Body composition as a frailty marker for the elderly community

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Background: Body composition (BC) in the elderly has been associated with diseases and mortality; however, there is a shortage of data on frailty in the elderly.

Objective: To investigate the association between BC and frailty, and identify BC profiles in nonfrail, prefrail, and frail elderly people.

Methods: A cross-sectional study comprising 235 elderly (142 females and 93 males) aged ≥65 years, from the city of Amparo, State of São Paulo, Brazil, was undertaken. Sociodemographic and cognitive features, comorbidities, medication, frailty, body mass index (BMI), muscle mass, fat mass, bone mass, and fat percent (%) data were evaluated. Aiming to examine the relationship between BC and frailty, the Mann–Whitney and Kruskal–Wallis nonparametric tests were applied. The statistical significance level was P<0.05.

Results: The nonfrail elderly showed greater muscle mass and greater bone mass compared with the prefrail and frail ones. The frail elderly had greater fat % than the nonfrail elderly. There was a positive association between grip strength and muscle mass with bone mass (P<0.001), and a negative association between grip strength and fat % (P<0.001). Gait speed was positively associated with fat mass (P=0.038) and fat % (P=0.002). The physical activity level was negatively associated with fat % (P=0.022). The weight loss criterion was positively related to muscle mass (P<0.001), bone mass (P=0.009), fat mass (P=0.018), and BMI (P=0.003). There was a negative association between fatigue and bone mass (P=0.008).

Discussion: Frailty in the elderly was characterized by a BC profile/phenotype with lower muscle mass and lower bone mass and with a higher fat %. The BMI was not effective in evaluating the relationship between BC and frailty. The importance of evaluating the fat % was verified when considering the tissue distribution in the elderly BC.

Keywords: elderly, body composition, frailty

Introduction

Considered as a metabolic and functional component, the body composition (BC) undergoes significant changes in the elderly,¹ which are mainly expressed by the negative variation in fat-free mass (FFM).²³ Changes in lean body mass, bone mass, and fat mass in the elderly have a great impact on health status,¹ functional capacity, and quality of life.²

The variability of BC components contributes to the onset and progression of pathologies and disabilities, such as cardiovascular diseases, diabetes mellitus, osteoporosis,⁴ osteoarthritis, certain types of cancer,⁵ frailty,⁶ mobility implications, falls, fractures, limitation in self-care tasks, and to an independent living, in addition to representing a mortality predictor factor.⁷

The synergy verified among BC components throughout the life course refers to the development of BC profiles/phenotypes in old age, such as sarcopenic, obese, and obese sarcopenic ones. These phenotypes are associated not only with comorbidities...
and mortality, but also with a low level of physical activity, reduced muscle strength, and physical performance. Evidence presented in the literature points to obesity and sarcopenia as risk factors for disability in old age.\(^8\)

As a better understanding of the relationship between BC and frailty will be of considerable importance in evolving preventive, diagnostic, and treatment measures for the elderly population,\(^4\) this study set out to investigate the relationship between muscle mass, bone mass, fat mass, fat %, and nonfrail, prefrail, and frail conditions in the elderly community aged 65 years or over. We hypothesized that the elderly group with low FFM and high fat mass would be at greater risk for the frailty syndrome.

**Methods**

**Participants**

This cross-sectional study initially comprised a random sample of 278 individuals aged 65 years or older, residing in the community of the city of Amparo, State of São Paulo, Brazil. The research occurred in different places. Initially, the participants were submitted to an interview (self-reported questionnaire), which was applied in their own homes. In the University of Campinas (Unicamp), they underwent anthropometric assessment, physical tests, and BC evaluation.

Individuals with poor performance in the Mini-Mental State Examination\(^7\) were excluded from the study, being the cutoff points adjusted to education.\(^9\) In addition to this criterion, those presenting with the following characteristics were also excluded: permanent or temporary inability to walk indicated by the use of a wheelchair, but people using a walking stick were allowed; severe sequelae of cerebrovascular accident; Parkinson’s disease in severe or unstable stage; severe hearing or vision deficits; and being in the terminal stage. Applying these exclusion criteria reduced the sample to 235 elderly.

This research was approved by the Research Ethics Committee of Unicamp, under protocol number 835.715/2014. All volunteers signed a consent form before starting to participate in the evaluations.

**Instruments and measures**

**Sociodemographic data**

Age, sex, education, and income.

**Health conditions**

Self-reported data: cardiovascular disease, stroke, diabetes, hypertension, arthritis or rheumatism, lung disease, cataract, depression, and thyroid disease. The medicines used were evaluated as well.

**Anthropometry**

Considering weight and height, the body mass index (BMI) was obtained by using the formula, weight/height\(^2\).

**Body composition measures**

The BC was evaluated by the dual energy X-ray absorptiometry (DXA) (GE/Lunar enCore/model iDXA, GE Healthcare, Madison, WI, USA). This imaging technique examined muscle mass, bone mass, and total body fat mass in grams (g). The percent (%) of body fat was also evaluated using cutoff point values $\geq 27\%$ of body fat for men and $\geq 38\%$ for women.\(^11\) Rothney et al considered DXA as a valid and reliable method for measuring BC in adults and the elderly.\(^12\)

**Frailty syndrome**

Phenotypic frailty components were identified on the basis of the model proposed by Fried et al\(^1\) as follows: 1) Unintentional weight loss $\geq 4.5$ kg or $>5\%$ of body weight in the last year. 2) Exhaustion analyzed using two questions from the Center for Epidemiological Studies-Depression, by items 7 (“I felt that I had to make an effort to do usual tasks”) and 20 (“Could not go forward with his/her things”). 3) Palmar grip strength was measured using a dynamometer (Jamar\(^8\), Sammons Preston Rolyan, Bolingbrook, IL, USA), placed in the dominant hand. 4) Gait speed, indicated by the average time in seconds (s) in which each elderly toured three times a distance of 4.6 m. 5) Physical activity levels were evaluated by the weekly expenditure of energy in kilocalories (kcal) in physical activities and exercises, based on the Minnesota Leisure Time Physical Activity Questionnaire.

Those who scored for three or more criteria were considered frail. The elderly who scored for one or two components were characterized as prefrail. Those who did not score for any of the criteria were classified as nonfrail.\(^13\)

**Statistical analysis**

Aiming to evaluate the frailty distribution according to sex, the Chi-square test was applied, and its agewise distribution was analyzed by the Fisher’s exact test. The Mann–Whitney nonparametric test investigated the association between BC components and frailty, aiming to compare numeric value averages between two groups. To compare more than two groups, the Kruskal–Wallis test was performed. The significance level adopted in the tests was of 5% or $P<0.05$. The data were analyzed using the SAS software for Windows (Statistical Analysis System, SAS Institute Inc., Cary, NC, USA), version 9.4.
Results
According to the analysis by sex, males showed higher income, better cognitive performance, and greater kcal/week expenditure. Women reported a greater number of diseases and a higher average of medicines used; they had a higher risk of scoring in the frailty criteria; in addition, they were slower in gait speed and had a lower average in grip strength. Women showed lower muscle and bone mass; however, they had fat mass and fat % greater than men (Table 1). The sample comprised 12.77% of frail, 48.09% of prefrail, and 39.15% of nonfrail elderly.

According to the analysis between BC and frailty levels, nonfrail elderly differed from prefrail and frail individuals once the former showed greater muscle and bone mass. The fat mass did not differ in relation to the frailty levels. The body fat % showed variation between the nonfrail and frail individuals (Table 2).

The analysis of association between BC and frailty criteria is shown in Table 3. When investigating the grip strength, the association of this criterion with the muscle mass, bone mass, and fat % was found. The elderly with better performance for grip strength showed greater muscle and bone mass, in addition to lower fat %. Gait speed was associated with fat mass and fat %.

The elderly with better gait performance had lower fat mass and fat %. In regard to the physical activity level, an association with fat % was noticed. Therefore, the more sedentary individuals showed a higher fat %. The weight loss criterion was related to the muscle, bone, and fat mass, and to BMI. Those with ponderal weight loss showed lower muscle, bone and fat mass, and lower BMI, compared with the elderly who did not score for this criterion. Regarding fatigue, only a relationship with bone mass was observed.

Discussion
Regarding stratification by sex, this study showed that women had worse health conditions because of the higher number of diseases, higher number of drugs used, lower performance on cognitive test, grip strength, and gait speed in comparison with men. This result corroborates the literature, as the female sex and old age are important risk factors for health. Sex and age synthesize biological, psychological, social, historical, and cultural influences, representing indicators of conditions and influences accumulated over the course of life.

When considering BC, women had lower muscle mass and lower bone mass, although they had shown higher fat mass

### Table 1 Characteristics of elderly living in the city of Amapá (State of São Paulo, Brazil), who participated in the study

<table>
<thead>
<tr>
<th>Sociodemographic aspects</th>
<th>Total sample (average ± SD)</th>
<th>Men (average ± SD)</th>
<th>Women (average ± SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>71.76±5.06</td>
<td>71.96±5.01</td>
<td>71.63±5.10</td>
<td>0.532</td>
</tr>
<tr>
<td>Education</td>
<td>3.55±3.03</td>
<td>3.97±3.47</td>
<td>3.28±2.69</td>
<td>0.289</td>
</tr>
<tr>
<td>Income</td>
<td>861.39±582.77</td>
<td>1,061.67±543.58</td>
<td>730.23±571.88</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Behavioral aspects</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedentariness* (n=233)</td>
<td>2,473.01±4,025.76</td>
<td>3,866.77±5,331.04</td>
<td>1,547.15±2,465.10</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Health conditions</th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE (n=235)</td>
<td>24.58±3.06</td>
<td>25.20±2.88</td>
<td>24.17±3.11</td>
<td>0.014</td>
</tr>
<tr>
<td>GDS (n=235)</td>
<td>6.99±1.90</td>
<td>6.87±1.62</td>
<td>7.06±2.06</td>
<td>0.227</td>
</tr>
<tr>
<td>Weight loss (in kg) (n=68)</td>
<td>7.29±12.11</td>
<td>6.70±6.37</td>
<td>7.54±13.88</td>
<td>0.871</td>
</tr>
<tr>
<td>Frailty* (n=235)</td>
<td>1.09±1.11</td>
<td>0.65±0.91</td>
<td>1.38±1.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medication (n=235)*</td>
<td>4.09±2.81</td>
<td>3.60±2.58</td>
<td>4.41±2.92</td>
<td>0.030</td>
</tr>
<tr>
<td>Disease number (n=235)</td>
<td>2.88±1.75</td>
<td>2.34±1.53</td>
<td>3.23±1.81</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BC and physical performance</th>
<th>Total sample (average ± SD)</th>
<th>Men (average ± SD)</th>
<th>Women (average ± SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (n=235)</td>
<td>28.05±4.79</td>
<td>27.77±4.73</td>
<td>28.23±4.84</td>
<td>0.368</td>
</tr>
<tr>
<td>Total muscle mass (n=235)</td>
<td>41,456.81±101.31</td>
<td>48,861.74±545.23</td>
<td>36,607.10±4,595.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total fat mass (n=235)</td>
<td>27,101.54±9,194.29</td>
<td>24,447.12±9,254.60</td>
<td>28,840.00±8,758.86</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total bone mass (n=235)</td>
<td>2,228.29±544.73</td>
<td>2,732.75±440.93</td>
<td>1,897.90±296.33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fat % (n=235)</td>
<td>37.80±8.20</td>
<td>31.30±6.67</td>
<td>42.05±6.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grip strength (n=234)</td>
<td>21.55±18.56</td>
<td>29.09±7.62</td>
<td>16.62±4.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gait speed (n=234)</td>
<td>4.87±1.94</td>
<td>4.33±1.34</td>
<td>5.22±2.18</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Notes: Average values and standard deviation, expenditure on activities in kilocalories, number of frailty criteria scored, medication number. Data in bold indicates P<0.05.

Abbreviations: BC, body composition; BMI, body mass index; SD, standard deviation; GDS, geriatric depression scale; MMSE, Mini-Mental State Examination.
and higher fat % compared with men. According to Fragala et al., men and women differ significantly in their BC; men have higher FFM and lesser adipose tissue. The sarcopenia etiology seems to evolve in a differentiated manner between the sexes, being most prevalent in women and in the younger age group (59–69 years), while in men, the muscle loss rate is faster and more significant with age advancement.

Still referring to the perspective of BC differences between the sexes, a variation in bone component is recognized. The pattern of this variability is shown to be similar in men and women less than 50 years of age. However, following menopause, the decrease in the amount of bone mass becomes much faster in women. Thus, changes in the absorption and reabsorption processes related to aging predispose women to a lower bone mineral density and increased risk of fracture.17

Centralization and internalization of fat are observed with regard to fat mass in men, while there was peripheral tissue distribution in women, resulting in reduced visceral adiposity. However, changes associated with menopause induce a fat concentration in the abdominal region in women. Approximately at 80 years of age, there is a decrease in fat accumulation, and this process is more pronounced in women than in men.

A follow-up study of individuals between 46 and 78 years, for a period of 10 years, found that women who have maintained relatively stable body weight gained fat mass of 1.1 kg, and men gained 1.0 kg. Thus, in subjects with stable weight throughout the study, there was a reduction in FFM and an increase in adipose tissue. In the elderly, there was a preferential increase in visceral fat combined with a decreased subcutaneous fat, which can occur independently of changes in body weight, total fat, or waist circumference.18

Table 2

<table>
<thead>
<tr>
<th>Variables</th>
<th>Muscle mass</th>
<th>Bone mass</th>
<th>Fat mass</th>
<th>Fat %a</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFb</td>
<td>44,264.75±5,580.67</td>
<td>2,467.65±589.17</td>
<td>26,786.47±10,067.59</td>
<td>35.79±8.68</td>
<td>27.90±4.97</td>
</tr>
<tr>
<td>PPb</td>
<td>40,349.17±7,429.10</td>
<td>2,114.01±445.04</td>
<td>27,075.20±8,720.14</td>
<td>38.47±7.90</td>
<td>28.15±4.63</td>
</tr>
<tr>
<td>Fc</td>
<td>37,017.93±5,933.44</td>
<td>1,924.70±460.61</td>
<td>26,866.96±8,300.26</td>
<td>41.44±6.04</td>
<td>28.15±4.97</td>
</tr>
<tr>
<td>Pa</td>
<td>P=0.002</td>
<td>P&lt;0.001</td>
<td>P=0.641</td>
<td>P=0.002</td>
<td>P=0.761</td>
</tr>
</tbody>
</table>

Notes: *n=235; average values and standard deviation in kilograms. "NF (n=92); FF (n=113); F (n=30). "Data are represented as mean ± standard deviation. "P-value regarding the Kruskal–Wallis test. Data in bold indicates P<0.05.

Abbreviations: BMI, body mass index; F, frail; NF, nonfrail; FF, prefrail.

Table 3

<table>
<thead>
<tr>
<th>Variables</th>
<th>Muscle massa</th>
<th>Bone massa</th>
<th>Fat massa</th>
<th>Fat %a</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grip strengtha</td>
<td>36,620.79±5,595.32</td>
<td>1,873.33±355.30</td>
<td>29,204.05±9,348.11</td>
<td>42.31±6.71</td>
<td>28.84±5.16</td>
</tr>
<tr>
<td>No</td>
<td>42,698.14±8,189.78</td>
<td>2,319.40±548.22</td>
<td>26,561.86±9,101.38</td>
<td>36.64±8.16</td>
<td>27.85±4.68</td>
</tr>
<tr>
<td>P-valuea</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.052</td>
<td>&lt;0.001</td>
<td>0.173</td>
</tr>
<tr>
<td>Gait speeda</td>
<td>39,450.08±7,143.59</td>
<td>2,072.79±484.13</td>
<td>29,817.99±9,696.18</td>
<td>41.23±7.74</td>
<td>29.05±4.95</td>
</tr>
<tr>
<td>No</td>
<td>41,932.34±8,281.50</td>
<td>2,264.24±553.92</td>
<td>26,453.07±8,992.78</td>
<td>36.98±8.13</td>
<td>27.81±4.74</td>
</tr>
<tr>
<td>P-valuea</td>
<td>0.125</td>
<td>0.060</td>
<td>0.038</td>
<td>0.002</td>
<td>0.110</td>
</tr>
<tr>
<td>Physical activity levela</td>
<td>39,565.65±6,491.04</td>
<td>2,094.87±418.51</td>
<td>28,507.80±8,360.27</td>
<td>40.24±6.88</td>
<td>29.12±4.74</td>
</tr>
<tr>
<td>No</td>
<td>41,929.60±8,404.68</td>
<td>2,261.64±568.01</td>
<td>26,749.98±9,379.09</td>
<td>37.19±8.40</td>
<td>27.78±4.78</td>
</tr>
<tr>
<td>P-valuea</td>
<td>0.147</td>
<td>0.141</td>
<td>0.185</td>
<td>0.022</td>
<td>0.092</td>
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<tr>
<td>Weight lossa</td>
<td>37,967.09±6,428.63</td>
<td>2,046.93±437.32</td>
<td>24,413.67±7,258.95</td>
<td>37.53±7.47</td>
<td>26.48±4.58</td>
</tr>
<tr>
<td>No</td>
<td>42,399.98±8,261.74</td>
<td>2,277.31±561.32</td>
<td>27,827.99±9,538.37</td>
<td>37.87±8.40</td>
<td>28.47±4.77</td>
</tr>
<tr>
<td>P-valuea</td>
<td>&lt;0.001</td>
<td>0.009</td>
<td>0.018</td>
<td>0.003</td>
<td>0.003</td>
</tr>
<tr>
<td>Fatiguea</td>
<td>40,161.56±751.625</td>
<td>2,073.86±504.06</td>
<td>27,075.03±7,161.11</td>
<td>38.91±7.38</td>
<td>28.00±3.64</td>
</tr>
<tr>
<td>No</td>
<td>41,931.23±8,275.47</td>
<td>2,284.85±549.47</td>
<td>27,111.25±9,833.22</td>
<td>37.39±8.46</td>
<td>28.07±5.16</td>
</tr>
<tr>
<td>P-value</td>
<td>0.211</td>
<td>0.008</td>
<td>0.482</td>
<td>0.172</td>
<td>0.471</td>
</tr>
</tbody>
</table>

Notes: *n=235; average values and standard deviation in kilograms. "Grip strength, weight loss, fatigue, and physical activity level (n=235); gait speed (n=234). "P-value regarding the Mann–Whitney test. Data in bold indicates P<0.05.

Abbreviation: BMI, body mass index.
In the sample of this research, the frailty prevalence was close to the values obtained by Fried et al. According to the Cardiovascular Health Study data, the prevalence in the American elderly community (≥65 years) ranged from 7% to 12%. The syndrome presence increases with advancing age, and Ko and Walston observed a prevalence of 3.9% in the elderly from 65 to 74 years and of 25% in those aged 85 years and more. According to the American Medical Association, 40% of the elderly aged 80 years or more are frail. A survey of the elderly community of ten European countries found a frailty prevalence of 17%, with variation in different locations: 27% of the elderly in Spain, 23% in Italy, 5.8% in Switzerland, and 8.6% in Sweden. Frailty shows sex differences, these being more frequent in women than in men. A study carried out on the elderly from Central and South America identified a variation in prevalence from 30% to 48% for females and from 22% to 35% for males.

The nonfrail elderly people of this study were characterized by a BC profile/phenotype, with increased FFM and lower fat tissue when compared with the prefrail and frail ones. The frailty shows complex and multifactorial etiology, which includes interaction among neuromuscular disorders, endocrine disruption, and immune system dysfunction. BC changes in frail individuals are highlighted as one of the adverse outcomes associated with this interaction, which are expressed by muscle mass and bone tissue reduction and increased adipose tissue, with a great impact on functional capacity.

The best performance of the elderly in grip strength is due to great muscle mass and bone mass as well as the low fat %. Such data indicate muscle tissue composition changes and, consequently, its functional decline. Associated with aging, there is a loss of type I muscle fibers and a more expressive reduction of type II fibers, resulting in decreased muscle strength. Body fat also triggers an adverse effect on muscle function; thus, the greatest amount of adipose tissue is associated with intramuscular fat and lower muscle quality. In this context, in the obese sarcopenic elderly, low FFM, poor muscle quality, and low physical functionality are observed.

A relevant datum in this study refers to the association between body fat % and grip strength, and second, the lack of association between fat mass and grip strength. This finding indicates the importance of considering the fat % in the evaluation of BC to identify the distribution of body tissues; ie, the high fat % signals for a reduced amount of muscle mass and bone mass, with negative effects on functioning and health status in the elderly.

Regarding gait speed, the elderly with better performance showed reduced fat mass and fat %. For this frailty component, muscle mass was not an important performance predictor. Researchers have already reported negative associations of fat % and BMI with physical functionality in the elderly. Adipose tissue is an endocrine organ that secretes inflammatory and immune mediators that impact various metabolic functions. Chronic inflammatory state induced by obesity leads to muscle catabolism. Fat infiltration in the muscle still represents an overload for locomotion, due to the additional mass to be transported, in addition to reducing muscle quality and physical performance.

Another association found refers to the low physical activity level and the greater fat %. The frailty is characterized by increased inflammatory markers, with adverse effects on the musculoskeletal system. Thus, the relationship between fat % and the level of physical activity found in the study points to the influence of an anti-inflammatory mediator mechanism of regular physical activity, which can minimize the inflammatory process. Conversely, excess body fat in the elderly limited functionality, resulting from the greater amount of body fat, leading to overload by limiting the movements, increasing stress on joints and muscles, and accentuating the risk of disability.

Weight loss was found to be associated with muscle, bone, fat, and BMI, which suggests an interrelation among BC tissues. In this study, weight loss interacts with reduction of the three BC compartments, with repercussions for BMI. However, it is not clear whether bone tissue reduction is secondary to muscle component loss, or whether both processes are determined by the same physiopathologic mechanism.

For the fatigue criterion, only the relationship with bone mass was identified. The finding confirms the frailty cycle established by Fried et al. The fatigue, expressed by the negative energy balance, can trigger a low physical activity level and physiological anorexia. This framework leads to loss of body weight and change in BC components, including the bones. The association between fatigue and bone mass identified in this study can also be explained by the deregulation of the immune and endocrine systems, with the actuation of interleukin-1, interleukin-6, tumor necrosis factor-α, and C-reactive protein, which feature a catabolic action on the organism. These markers are involved in sarcopenia and osteoporosis mechanisms and in frailty.

**Limitations**

This study shows some limitations. Additional studies need to be performed with larger samples, which allow greater...
extrapolation of data to the general population and an increase in the power of statistical tests. It is suggested that future research investigate the impact of fat infiltration on muscle tissue in the elderly, in the three frailty levels. In addition, on the basis of the exclusion criteria adopted in this study, the relationship between BC and frailty was assessed only in the elderly community, which has better health conditions, a factor that possibly excluded the most sick and debilitated individuals.

**Conclusion**

This study highlights the relationship of BC with frailty levels and criteria. The BC profile/phenotype of the frail elderly was found to be characterized by lower muscle mass and bone mass, as well as with greater fat %, compared with the nonfrail profile/phenotype. BMI did not represent an effective instrument to determine the relationship between BC and frailty. The importance of conducting an assessment of the fat %, considering the tissue distribution for the elderly and frailty. The importance of conducting an assessment of the frailty, considering the tissue distribution for the elderly BC, was also highlighted.

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**Disclosure**

The authors report no conflicts of interest in this work.

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