



Circulating BMP-7 Level is Independent of Sarcopenia in Older Asian Adults

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Background: In vitro and animal studies have demonstrated that bone morphogenetic protein-7 (BMP-7), renowned for its osteogenic properties, also exerts beneficial effects on muscle metabolism by enhancing myogenesis and reversing muscle atrophy. Despite being proposed as a common regulatory factor for both muscle and bone, the impact of BMP-7 on human muscle health has not been thoroughly investigated. **Methods:** This cross-sectional study involved 182 community-dwelling older adults who underwent a comprehensive geriatric assessment in South Korea. Sarcopenia was diagnosed using Asian-specific cutoffs, and serum BMP-7 levels were quantified via enzyme immunoassay. **Results:** The mean age of the participants was 72.2±7.3 years, with 62.6% being female. After adjustments for confounders, serum BMP-7 levels were not significantly different between individuals with and without sarcopenia, nor were there differences based on skeletal muscle mass, strength, or physical performance levels ($p=0.423$ to 0.681). Likewise, no correlations were detected between circulating BMP-7 levels and any sarcopenia assessment metrics such as skeletal muscle index, grip strength, gait speed, or chair stand completion times ($p=0.127$ to 0.577). No significant associations were observed between increases in serum BMP-7 concentrations and the risk of sarcopenia or poor muscle phenotypes ($p=0.431$ to 0.712). Stratifying participants into quartiles based on serum BMP-7 levels also indicated no differences in sarcopenia-related parameters ($p=0.663$ to 0.996). **Conclusion:** Despite experimental evidence supporting BMP-7's role in muscle metabolism, this study found no significant association between serum BMP-7 levels and clinical indicators of muscle health in older adults. These findings challenge the utility of serum BMP-7 as a biomarker for sarcopenia in this demographic.

Key Words: Bone morphogenetic protein 7, Sarcopenia, Biomarker, Older adults, Aging, Skeletal muscle

INTRODUCTION

Sarcopenia is a geriatric syndrome characterized by the reduction of skeletal muscle mass, strength, and/or physical performance.¹⁻⁴⁾

This condition leads to a range of adverse outcomes, including higher incidences of falls, increased hospital admissions, elevated

mortality rates, diminished quality of life, and increased healthcare costs.⁵⁻⁷⁾ The etiological pathways involved in the onset and aggravation of sarcopenia remain partially elucidated, with numerous cellular and molecular factors implicated in its pathophysiology.^{8,9)} These factors include insulin-like growth factor 1 (IGF-1), forkhead box O (FoxO) transcription factors, and elements of the

transforming growth factor-beta (TGF- β) superfamily, which are crucial in maintaining muscle homeostasis.^{10,11} However, despite significant research efforts, there are currently no FDA-approved treatments specifically targeting the underlying pathophysiology of sarcopenia. Consequently, the identification of biomarkers for early screening of high-risk individuals and the development of effective interventions are imperative to maintain independence in older adults.¹²⁻¹⁴

Bone morphogenetic proteins (BMPs), originally identified in decalcified bone matrices,¹⁵ are part of the TGF- β superfamily and interact with type I and type II serine-threonine kinase receptors to phosphorylate Smad proteins.¹⁶ Among these, BMP-7 has been FDA-approved for its role in bone formation^{17,18} and is also recognized as a myokine—a molecule produced by muscle fibers that exerts autocrine, paracrine, or endocrine effects.¹⁹⁻²¹ Experimental studies *in vitro* and in animal models have shown that BMP-7 promotes hypertrophic signaling and protects against skeletal muscle diseases.²² Notably, BMP-7 has demonstrated efficacy in reducing muscle atrophy in denervated or diabetic mice^{22,23} and normalizing aberrant cytokine expression in cultured muscle cells from patients with rheumatoid arthritis.²⁴ Despite these promising experimental results, the role of BMP-7 in human muscle health remains to be clarified. This study aims to measure serum BMP-7 levels to explore their potential association with sarcopenia status and related physiological parameters.

MATERIALS AND METHODS

Study Participants

This investigation utilized a cross-sectional design to study a cohort of elderly individuals living in a community-based setting in South Korea. Recruitment of participants took place at the geriatric outpatient clinic of Asan Medical Center, a teaching hospital in Seoul, from March 2019 through February 2021. The cohort was evaluated for various health issues, including chronic conditions such as osteoporosis, osteoarthritis, hyperlipidemia, and hypertension, as well as prevalent age-related symptoms including fatigue and diminished appetite. Exclusion criteria were stringent, excluding those with end-stage renal disease on dialysis, active heart failure symptoms, or a life expectancy under 1 year due to advanced malignancies. All participants were non-institutionalized and ambulatory, either independently or with mobility aids. A total of 182 participants, who met the eligibility criteria, provided written informed consent and were enrolled for blood sample collection. The study adhered to the ethical guidelines of the 1964 Declaration of Helsinki and subsequent modifications, receiving approval from the Asan Medical Center Institutional Review Board (IRB

No. 2020-0259).

Evaluation of Sarcopenia

Experienced nurses gathered demographic data and medical histories through interviews and examination of medical records. Body composition metrics, including muscle mass, were determined using bioelectrical impedance analysis employing an InBody S10 device (InBody, Seoul, South Korea) at multiple frequencies: 1, 5, 50, 250, 500, and 1,000 kHz. Appendicular skeletal muscle mass (ASM), reflecting total muscle mass in the limbs, was quantified. Subsequently, the skeletal muscle mass index (SMI) was calculated by dividing ASM by the square of the participant's height (kg/m^2). Muscle strength was evaluated by measuring handgrip strength in the dominant arm with a hand dynamometer (Patterson Medical, Warrenville, IL, USA).²⁵ During the assessment, participants sat with elbows at a 90° angle and exerted maximum effort on the dynamometer; two attempts were made with a 1-minute rest in between, recording the highest value achieved. Gait speed was measured over a 4-m distance, and the duration to complete five chair stands was recorded.²⁶ Additionally, the Short Physical Performance Battery (SPPB), encompassing chair stands, standing balance tests, and gait speed, was administered.²⁷

The diagnostic criteria for sarcopenia followed the 2019 Consensus Guidelines by the Asian Working Group for Sarcopenia.¹ Sarcopenia was identified in participants displaying low muscle mass alongside either reduced muscle strength or diminished physical performance. Low muscle mass was defined as an SMI of $< 7.0 \text{ kg}/\text{m}^2$ for men and $< 5.7 \text{ kg}/\text{m}^2$ for women. Muscle strength was deemed weak if handgrip strength fell $< 28 \text{ kg}$ for men and $< 18 \text{ kg}$ for women. Poor physical performance was characterized by gait speeds of $< 1.0 \text{ m}/\text{s}$, more than 12 seconds to complete the five chair stand tests, or an SPPB score of 9 or less.

Measurement of Serum BMP-7

Blood samples were obtained from participants' antecubital veins following an overnight fast and were immediately subjected to centrifugation at 3,000 rpm for 5 minutes at 4°C. Post-centrifugation, the supernatant was decanted to eliminate cellular debris, and samples exhibiting hemolysis or clotting were excluded from further analysis. The serum was then aliquoted and preserved at -80°C for subsequent evaluations. The concentration of serum BMP-7 was measured using a Quantikine ELISA kit (Cat. No. DBP700; R&D Systems, Minneapolis, MN, USA), adhering to the manufacturer's protocol. The assay's sensitivity was confirmed with a minimum detectable limit of 0.79 pg/mL. To ensure measurement accuracy, both intra-assay and inter-assay variability were kept below 6.8% and 9.5%, respectively.

Statistical Analysis

Data are presented as means $\pm$ standard deviation (SD) for continuous variables, and as frequencies and percentages for categorical variables. We compared the baseline characteristics of participants with and without sarcopenia using Student t-test for continuous variables and the chi-square test for categorical variables. Analysis of covariance (ANCOVA) was employed to evaluate the adjusted means of serum BMP-7 levels based on sarcopenia status and associated parameters, with adjustments for sex, age, and body mass index (BMI). Linear regression analyses were utilized to explore the relationships between serum BMP-7 levels and muscle parameters pertinent to sarcopenia, both unadjusted and adjusted for sex, age, and BMI. Logistic regression was conducted to estimate the odds ratios (ORs) for the risk of sarcopenia and adverse muscle outcomes with each SD increase in serum BMP-7 levels. Furthermore, ANCOVA was used to compare the adjusted means of sarcopenia parameters across quartiles of serum BMP-7 levels. All statistical analyses were performed using R Software (version 3.6.3; <https://www.r-project.org/>), with a criterion for statistical significance set at a two-sided p-value of less than 0.05.

RESULTS

Table 1 presents the baseline characteristics of the 182 study participants, divided into 37 sarcopenic cases and 145 non-sarcopenic controls. Among these, 70.3% (26 individuals) of the sarcopenic group and 60.7% (88 individuals) of the control group were women ($p = 0.343$). The mean age was 76.2 ± 7.0 years for the sarcope-

nic group and 71.1 ± 7.0 years for the control group ($p < 0.001$). Compared to the non-sarcopenic participants, those with sarcopenia had significantly lower body weight, height, BMI, ASM, SMI, handgrip strength, gait speed, and SPPB scores, along with slower times to complete five chair stands ($p < 0.001$ to 0.039).

Differences in serum BMP-7 concentrations based on the presence of sarcopenia and its diagnostic components were evaluated using ANCOVA (**Fig. 1**). The analyses, performed before and after adjustments for sex, age, and BMI, revealed no statistically significant differences in BMP-7 levels between participants with and without sarcopenia, low muscle mass, weak muscle strength, or poor physical performance ($p = 0.089$ to 0.681).

Linear regression analyses were performed to evaluate the associations between serum BMP-7 levels and the parameters assessing sarcopenia, including SMI, grip strength, gait speed, time required to complete five chair stands, and SPPB score (**Table 2**). In both the unadjusted and adjusted analyses, no significant correlations were found between serum BMP-7 concentrations and any of the sarcopenia assessment parameters ($p = 0.104$ to 0.886). Consistently, there was no significant association between the increase in SD of circulating BMP-7 levels and the risk of sarcopenia, low muscle mass, weak muscle strength, or poor physical performance in the logistic regression analyses, regardless of adjustment models ($p = 0.093$ to 0.712) (**Table 3**).

To investigate the potential existence of a threshold effect of circulating BMP-7 on human muscle phenotypes, participants were stratified into four quartiles based on their serum BMP-7 levels (**Fig. 2**). Analyses, both before and after adjusting for confounding

Table 1. Baseline characteristics of the study participants according to their sarcopenia status

Characteristic	Sarcopenia (n = 37)	No sarcopenia (n = 145)	p-value
Sex			0.343
Female	26 (70.3)	88 (60.7)	
Male	11 (29.7)	57 (39.3)	
Age (y)	76.2 ± 7.0	71.1 ± 7.0	< 0.001
Weight (kg)	56.8 ± 7.6	65.5 ± 11.1	< 0.001
Height (cm)	153.9 ± 6.2	159.1 ± 9.2	< 0.001
BMI (kg/m^2)	24.0 ± 3.0	25.8 ± 3.3	0.002
ASM (kg)	13.2 ± 2.3	17.8 ± 4.7	< 0.001
SMI (kg/m^2)	5.52 ± 0.66	6.91 ± 1.15	< 0.001
Grip strength (kg)	21.6 ± 6.4	28.5 ± 9.4	< 0.001
Gait speed (m/s)	0.82 ± 0.31	1.02 ± 0.36	0.001
Chair stand (s)	16.6 ± 14.1	11.4 ± 8.2	0.039
SPPB score (range, 0–12)	9.14 ± 2.67	10.58 ± 2.11	0.001

Values are presented as number (%) or mean $\pm$ standard deviation.

BMI, body mass index; ASM, appendicular skeletal muscle mass; SMI, skeletal muscle mass index; SPPB, Short Physical Performance Battery.

Continuous variables were compared between the two groups using the Student t-test, and categorical variables were assessed with the chi-square test.

Bold indicates statistical significance.

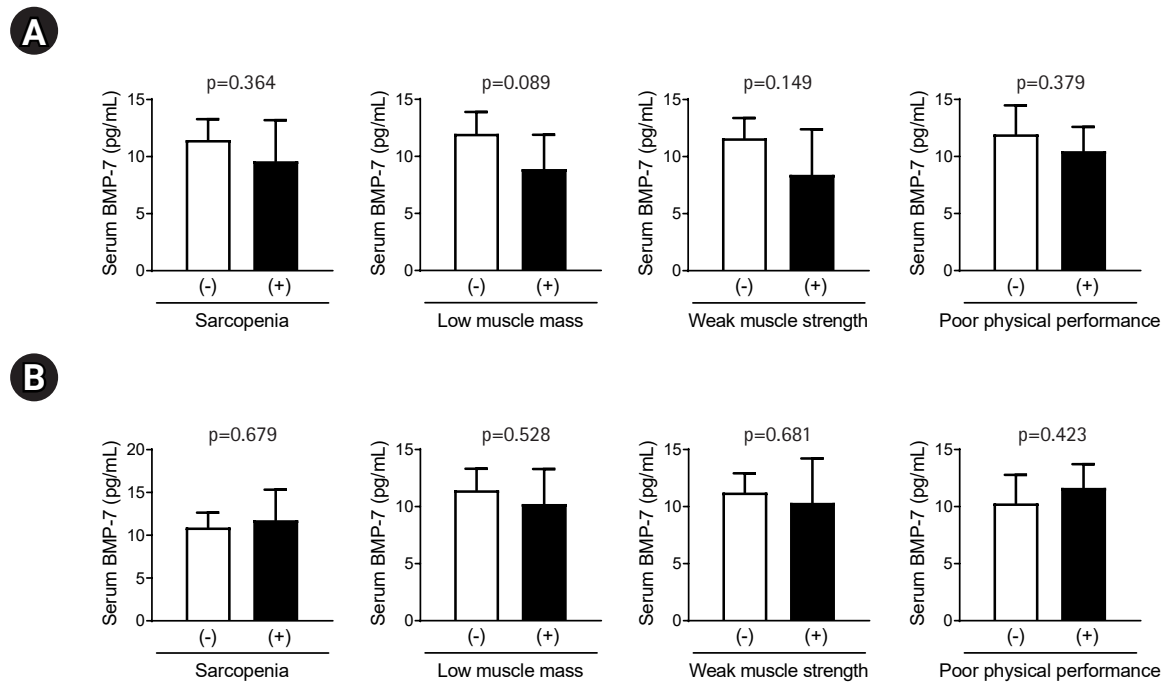


Fig. 1. Serum bone morphogenetic protein-7 (BMP-7) levels relative to sarcopenia status and associated parameters. (A) Unadjusted analysis. (B) Analysis adjusted for sex, age, and body mass index. The estimated means along with their 95% confidence intervals were calculated and compared using analysis of covariance.

Table 2. Linear regression analyses to determine the association between serum BMP-7 levels and sarcopenia parameters

	Unadjusted				Adjusted ^{a)}			
	B	SE	β	p-value	B	SE	β	p-value
SMI	0.011	0.009	0.097	0.218	0.008	0.006	0.077	0.155
Grip strength	0.108	0.066	0.129	0.104	0.050	0.044	0.060	0.262
Gait speed	-0.001	0.003	-0.041	0.610	-0.003	0.002	-0.099	0.187
Chair stand test	0.010	0.072	0.012	0.886	0.040	0.071	0.045	0.577
SPPB score	-0.015	0.017	-0.072	0.381	-0.025	0.016	-0.119	0.127

The Enter method was applied to this model.

BMP-7, bone morphogenetic protein-7; SMI, skeletal muscle mass index; SPPB, Short Physical Performance Battery; B, unstandardized regression coefficient; SE, standard error; β , standardized regression coefficient.

^{a)} Adjusted for sex, age, and body mass index.

Table 3. Logistic regression analyses to determine the odds ratios for sarcopenia and the related parameters according to the increase in serum BMP-7 levels

	SD increment in serum BMP-7			
	Unadjusted		Adjusted ^{a)}	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Sarcopenia	0.83 (0.56–1.24)	0.363	1.15 (0.75–1.78)	0.521
Low muscle mass	0.73 (0.51–1.05)	0.093	0.91 (0.61–1.36)	0.631
Weak muscle strength	0.71 (0.44–1.14)	0.154	0.91 (0.54–1.52)	0.712
Poor physical performance	0.88 (0.65–1.18)	0.378	1.14 (0.82–1.59)	0.431

BMP-7, bone morphogenetic protein-7; SD, standard deviation; OR, odds ratio; CI, confidence interval.

^{a)} Adjusted for sex, age, and body mass index.

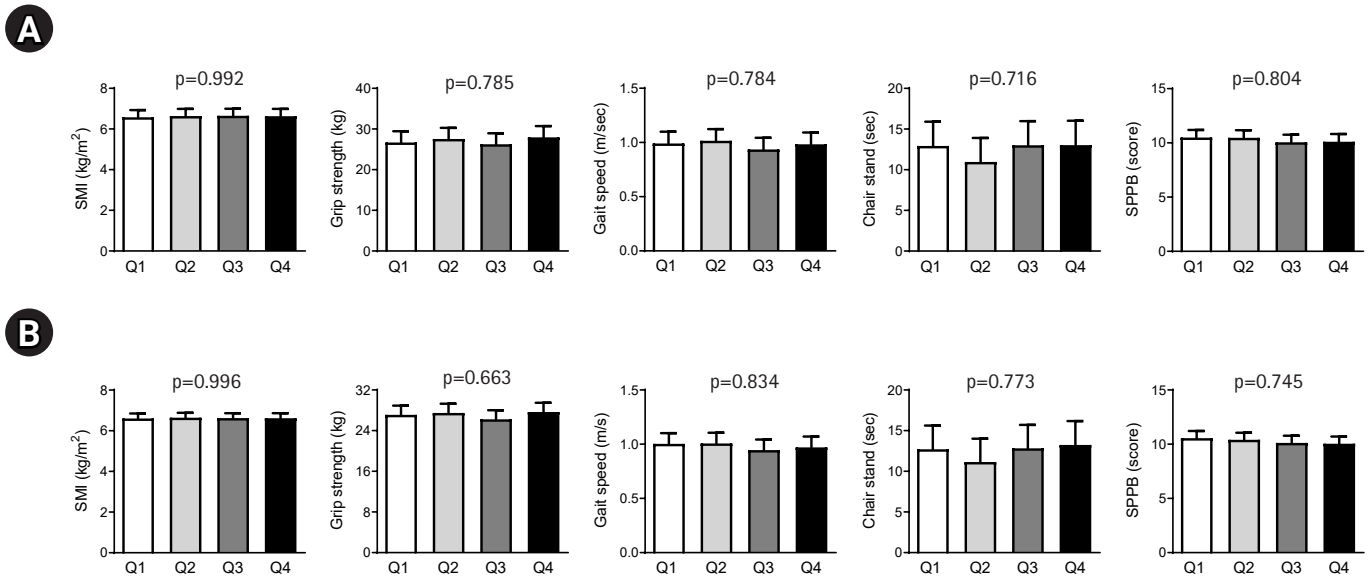


Fig. 2. Differences in sarcopenia components—skeletal muscle mass index (SMI), grip strength, gait speed, chair stand, and Short Physical Performance Battery (SPPB)—based on serum BMP-7 quartiles. (A) Unadjusted analysis. (B) Analysis adjusted for sex, age, and body mass index. The estimated means along with their 95% confidence intervals were calculated and compared using analysis of covariance. Serum BMP-7 quartiles: Q1, 1.04–2.72 pg/mL; Q2, 2.73–7.09 pg/mL; Q3, 7.10–16.1 pg/mL; Q4, 16.2–48.6 pg/mL. BMP-7, bone morphogenetic protein-7.

factors, showed no significant differences in SMI, grip strength, gait speed, time required to complete five chair stands, or SPPB scores across the BMP-7 quartile groups ($p = 0.663$ to 0.996).

DISCUSSION

This study analyzed 182 older Korean adults to explore a potential relationship between serum BMP-7 levels and sarcopenia, including its related parameters. Our findings revealed no significant differences in circulating BMP-7 levels among groups with or without sarcopenia, low muscle mass, weak muscle strength, or poor physical performance. Furthermore, there was no significant correlation between serum BMP-7 concentration and sarcopenia assessment metrics such as SMI, grip strength, gait speed, time to complete five chair stands, and SPPB score. These results remained consistent even after adjusting for age, sex, BMI, and threshold effects. To our knowledge, this is the first clinical study to investigate the association between circulating BMP-7 levels and muscle health in older adults.

Muscles and bones represent the largest tissues in humans and are intricately linked throughout the life cycle, including development, growth, and aging.²⁸⁾ Together, they form a mechanical unit essential for protecting organs and facilitating movement. Notably, sarcopenia, characterized by a decline in muscle strength, and osteoporosis, marked by decreased bone strength, often co-occur in aging individuals.^{29,30)} This phenomenon, known as coupling, un-

derscores their recognition as concomitant age-related diseases potentially driven by shared etiological factors.^{31,32)} Indeed, myoblasts, pivotal in muscle formation, and osteoblasts, central to bone formation, both originate from mesenchymal stem cells and share similar cellular physiology.³³⁾ This suggests that identical factors may influence both muscle and bone metabolism simultaneously. The development of pharmacological interventions that target these common regulatory factors in muscle-bone interactions promises to simultaneously address two prevalent conditions in the elderly, potentially enhancing overall health outcomes in this population and thus garnering significant interest in aging research.

Among its varied biological functions, BMP-7 primarily facilitates the differentiation of mesenchymal stem cells into osteoblasts.³⁴⁾ Consequently, BMP-7 is extensively utilized in clinical settings to enhance the healing of complex fractures and in spinal fusion surgeries,^{18,35)} and it is considered a promising therapeutic target for osteoporosis due to its robust osteogenic properties. Interestingly, numerous studies involving cellular and animal models have demonstrated BMP-7's beneficial effects on muscle metabolism, including the promotion of myogenesis and the reversal of muscle atrophy.^{21,24)} These findings position BMP-7 as a dual regulator of muscle and bone, highlighting its significance not only in fracture healing and osteoporosis management but also in the diagnosis and treatment of sarcopenia. However, despite these promising applications, research on the role of BMP-7 in human muscle health is limited; furthermore, our observational study of

individuals aged 65 and older showed that serum BMP-7 levels did not correlate with any muscle phenotype or the risk of sarcopenia. While these results do not negate BMP-7's potential as a therapeutic target for sarcopenia, its utility as a blood-based biomarker for predicting this condition in humans appears limited.

Despite the established role and plausible mechanisms of BMP-7 as a muscle anabolic factor in experimental research, our study did not find a significant association between circulating BMP-7 levels and sarcopenia status in older adults. While the exact reasons for this discrepancy remain unclear, several hypotheses can be considered. First, most prior experiments investigating BMP-7's effects on skeletal muscle were conducted in biomolecular environments vastly different from those in the human body. For instance, one study treated muscle cells with 750 ng/mL of BMP-7,²⁴⁾ whereas our findings indicate mean serum concentrations of merely 11.1 pg/mL. Consequently, the magnitude of BMP-7's effect on muscle homeostasis may not be as pronounced in humans as observed in vitro or in animal models. Secondly, despite their biological similarities to humans, mice exhibit significant differences in genetic regulation and chromatin organization,^{36,37)} which might account for their divergent responses to pharmacological interventions and variations in biological systems such as immunity and metabolism. These genetic differences may also contribute to the inconsistent results observed in the effects of BMP-7 on muscle homeostasis between humans and mice. Furthermore, the absence of an association between serum BMP-7 levels and sarcopenia may underscore the complex nature of sarcopenia, which is influenced by multiple pathways and factors, each contributing a relatively modest effect.^{9,38)} This complexity suggests that BMP-7 alone may not significantly impact sarcopenia. Therefore, additional research incorporating various other factors is essential, and a larger cohort might be necessary to detect the relatively subtle effects of BMP-7.

Compared to many prior studies that focused solely on specific muscle phenotypes, our study possesses significant strengths as it encompassed all critical factors necessary for diagnosing sarcopenia, including muscle mass, muscle strength, and physical performance. Moreover, we employed Asian-specific cutoffs to account for ethnic differences, enhancing the relevance and precision of our findings for this demographic. However, the interpretation of our results is subject to several limitations. The primary limitation of our study is its cross-sectional design, which inhibits our ability to establish causality or analyze the progression of sarcopenia. Additionally, being a single-center study involving older outpatient subjects, the results may be subject to selection bias and may not be generalizable to broader populations. Furthermore, the relatively modest sample size limited our ability to adjust for key confounding factors in the analysis, such as underlying comorbidities,

which may have influenced our findings. Finally, we cannot rule out the possibility that uncontrolled variables, including specific medications that may impact blood BMP-7 levels or muscle metabolism, could have affected the results.

In summary, serum BMP-7 levels were not significantly different between older adults with and without sarcopenia, a result that remained consistent across various adjustment models. Additionally, whether analyzed as a continuous variable or categorized into quartiles, serum BMP-7 levels showed no association with skeletal muscle mass, grip strength, or different types of physical performance. These findings do not support the hypothesized role of BMP-7 in human muscle health, as suggested by prior experimental research. Consequently, further large-scale, prospective studies are required to determine the clinical significance of BMP-7 in assessing the risk of sarcopenia.

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CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization, AC, JYB, BK; Data acquisition, AC, JYB, IJ, HJ, EL, BK; Data analysis and interpretation, AC, JYB, SJP, EJ, BK; Writing original draft, AC, JYB, DR, BK; Writing review & editing, AC, JYB, HJ, SJP, EJ, YJ, EL, DR, BK. BK takes responsibility for the integrity of the data analysis.

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