elevated inflammatory cytokines, insulin resistance, atherosclerosis, and cardiovascular problems (41).

The present study has several strengths. The large sample size is a strength of this study. It is also the first study that has been conducted on the Iranian Kurdish ethnic group. Therefore, it could be an appropriate reference for future studies that will be conducted on other ethnicities since it provides the possibility of comparisons between ethnicities. Despite these strengths, our study has some limitations. The cross-sectional design is one of the main limitations of this study that prevents us from identifying causal relationships. Another study limitation is that BIA is not a gold-standard tool for the measurement of body composition; however, this tool is reasonably accurate for use in large studies. Finally, the study was conducted on the Kurdish population and therefore, extrapolation of the present findings to other ethnic groups might not be done. Thus, a well-design prospective cohort study on a large population and different racial groups is recommended.

CONCLUSION

In conclusion, this study showed that obesity was significantly linked with hypertension; however, we failed to find a significant association between sarcopenia and sarcopenic obesity and odds of hypertension.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of the article will be made available by the authors, on reasonable request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Research and Technology Deputy and the Ethical Committee of Kermanshah University of Medical Sciences. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YP, FN, AB, and BH contributed to the planning of the study. Statistical analyses were completed by SR and MD. AB controlled data quality and wrote the paper. All authors contributed to the interpretation of results, editing of the manuscript, read, and approved the final manuscript.

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