Sarcopenia, but not excess weight or increased caloric intake, is associated with coronary subclinical atherosclerosis in the very elderly

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ABSTRACT

Background and aims: Excess weight is a widespread condition related to increased risk of coronary heart disease (CHD). Sarcopenia is a catabolic pathway common of the aging process and also associated with CHD. In the elderly, both changes occur concurrently and it remains unclear the relative contribution on CHD risk. We aimed to investigate whether sarcopenia, excess weight, or both are associated with subclinical atherosclerosis and/or endothelial dysfunction in very elderly individuals.

Methods: We performed a cross-sectional study of cohort enrolled individuals, aged 80 years or older (n = 208), who had never manifested cardiovascular diseases. Blood tests, medical and nutritional evaluations, cardiac computed tomography, flow-mediated dilation (FMD) and physical performance tests were obtained at the study admission. Odds ratio (OR) was calculated by multivariate regression models using coronary calcium score (CCS) categories and FMD as dependent variables. Adjustment for potential confounders was done.

Results: Muscle mass, but not fatty mass, was inversely associated with CCS categories [OR:2.54(1.06–6.06); p = 0.018]. The lowering of gait speed was negatively related to CCS > 100 [OR:2.36(1.10–5.06); p = 0.028] and skeletal muscle index was directly associated with FMD [OR:5.44(1.22–24.24); p = 0.026]. Total caloric intake was positively related to fatty mass [OR:2.71(1.09–6.72); p = 0.031], but was not related to CCS.

Conclusions: This study reveals that sarcopenia - comprised by reduction of muscle mass and its strength - is associated with subclinical atherosclerosis and endothelial dysfunction. Surprisingly, the excess of fatty mass seems not to be related to atherosclerotic burden in very elderly individuals.

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1. Introduction

Excess weight is a worldwide risk factor for coronary heart disease (CHD) [1]. Although this condition is strongly associated with cardiovascular morbidity and mortality in middle-aged adults, the risk remains controversial in elderly individuals, given that excess weight seems to play a protective role in this age group [2]. Evidence points to a U-shaped curve where the resumption of CHD mortality risk occurs with a body mass index (BMI) ≥ 35 kg/m² [3]. Paradoxically, several large-scale studies have shown that overweight is related to increased mortality, including cardiovascular causes [4–6].

Among the elderly, the increase in fatty mass is concomitant with the decrease of lean mass, a situation in which adiposity may occur without overweight. Nutritional changes and the prevalence of redistribution of fatty mass to the abdominal region are particular of this age group [7]; both factors may contribute to the development of atherosclerosis.

In the same context of aging, sarcopenia has been defined as a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength, increasing the risk of adverse outcomes such as physical disability, poor quality of life, and death [8]. Sarcopenia begins at approximately 40 years of age and there is an estimated muscle mass loss of about 8% per decade, stretching until the age of 70 years; after that age, a 15% loss ensues per decade [9]. As added factor, the very process of sarcopenia has been
2. Materials and methods

2.1. Participants and study design

For this investigation, we selected participants (n = 208) who were enrolled in the Brasilia Study on Healthy Aging (BSHA — ClinicalTrials.gov Identifier: NCT02366104). Briefly, BSHA is a prospective cohort, which was designed to identify markers of cardiovascular risk in very elderly individuals (aged 80 years or older), in a primary prevention setting. The subjects were non-institutionalized and voluntarily accepted to participate in BSHA. They were subsequently followed at the outpatient clinic of the Biocardios Institute of Cardiology (Brasilia, Brazil) from December 2008 to August 2011, as described elsewhere [15]. Exclusion criteria were (i) manifested atherosclerotic disease (MI, stroke, or peripheral arterial disease) as indicated by a medical evaluation, electrocardiogram or echocardiogram, (ii) functional dependence or institutionalization, (iii) cognitive impairment assessed by mini-mental state examination (< 24), (iv) current or previous diagnosis of immune inflammatory disease in the last 3 months, (v) left ventricle ejection fraction < 50% on echocardiography and (vi) neoplastic disease at admission or during the first year after enrollment. Neoplastic disease was investigated by evaluation of fecal occult blood, mammography and clinical breast exam, prostate-specific antigen plasma assay, digital rectal examination, and Papanicolaou smear analysis according to current guidelines [16].

The study was carried out in accordance with The Declaration of Helsinki and was approved by the local Ethics Committee (213/08). Participants were only enrolled after they (or their relatives) signed a term of informed consent.

2.2. Clinical evaluation

Study participants from BSHA underwent blood collection for biochemical analysis, imagining tests, physical, clinical and nutritional evaluations, all of them performed in a time interval of up to one week.

Regarding clinical evaluations, ex-smoking status was defined as smoking cessation during at least the last 6 months. Diabetes was defined as the use of anti-diabetic medications, fasting glycaemia ≥ 126 mg/dL, or glycated hemoglobin (HbA1c) ≥ 6.5%. Hypertension was defined by the use of antihypertensive drugs, presence of systolic blood pressure (SBP) ≥ 140 mmHg, or diastolic blood pressure (DBP) ≥ 90 mmHg. Sedentary individuals were considered those who do not practice physical activity according to the criteria established by World Health Organization [17].

2.3. Biochemical analysis

Twelve-hours overnight fasting blood samples were collected with EDTA at admission and were centrifuged at 5 °C and at 4500 rpm for 15 min to separate plasma from cells. An automatic chemical analyzer (Hitachi 917, Roche Diagnostics) was used to perform the following analyses: C-reactive protein (CRP; high-sensitivity assay, Cardiophase, Dade Behring, Marburg, Germany), total cholesterol (CHOD-PAP, Roche Diagnostics, Mannheim, USA), high-density lipoprotein cholesterol (HDL-C, Roche Diagnostics, Mannheim, USA), triglycerides (GPO-PAP, Roche Diagnostics, Mannheim, USA), urea and creatinine (GLDH, Hitachi, Tokyo, Japan), glucose (Glucose GOD-PAP, Roche Diagnostics, Mannheim, USA), HbA1c (Variant II, Bio-Rad Laboratories, Hercules, CA, USA). Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula. Glomerular filtration rate (GFR) was estimated by the abbreviated MDRD equation (mL/min/1.73 m²).

2.4. Physical performance

The adopted cutoffs are recommended by European Consensus on Definition and Diagnosis of Sarcopenia [8]. In case of cutoffs duplicity, it was chosen from the most accurate study in which participants had an average age closer to the individuals of this study [18].

2.4.1. Gait speed

Participants coursed a 2.44 m-long track in their usual pace from a standing start with both feet together on the ground. A timer was activated at the touch of the first foot after the start line. It was paused when the participant’s first foot touched the ground beyond the finish line. The test was performed three times, and the mean duration was used to estimate gait speed (m/s). None of the participants used walking aids for the test (i.e., walkers, crutches, etc.). The cutoff points for sarcopenia were <0.65 m/s, if height <173 cm for male and <159 cm for female; and <0.76 m/s, if height >173 cm for male and >159 cm for female.

2.4.2. Handgrip strength

Participants were instructed to remain seated and to keep the dominant arm close to the trunk and with the elbow flexed to a right angle (90°). A mechanical hand dynamometer (Crown, São Paulo, Brazil) was used and grip strength (kgf) expressed as the mean of three measurements with 2-min rest periods intervening. Grip size was individually adjusted for comfort. The cutoff for sarcopenia varied with BMI and in male were ≤29, 30 and 32 kgf, if BMI ≤24, 24.1–28 and > 28 kg/m², respectively. In female, the cutoffs were ≤17, 17.3, 18 and 21, if BMI ≤23, 23.1–26, 26.1–29 and > 29 kg/m², respectively.

2.5. Assessment of total caloric intake and population-adjusted total energy expenditure

A food frequency intake questionnaire (FFQ) that estimates caloric intake was previously validated in a Brazilian Population [19]. Participants reported the intake of food consumed during the previous 3 months. Their food intake was clustered in 62 items, including the use of nutritional supplements. The approximate portion of usual intake of each item was recalled by patients with the aid of a photographic record for dietary surveys and subsequently quantified in weight. The total caloric intake was calculated based on a food composition database of the Brazilian Table of Food Composition (TACO) [20]. Briefly, TACO is based on a systematic collection of samples of processed food, in triplicate, held in 9 cities that are spread throughout five different geopolitical regions in

previously linked to both an unfavorable metabolic profile and development of atherosclerotic disease, evidenced by the presence of aortic calcification, carotid atherosclerosis, and endothelial dysfunction [10–14].

Worldwide, the proportion of individuals 80 years or older has increased more than other age groups; and a substantial number of them are healthy and suitable for a primary prevention strategy. However, the evidence for this age group is scarce to indicate the contribution of body composition in the development of subclinical atherosclerotic disease. Hence, this study aims to investigate whether sarcopenia, obesity, or both are associated with subclinical cardiovascular disease, in a carefully evaluated cohort of very elderly individuals, in primary prevention setting.
Brazil. The samples are composed of the main trademarks of the products and are collected in super/hypermarkets, which accounts for about 85% of total food purchases in the country.

Population-adjusted total energy expenditure (PATEE), previously validated and applied in the Women’s Health Initiative studies [21], was estimated for individuals based on basal metabolic rate weighed by the age and gender-specific median caloric intake derived from the National Health and Nutritional Examination Survey [22].

2.6. Dual-energy X-ray absorptiometry

Bone mineral content (BMC), fatty mass, and free-fat mass were determined by using Lunar Prodigy Advance, GE Healthcare, USA. All scans were performed while individuals were wearing light indoor clothing without removable metal objects. The typical scan time was 5 min and depended on height. The radiation exposure per whole-body scan is estimated to be 2 μSv. Appendicular composition was considered equivalent to the sum of both right and left upper and lower limbs. Skeletal muscle mass index was defined as appendicular skeletal muscle mass/height² (kg/m²). The cutoff points for sarcopenia were chosen from the more accurate study in which participants had a mean age closer to ours. The cutoffs were <7.23 kg/m² for male and <5.67 kg/m² for female [23].

2.7. Brachial artery reactivity

Exams were performed after 12-h overnight fasting and at least 24-h after withdrawal of vasoactive drugs. After 10 min of rest in a quiet room with the temperature controlled around 22 °C, the brachial artery was located above the elbow and a longitudinal image of 6–8 cm was taken as the resting scan. Multiple measurements were taken at the same time in the cardiac cycle (T-wave peak) with the patients in the supine position. Brachial artery dilation was measured by ultrasound using a high-resolution linear vascular transducer (Philips, model IE 33, 3–9 MHz linear transducer, Philips Medical Systems, Andover, MA, USA) that was synchronized with ECG monitoring. Applied technique was previously described [24]. A blood pressure cuff was placed on the forearm and inflated to 50 mmHg above the systolic blood pressure for 5 min. The cuff was deflated and the flow-mediated dilation (FMD) scan was obtained during 2 min, which was in accordance to the guidelines of the International Brachial Artery Reactivity Task Force. The percent diameter change in FMD was calculated in relation to the baseline diameter and was expressed as a percentage of the baseline diameter before and after the strain.

2.8. Cardiac computed tomography

Cardiac CT was performed to evaluate Coronary Calcium Score (CCS) on a 64-detector row scanner (Aquilion 64, Toshiba, Ottawa, Tokyo, Japan). Axial slices of 3-mm thickness were acquired in synchrony with an electrocardiographic tracing in 70% of the RR interval. Coronary calcifications were defined by at least three continuous pixels with a minimum of 130 Hounsfield units (HU), and were analyzed by a single certified radiologist. The Agatston method was used to express the values of coronary calcification.

2.9. Statistical analysis

Normally distributed baseline data are presented as mean ± SD and skewed data as median and interquartile range (IQR). Multivariate ordinal logistic regression was used to assess the association between Agatston coronary calcium score (CCS) cutoffs (mild ≤100; moderate 101–399 and severe ≥400) [25] and independent continuous variables categorized in tertiles: (i) body composition (muscle mass, skeletal muscle mass index and fatty mass) and (ii) total caloric intake. Also, it was used to assess the association between the skeletal muscle mass index and endothelial function measured by FMD. Multivariate binary logistic regression was used to assess the association between physical performance tests (gait speed and handgrip strength) and CCS >100. Adjustment for potential confounders was done. Odds ratios (OR) and respective 95% confidence intervals (95% CI) were calculated for unadjusted (Model 1) and fully adjusted analyses (Model 2). All statistical analyses were performed using SPSS® version 21 for Mac (IBM). A p-value of <0.05 was considered statistically significant.

3. Results

3.1. Clinical and laboratorial characteristics

According to the selection criteria, all participants were fully capable of independently performing their daily activities and had adequate daily dietary intake for their weight, gender, and age. All participants had BMI >19 kg/m² and plasma albumin >4.0 mg/dL. None of the participants were classified as undernourished, according to Mini Nutritional Assessment (MNA) method [26]. Clinical and laboratorial characteristics of the enrolled participants are shown in Table 1.

3.2. Body composition

Muscle mass was inversely and independently associated with CCS categories (Table 2 — Models 1). This finding remained strongly significant after correction of muscle mass for the participant height — as noticed in skeletal muscle index — and even after fully adjustment for confounder variables (Table 2 — Models 2). Physical exercises were neither inversely associated with the skeletal muscle mass index [OR = 0.90 (0.43–1.90); p = 0.900], nor with CCS >100 [OR = 1.13 (0.64–2.01); p = 0.672]. However, no association was found between fatty mass and CCS categories (Table 2). Binary logistic regression models were assessed to corroborate the resumption of cardiovascular risk may

### Table 1. Baseline characteristics of participants.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Participants, n = 208</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>83 (164)</td>
</tr>
<tr>
<td>Gender: female, % (n)</td>
<td>79 (164)</td>
</tr>
<tr>
<td>Diabetes mellitus, % (n)</td>
<td>23 (48)</td>
</tr>
<tr>
<td>Hypertension, % (n)</td>
<td>76 (158)</td>
</tr>
<tr>
<td>Current smoking, % (n)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Prior smoking, % (n)</td>
<td>26 (55)</td>
</tr>
<tr>
<td>Sedentary lifestyle, % (n)</td>
<td>59 (122)</td>
</tr>
<tr>
<td>Glycemia, (mg/dL)</td>
<td>94 (17)</td>
</tr>
<tr>
<td>HbA1c, (%)</td>
<td>5.9 (0.6)</td>
</tr>
<tr>
<td>Total cholesterol, (mg/dL)</td>
<td>196 ± 45</td>
</tr>
<tr>
<td>HDL-C, (mg/dL)</td>
<td>55 ± 14</td>
</tr>
<tr>
<td>LDL-C, (mg/dL)</td>
<td>114 ± 36</td>
</tr>
<tr>
<td>Triglycerides, (mg/dL)</td>
<td>115 (66)</td>
</tr>
<tr>
<td>C-reactive protein, (mg/dL)</td>
<td>1.9 (2.4)</td>
</tr>
<tr>
<td>Systolic blood pressure, (mmHg)</td>
<td>142 (25)</td>
</tr>
<tr>
<td>Diastolic blood pressure, (mmHg)</td>
<td>73 (15)</td>
</tr>
<tr>
<td>Heart rate, (bpm)</td>
<td>73 (15)</td>
</tr>
<tr>
<td>Albumin, (g/dL)</td>
<td>4.5 (0.5)</td>
</tr>
<tr>
<td>Glomerular filtration rate, (ml/min)</td>
<td>68.4 ± 25.4</td>
</tr>
<tr>
<td>Body Mass Index, (kg/m²)</td>
<td>25.9 (5.9)</td>
</tr>
<tr>
<td>Abdominal circumference, (cm)</td>
<td>94 (15)</td>
</tr>
<tr>
<td>Male</td>
<td>96 (16)</td>
</tr>
<tr>
<td>Female</td>
<td>102 (117)</td>
</tr>
</tbody>
</table>
occurred from BMI ≥35 kg/m². At least in the very elderly individuals, the excess weight seems not to be associated with subclinical atherosclerosis \( \text{OR} = 1.51 \times \text{OR} \) and diabetes mellitus and statin use. Regression. Skeletal muscle mass index was direct and independently associated with flow-mediated dilation measures (Table 4 – Model 1), even after adjustment for confounders variables (Table 4 – Model 2). In contrast, no association between physical exercises and endothelial function was observed \( \text{OR} = 1.38 \times \text{OR} \), even after full adjustment for confounder variables. Total calorie intake and population-adjusted total energy expenditure. The mean of the differences between energy intake estimated by FFQ and PATEE was \( +49.6 \pm 597.0 \) kcal. However, no difference was observed through the paired comparative analysis between energy intake and expenditure \( p = 0.446 \).

As shown in Table 5, both caloric intake and PATEE were not related to subclinical atherosclerosis, even after adjustments for confounder variables. Total caloric intake was directly associated with total fatty mass \( \text{OR} = 2.71 \times \text{OR} \) and subclinical atherosclerosis. However, neither fatty mass and strength – was inversely and independently associated with CCS >100 (Table 3 – Model 1). This association remained significant even after full adjustment for confounder variables. However, physical exercises were not directly associated with gait speed and handgrip strength \( \text{OR} = 0.76 \times \text{OR} \) and \( p = 0.356 \) and \( \text{OR} = 0.46 \times \text{OR} \) and \( p = 0.194 \), respectively.

### 3.4. Flow-mediated dilation

Given that endothelial dysfunction and sarcopenia could share common pathways, the association between skeletal muscle index and endothelial function was assessed by ordinal logistic regression. Skeletal muscle mass index was direct and independently associated with flow-mediated dilation measures (Table 4 – Model 1), even after adjustment for confounders variables (Table 4 – Model 2). In contrast, no association between physical exercises and endothelial function was observed \( \text{OR} = 1.38 \times \text{OR} \), even after full adjustment for confounder variables. Total calorie intake and population-adjusted total energy expenditure. The mean of the differences between energy intake estimated by FFQ and PATEE was \( +49.6 \pm 597.0 \) kcal. However, no difference was observed through the paired comparative analysis between energy intake and expenditure \( p = 0.446 \).

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### 3.3. Physical performance test

Muscle strength seems to be also related to subclinical atherosclerosis, since gait speed – but not handgrip strength – was inversely and independently associated with CCS >100 (Table 3 – Model 1). This association remained significant even after full adjustment for confounder variables. However, physical exercises were not directly associated with gait speed and handgrip strength \( \text{OR} = 0.76 \times \text{OR} \) and \( p = 0.356 \) and \( \text{OR} = 0.46 \times \text{OR} \) and \( p = 0.194 \), respectively.

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excessive weight nor enhanced caloric intake was directly associated with CCS.

Sarcopenia was deeply associated with CCS since the decline of muscle mass increased 3.6-fold the atherosclerotic burden in elderly participants. Given that sarcopenia is not only defined by a single lowering of muscle mass, but also by the combined loss of muscle strength, physical performance was tested. Gait speed is considered a clinical predictor of muscle mass and strength [29] and is indirectly related to well-being and adverse health events among elders [30,31]. Our results corroborate this concept since the individuals below the cutoff points of gait speed had almost a 2.5-fold increase in risk for subclinical atherosclerosis in comparison to the ones above the gait speed cutoff. However, no association was observed between handgrip strength and CCS scores. The disagreement in findings between physical performance tests could be explained by the fact that muscle strength has a linear relation to handgrip test [32], while leg strength has a curvilinear relation to gait speed [33]. Thus, small changes in the physiological capacity of elderly individuals could be more impactful on gait speed than on handgrip strength. According to our findings, gait speed seems to be a more sensitive, and possibly an earlier marker of subclinical atherosclerosis which compared with handgrip strength. This assumption, however, needs to be confirmed in a prospective follow-up of these participants.

Although central obesity and fat redistribution have been described as strong predictors of CHD in elders [5,34–36], our results do not corroborate these findings. Increasing of total fatty mass and/or BMI >35 kg/m² were not associated with CCS in very elderly individuals. Even using different methods of body composition measurement, the lack of association between fatty mass and CCS remained consistent leading us to infer that the decline of lean mass could be a more potent predictor of atherosclerotic burden than gain of fatty mass in very elderly individuals. Although BMI does not seem to be the most appropriate predictor in the elderly, because of its inability to detect age-related body fat redistribution [37], it is the most widely used method to quantify body fatty mass in clinical practice. We add to the clinical applicability of BMI the precision of DEXA, a well-validated and accurate method of fatty mass measuring, especially in elderly individuals [38]. It is well established that endothelial function declines with advancing age and that this liaison favors the aging-related acceleration of atherogenesis [39–42]. In parallel, peripheral lean mass has been directly linked to endothelial function in individuals aged 50–75 years [43]. In agreement with these concepts, we found a direct association between muscle mass and endothelial function. Thus, it is possible that sarcopenia identifies a spectrum of atherogenic mechanisms.

Nutritional behavior contributes to the gain of adiposity in a well-known manner [48]. As one may expect, an increased caloric intake was associated with a 2.7-fold risk of excessive fatty mass in our participants. By contrast, muscle mass was not influenced by the caloric intake, but it was related to caloric expenditure, as estimated by PATEE. FFQ is commonly used as a recall method to assess diet consumption, but it could underestimate the energy intake, particularly among the elderlies. Accordingly, we also used PATEE, considering the fact that energy expenditure and intake have been shown to be quite similar in younger old women [21]. Although the difference between FFQ and PATEE did not reach statistical significance, the distinct association of them with fatty and muscle mass suggests that in our population an unbalance may exist in the distinct players that modulate these parameters. Most importantly, increased caloric intake and expenditure were both not related to CCS, corroborating the concept that adiposity — and its determinant factors — do not seem to be related to atherosclerotic disease in the very elderly.

Although some evidence indicates that the usual practice of physical activity may attenuate age-related endothelial dysfunction [46,47], this association was not caught in our data. Play of chance, particularly motivated by the cross-sectional design of study, may justify the contrast. However, we must also consider that sarcopenia is not usually pondered as a confounding variable in these analyses, and according to our findings it must be taken otherwise to investigate a direct link.

Our study has some limitations that must be considered. Mainly,
the enrollment and, by this way, the sample size were limited due to the strict inclusion criteria designed to exclude as much as possible co-morbidities. This limitation may favor an over- or underestimation of the magnitude of the associations found and may also influence the lack of statistical significance in some of the analyses. Moreover, the cross-sectional nature of the study design does not allow any causal inference and reverse causality must be considered: generalized atherosclerosis process – measured by high CAC scores – leading to sarcopenia. Nevertheless, the uniqueness of the data and its consistency with age-related biological processes involved in atherosclerotic disease make it relevant and plausible.

In conclusion, the decline of muscle mass and its strength, but not excess weight or excessive caloric diet, are predictors of subclinical atherosclerosis and endothelial dysfunction in the very elderly.

**Conflict of interest**

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

**Author contributions**

AMC, FAM: preparation of manuscript; SNS, WMF: acquisition of subjects and/or data; AMC, FAM: analysis and interpretation of data; ACS: study concept and design, manuscript revision and important intellectual content.

**References**


