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Original Research

Genetic determinants of muscle health: A population-based study

Sylvia Maria Affonso da Silva[1], Priscila Farias Tempaku[1], Ronaldo D Piovezan, Monica Levy Andersen, Sergio Tufik, Vânia D'Almeida*

Department of Psychobiology, Universidade Federal de São Paulo, Brazil

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ABSTRACT

Background: Muscle mass is associated with physical and functional performance across adulthood. Its reduction plays a crucial role in the development of age-related conditions such as frailty and sarcopenia. Genetic variations potentially impact muscle health, particularly in an aged population.
Objectives: For this reason, we aimed to evaluate the association between genetic biomarkers and appendicular lean mass index (ALMI), a marker of muscle health, to identify possible risk factors for age-related sarcopenia in a population-based study.
Materials and Methods: We cross-sectionally analyzed data collected in 2015 from the São Paulo Epidemiologic Sleep Study (EPISONO). Participants underwent bioelectrical impedance and genetic evaluations.
Results: After adjusting the data for age and sex, 12 single nucleotide polymorphisms (SNP) were significantly associated with ALMI. Among them, rs9928094 (beta = −0.031 p = 0.029) and rs9930333 (beta = −0.030 p = 0.035) are located in the *FTO* gene, which is related to obesity and fat gain and, rs16839632 (beta = 0.038 p = 0.029) located in the *FMN2* gene, responsible for actin cytoskeleton and cell polarity.
Conclusions: Poor muscle health is a multifactorial condition and genetic biomarkers can support the stratification of the risk for adverse body composition states affecting muscle and physical performance across adulthood.

1. Introduction

The extension in life expectancy leads to an increased prevalence of chronic diseases that can interact with genetic characteristics associated with a higher risk of morbidity, decreased physical capacity, joint fragility, poor muscle health, an increased number of falls, and, ultimately, death [1,2]. Age-related alterations in muscular and fat tissues are related to reductions in muscle strength and physical endurance, increasing the risk of falls and functional decline [3].

Several factors, such as gender, diet, genetic aspects, sleep, and physical activity, promote progressive changes in body composition across adulthood. The term sarcopenia was first used in 1987 by Rosenberg to classify patients who showed loss of function associated with muscle mass decrease correlated to the aging process [4]. Additionally, the combined presence of sarcopenia with obesity led to the definition of sarcopenic obesity [5]. Considering the dramatic social and economic repercussions of an aging global population [6], sarcopenia, sarcopenic obesity and their consequences should be a main component of preventive and therapeutic strategies since early adulthood, due to the early onset of their preclinical stages and their imminent public health implications.

Timely identifying early predictors of adverse body composition phenotypes through genetic markers can support decisions for tailored preventive and therapeutic strategies, which align with promising aspects of precision medicine. In this study, we aimed to identify genetic variants significantly associated with appendicular lean mass (ALM), a diagnostic component of sarcopenia, in a large population-based cohort study. The variants selected for investigation are potentially correlated with pathophysiological pathways of sarcopenia, such as inflammation and obesity. Our hypothesis is that SNPs in genes of inflammatory pathways, aging, and those related to body composition may be associated with variations in the ALM.

2. Material and methods

2.1. Studied design population

This is a cross-sectional study using data from the São Paulo Epidemiologic Sleep Study (EPISONO), a population-based cohort study representative of a large city in Brazil (August to December 2007, n = 1042). Complete rational design, sampling, and procedures have been described elsewhere [7]. After eight years, EPISONO 2007 partic-

* **Correspondence author at** Universidade Federal de São Paulo, Rua Napoleão de Barros, 925 Vila Clementino - 04024-002, São Paulo/SP – Brazil.
E-mail address: valmeida@unifesp.br (V. D'Almeida).
[1] These authors contributed equally to this work.

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ipants were recalled for this phase (follow-up 2015; July 2015 to April 2016) through telephones, letters, and active search by professional investigators. Among those who were not included, change of address was the main reason, followed by death of the participant or lack of interest in this new phase of the study (n = 712). The study was approved by the Ethics Committee of Universidade Federal de São Paulo (CEP: 593/2006; 610,514/2014; and 7,482,020/2020). All participants signed informed consent forms.

Genetic analyses were carried out by personnel specialized in this type of evaluation and were done on the population from the baseline study, in 2007. Since the genetic background did not change during the lifetime, we used the participants' characteristics, including body composition, from a follow-up analysis in 2015.

2.2. Sociodemographic evaluation

To evaluate the socio-demographic history of participants, we used data from the *Critério de Classificação Econômica Brasil* questionnaire, which is a structured and validated tool to evaluate the social classes of the Brazilian population [8]. This questionnaire is calculated based on the education of the head of the family, the quantities owned of eight types of durable goods, and the number of monthly employees in the household.

2.3. Anthropometry and body composition measures

Height (stadiometer to the nearest 0.1 cm) and weight (electronic scale to the nearest 0.1 kg) were used to calculate the body mass index (BMI, kg/m^2). Body composition assessment was performed by a direct segmental multi-frequency bioelectrical impedance analysis (BIA) using InBody720 (Biospace Ltd, Seoul, Korea). Eight tactile electrodes (4 in contact with the palm and thumb of hands and 4 in contact with the sole of feet) measured the impedance of each body segment at 6 different frequencies (1, 5, 50, 250, 500, and 1000 kHz) separately. Measurements were controlled by a microprocessor, and data output was calculated according to the manufacturer's algorithm. Data included total and appendicular skeletal muscle and fat masses. Previous studies have validated the use of this instrument in different contexts [5,9,10]. During the measurements, subjects wore light clothes and fasted for at least 8 hours. Voiding was recommended before BIA measurements. Appendicular lean mass (ALM) was adjusted for BMI for each participant to obtain the appendicular lean mass index (ALMI), which was used in all analyses [5].

For the mental and physical activity evaluations, questionnaires were applied to Chalder's fatigue scale, which assesses mental and physical fatigue (score of 0 to 3 for each item according to the intensity of fatigue symptoms). The sum of the answers with a value greater than or equal to four characterizes the condition of fatigue [11] and the International Physical Activity Questionnaire (IPAQ) - short version—was applied to estimate habitual physical activity, assessing the time (in hours) that the individual carries out activities over a week and classified as mild, moderate, or vigorous activity [12].

2.4. Phenotype assessment

Lean body mass is a compound of total body weight subtracted from fat mass: bones, body water, skin, and other organs and muscles. The largest quantity of muscle mass is located on arms and legs, called ALM, and considered the sum of lean mass from both arms and legs, as those areas are responsible for (and contain) around 80% of the lean mass of the whole body (muscles and bones). Thus, we used the ALM, given by the sum of lean mass from both arms and legs.

ALMI has been used as the parameter to identify the lower body lean mass [2,13–15]. In this study, we used the index as a continuous variable to avoid the bias of an unvalidated/non-accurate cut-off score.

2.5. Genetic evaluation

All volunteers had 10 mL of blood collected in EDTA tubes for DNA isolation in the morning. The DNA was immediately isolated through the salting-out method [16] and then stored at −20 °C until further use. Genotyping was performed by the Human OmniExpress Bead Chip array (Illumina, USA). This technique is based on DNA microarrays with beads utilization, which was capable of genotyping simultaneously up to 730,525 single nucleotide polymorphisms (SNP) in each sample.

To ensure that only high-quality markers and samples were analyzed, several quality control (QC) parameters were evaluated. We excluded: samples with less than 99% of valid genotypes; markers that presented a minor allele frequency lower than 0.05; valid genotypes that were present in less than 99% of samples; and markers that were not in the Hardy-Weinberg Equilibrium ($p < 0.001$) [17].

After QC, a manual literature curation was conducted to select potential SNPs associated with sarcopenia-related pathways, which included age-related, inflammatory pathways, obesity, and cytoskeleton protein synthesis [18,19]. 205 SNPs were selected (as shown in the new Supplemental Table 1).

2.6. Statistical analysis

Descriptive analyses were performed to characterize the profile of the included sample according to age, gender, BMI, and overall health parameters. Associations between groups and categorical variables were made using the chi-square test, with differences noted by the adjusted residue. A generalized linear model (GLzMM) was used with Gamma distribution to determine the effect of each SNP on ALMI independently, considering sex and age as independent variables (confounders) and ALMI as the dependent variable. Also, a Bonferroni correction was applied. Statistical analyses were performed using the JAMOVI project (2021, Version 1.6 [Computer Software]. Retrieved from https://www.jamovi.org (Sydney, AU) and the significance level was set at 5%.

3. Results

Within the sample of 712 participants included in this study, the mean age was 50.3 years (95%CI = 49.2–51.2), and 45% were men. Regarding the self-reported ethnicity, 52.8% considered themselves as White; 23.3% as mixed ethnicity; 16.3% as Black; 2.9% as Asian; 2.1% as Indigenous and 2.5% as "other ethnicity." With regard to genetic ethnicity analysis, 70.7% were White, 14.7% African or mixed Black background; 2.7% native American, 0.6% Asian and 11.2% others mixed background [20]. The social condition was also analyzed and characterized according to the social class of the Brazilian population (EBEP, 2003): class A corresponds to people with high-level conditions of living and class E to the lowest condition of living. Using this characterization, 19% were classified as A, 45.6% as B, and 35.5% as C, and no individuals were found for levels D and E in our sub-sample.

Table 1 summarizes the health characteristics of the EPISONO cohort 2015 (n = 712). According to anthropometric measures, mean body mass index was 28.2 kg/m2 (95% CI: 27.8–28.6), mean neck circumference was 37.5 cm (95% CI: 37.2–37.8), mean waist circumference was 97.5 cm (95% CI: 96.5–98.5), and mean hip circumference was 104.2 cm (95% CI: 103.3–105.0) (Table 1a and 1b).

We also analyzed physical activity and its frequency. Among the individuals who responded to the questionnaire, 36.7% stated that they perform physical activities, being 1.5% less than once a week, 32.5% once or twice a week, 44.4% between 3 and 6 times a week, and 21.8% perform daily activities. Considering health-related intercurrences, 55.7% of the participants reported cramps, and the reported fatigue reached an average value of 3.5 (95%CI: 3.3–3.9) according to the scale used.

A total of 205 SNPs were tested, and 12 of them were significantly associated with ALMI (Table 2): rs9928094 (beta: −0.031, 95%CI:

Table 1a
Descriptive analysis of anthropometric and functional characteristics of the 2015 follow up EPISONO cohort.

	Min	Max	Mean (n = 712)	Confidence Interval 95%
BMI (kg/m^2)	14.7	48.5	28.2	27.8 – 28.6
Neck circumference (cm)	28	52	37.5	37.2 – 37.8
Waist circumference (cm)	53.5	146	97.5	96.5 – 98.5
Hip circumference (cm)	59	143.8	104.2	103.3 – 105.0
SBP (mmHg)	88	207	130	128.7 – 131.3
DBP (mmHg)	55	125	82.4	81.6 – 83.3
BDI	0	53	10.1	9.3 – 10.7
BAI	0	63	9.6	8.9 – 10.3

BMI: body mass index, SBP is systolic blood pressure, DBP: diastolic Blood Pressure, BDI: Beck Depression Inventory, BAI: Beck Anxiety Inventory.

Table 1b
Descriptive analysis including the percentage of frequency regarding clinical data of individual or follow-up EPISONO cohort participants.

	Frequency (%)	Number of responses
Diabetes (YES)	15.6	712
Self-reported heart attack (YES)	2.2	712
Hypertension (YES)	55.6	705
Metabolic Syndrome (YES)	56.8	706
Obesity (YES)	58.4	705
Dyslipidemia (YES)	63.3	705
Heart medication use (YES)	3.3	706
Hypertension medication use (YES)	25.8	706
Hypoglycemic medication use (YES)	10.3	706
Lipid lowering therapy mediation use (YES)	13.6	703
Central nervous system medication use (YES)	13.1	659

Table 2
Genome-level of significant and suggestive associations with ALMI and sarcopenia.

N	SNP	Chr	Cytogenetic Position	Genomic Position	REF	ALT	Beta	95%CI	p-value	GENE
1	rs6738433	2	p23.3	25,159,501	C	G	0.039	0.012 0.66	0.005	-
2	rs76662990	5	q13.3	73,847,916	A	G	0.178	0.040 0.320	0.011	-
3	**rs16839632**	**1**	**q43**	**240,361,446**	**A**	**G**	**0.038**	**0.004 0.072**	**0.029**	***FMN2***
4	**rs9928094**	**16**	**q12.2**	**53,799,905**	**A**	**G**	**-0.031**	**-0.059 -0.003**	**0.029**	***FTO***
5	**rs76246107**	**19**	**q13.33**	**50,121,274**	**G**	**A**	**0.132**	**0.013 0.251**	**0.029**	***PRR12***
6	rs1029576	7	p21.1	17,065,965	C	G	-0.030	-0.057 -0.002	0.035	*LOC105375170*
7	**rs9930333**	**16**	**q12.2**	**53,799,977**	**T**	**G**	**-0.030**	**-0.058 -0.002**	**0.035**	***FTO***
8	**rs303143**	**4**	**q28.1**	**124,155,197**	**A**	**G**	**-0.051**	**-0.009 -0.003**	**0.036**	***SPATA5***
9	rs157350	5	q33.3	156,139,569	A	G	-0.79	-0.155 -0.003	0.041	*SGCD / LOC105377673*
10	rs10189330	2	q11.2	99,389,870	G	T	0.031	-0.001–0.061	0.042	*LINC02611*
11	rs16852912	3	q26.2	168,686,676	C	T	0.121	0.002 0.240	0.047	*MECOM*
12	**rs11066301**	**12**	**q24.13**	**112,871,372**	**A**	**G**	**0.034**	**0.09e/2 -0.067**	**0.049**	***PTPN11***

We highlighted SNPs of interest that are related to genes associated with the risk of muscle mass loss. ALT: alternative allele; Beta: regression coefficient; CI: confidence interval; CHR: chromosome; p-value: statistical significance level; SNP: single nucleotide polymorphism; the reference genome used in the analysis was GRCh37.

–0.059–0.003; p = 0.029) and rs9930333 (beta: -0.030, 95%CI: -0.058–0.002; p = 0.035) associated with *FTO* gene; rs16839632 (beta: 0.038, 95%CI: 0.004–0.072; p = 0.029) *FMN2* gene; 6,246,107 (beta: 0.132; 95%CI: 0.013–0.251; p = 0.029) - *PRR12* gene; rs303143 - *SPATA5* gene; and rs11066301 (beta: 0.034; 95%CI: 0.09e/2 -0.067; p = 0.049) - *PTPN11* gene.

Table 3 indicates the allele frequency of 12 SNPs for the total sample and distributed into 4 genetic backgrounds: Caucasian, Asian, Native American, and Black or mixed Black.

4. Discussion

This study conducted in a large cohort from the general population showed associations of genetic biomarkers with an indicator of muscle health (ALMI), suggesting genetic traits are potential personalized risk factors for adverse body composition states, such as sarcopenia, and their outcomes. When sarcopenia symptoms and consequences occur, they are less likely to improve or reverse, particularly in older adults [2,18,21]. Current diagnostic criteria for sarcopenia are performed through the analysis of body composition, muscle strength, and functional tests. Additional information on genetic characteristics related to this condition can support its early detection in preclinical stages. Furthermore, to prevent the functional decline derived from muscle weakness, risk stratification by the identification of specific SNPs can be a more precise and timely strategy than the current use of clinical indicators.

In a study targeting genetic factors potentially associated with sarcopenia a GWAS meta-analysis including 256,523 individuals (male and female) of European descent aged 60 years and over from 22 independent cohorts found 15 loci associated with characteristics of sarcopenia, and, similar to our study, an SNP (rs8061064) was identified in the *FTO* gene. However, we also identified a match for two different SNPs in the *FTO* gene, (rs9928094 and rs9930333). Of note, this gene has been associated with regulations of feeding and fasting, and the RNAm levels

Table 3
Allele frequencies in percentage and sample size in brackets according to genetic ancestry from the EPISONO cohort baseline.

	TOTAL (n = 501)			CAUCASIAN (n = 329)			ASIAN (n = 9)			NATIVE AMERICAN (n = 12)			AFRICAN (n = 151)			p-value
	0/0	0/1	1/1	0/0	0/1	1/1	0/0	0/1	1/1	0/0	0/1	1/1	0/0	0/1	1/1	
rs6738433	32% (n = 155)	48% (n = 237)	20% (n = 109)	27% (n = 84)	49% (n = 157)	23% (n = 88)	38% (n = 4)	44% (n = 3)	19% (n = 2)	20% (n = 2)	44% (n = 8)	36% (n = 2)	42% (n = 65)	47% (n = 69)	11% (n = 17)	**<0.001**
rs76662990	86% (n = 438)	13% (n = 61)	1% (n = 2)	86% (n = 283)	14% (n = 44)	0.6% (n = 2)	100% (n = 9)	0% (n = 0)	0% (n = 0)	76% (n = 10)	24% (n = 2)	0% (n = 0)	87% (n = 136)	13% (n = 15)	0% (n = 0)	0.208
rs16839632	91% (n = 453)	9% (n = 48)	0% (n = 0)	90% (n = 292)	10% (n = 37)	0% (n = 0)	100% (n = 9)	0% (n = 0)	0% (n = 0)	88% (n = 11)	12% (n = 1)	0% (n = 0)	94% (n = 141)	6% (n = 10)	0% (n = 0)	0.669
rs9928094	34% (n = 165)	47% (= 238)	19% (n = 98)	32% (n = 105)	48% (n = 161)	19% (n = 63)	44.4% (n = 4)	44.4% (n = 4)	11.1% (n = 1)	40% (n = 4)	56% (n = 7)	4% (n = 1)	36% (n = 52)	44% (n = 66)	20% (n = 33)	0.264
rs76246107	82% (n = 417)	17% (n = 81)	1% (n = 3)	83% (n = 275)	16% (n = 52)	1% (n = 2)	56% (n = 5)	38% (n = 3)	6% (n = 1)	72% (n = 9)	28% (n = 3)	0% (n = 0)	84% (n = 128)	16% (n = 23)	0% (n = 0)	**0.024**
rs1029576	26% (n = 126)	49% (n = 251)	25% (n = 124)	28% (n = 90)	50% (n = 163)	22% (n = 76)	22.2% (n = 2)	55.6% (n = 5)	22.2% (n = 2)	24% (n = 4)	48% (n = 5)	28% (n = 3)	20% (n = 30)	50% (n = 78)	19% (n = 43)	0.374
rs9930333	34% (n = 164)	47% (n = 236)	19% (n = 101)	32% (n = 105)	48% (n = 160)	20% (n = 64)	44.4% (n = 4)	44.4% (n = 4)	11.1% (n = 1)	44% (n = 4)	52% (n = 7)	4% (n = 1)	35% (n = 51)	44% (n = 65)	21% (n = 35)	0.216
rs303143	94% (n = 480)	6% (n = 21)	0% (n = 0)	95% (n = 317)	5% (n = 12)	0% (n = 0)	100% (n = 9)	0% (n = 0)	0% (n = 0)	100% (n = 12)	0% (n = 0)	0% (n = 0)	93% (n = 142)	7% (n = 9)	0% (n = 0)	0.193
rs157350	84% (n = 418)	14% (n = 76)	1% (n = 7)	83% (n = 268)	17% (n = 57)	1% (n = 4)	100% (n = 9)	0% (n = 0)	0% (n = 0)	88% (n = 9)	8% (n = 2)	4% (n = 1)	88% (n = 132)	11% (n = 17)	1% (n = 2)	0.238
rs10189330	42% (n = 203)	45% (n = 229)	13% (n = 69)	38% (n = 120)	47% (n = 159)	15% (n = 50)	19% (n = 1)	63% (n = 6)	19% (n = 2)	41.7% (n = 5)	41.7% (n = 5)	16.7% (n = 2)	49% (n = 77)	42% (n = 59)	9% (n = 15)	**0.029**
rs16852912	89% (n = 452)	11% (n = 45)	1% (n = 4)	91% (n = 306)	8% (n = 21)	1% (n = 2)	100% (n = 9)	0% (n = 0)	0% (n = 0)	80% (n = 10)	20% (n = 2)	0% (n = 0)	84% (n = 127)	15% (n = 22)	1% (n = 2)	0.164
rs11066301	46% (n = 225)	43% (n = 219)	11% (n = 57)	36% (n = 117)	48% (n = 160)	17% (n = 52)	100% (n = 9)	0% (n = 0)	0% (n = 0)	64% (n = 7)	28% (n = 4)	8% (n = 1)	64% (n = 92)	28% (n = 55)	8% (N = 4)	**<0.001**

Genotypes: 0/0: wild homozygous allele, 0/1 heterozygous, 1/1 alternative homozygous allele.

of *Fto* in the brains of mice are abundant, particularly in hypothalamic nuclei governing energy balance [22]. These findings support the hypothesis that *FTO,* a fat mass- and obesity-associated gene, can be considered a significant contributor to the sarcopenia and sarcopenic obesity phenotypes.

In line with our hypothesis, a metabolomic profiling study from elderly men with and without sarcopenia found that fatty acid amide (FAA) levels, particularly docosahexaenoic acid ethanolamide (DHA EA), were significantly reduced in those with sarcopenia [23]. Notably, DHA EA levels showed a strong positive correlation with key indicators of muscle function, such as skeletal muscle mass index (SMI) and handgrip strength (HGS). Additionally, reduced DHA EA levels were linked to a 2.11-fold higher risk of sarcopenia, suggesting that DHA EA could enhance diagnostic accuracy when combined with traditional clinical measures.

This study adds valuable evidence supporting the role of metabolic markers in the pathophysiology of sarcopenia. It highlights DHA EA as a promising biomarker, along with genetic and metabolic markers, such as FTO variants in early sarcopenia detection and intervention, underscoring the importance of metabolomic and genetic profiling in age-related muscle health research.

More recently, in 2022, Jin and colleagues conducted a GWAS on a large, aged cohort of Korean individuals (n = 6961) to identify specific genetic variants associated with meta-analyses of lean body mass (LBM) and also a GWAS for appendicular skeletal muscle (ASM). They found 2 variants of which were genome-wide significant loci for LBM. The most significant variant was rs1187118 near Glutamate Metabotropic Receptor 4 (*GRM4*) and High Mobility Group AT-Hook 1 (*HMGA1*), followed by rs3768582 near Neutrophil Cytosolic Factor 2 (*NCF2*). In regard to the ASM analysis, the only significant variant was a genome-wide locus: rs6772958 near zinc finger protein 860 (*ZNF860*) and Glycerol-3-Phosphate Dehydrogenase 1 Like (*GPD1L*). These genes are expressed in skeletal muscle tissue as well a in adipose tissue, impairing adipogenesis, preventing diet-induced obesity, and insulin resistance [24].

A study focused on a community-based sample in the UK, showed highly significant correlations of skeletal muscular mass with endogenous metabolic factors assessed by non-targeted mass spec-based metabolomic profiling [25]. The authors found 162 metabolites significantly correlated with ALM, and genomic regions contributed to the variance in both metabolites and ALM. In the present study, we found 12 genetic variations associated with ALMI. Among them, three presented negative beta values, so the presence of polymorphism could be associated with a decreased ALMI, therefore increasing the risk of sarcopenia (lean mass loss) outcome. The SNPs rs9928094 and rs9930333 related to *FTO* gene, which in turn has a strong association with body mass index, obesity risk, and type 2 diabetes function, bringing some insights about another role of this gene [26]. The SNP rs303143 is related to *SPATA5* (spermatogenesis-associated protein 5) gene that encodes an ATPase with diverse activities defined by a highly conserved ATPase domain, participating in diverse cellular processes that include protein degradation. Mutations in the SPATA5 gene, on the other hand, can cause hearing loss, seizures, and movement disorders [27] and also, the most severe consequence of this SNP is to produce an intron variant. A possible relationship between this SNP and sarcopenia deserves more investigation.

The SNP rs16839632 showed a positive correlation with muscle mass. This SNP is associated with *FMN2* gene, which is a member of the formin homology protein family with essential roles in organization of the actin cytoskeleton and cell polarity, regulating adipogenic differentiation that controls the actin filament organization [28]. Another SNP positively correlated with muscle mass (rs76246107 is associated with the *PRR12* gene, which plays an essential role in nervous system development [29]. Muscle mass was also correlated with the SNP rs11066301, which is associated with *PTPN11* gene, a member of the protein tyrosine phosphatase family known to be signaling molecules

that regulate cellular processes including cell growth, differentiation, the mitotic cycle, and oncogenic transformation [30].

Although *FTO* and *FMN2* are well-known genes in the literature, what makes our study unique is that this is the first time these genes have shown significant associations in a diverse population like ours. The novelty lies in the fact that our sample, with its specific characteristics (e.g., demographics, phenotype, or ethnic diversity), has uncovered new relationships between these genes and ALMI that were previously underexplored or not detected in similar studies. This suggests that the role of *FTO* and *FMN2* may extend beyond their commonly understood functions and could be linked to more diverse biological pathways or phenotypes than those traditionally described. Therefore, while these genes are well-established in the field, our findings point to important new directions for research.

Previous studies on sarcopenia, including several data sources with European and American genetic backgrounds, included participants with predominantly Caucasian ethnicity [2,15]. The Brazilian population has an ethnic component with significant heterogeneity, which brings the need for a specific analysis considering its diversity. EPISONO is a representative study of the Brazilian population and a source of evidence for more diverse ethnic groups and, consequently, their distinct genetic characteristics. We have observed that the allele frequencies of the studied variants for sarcopenia are independently associated with ethnicity. In our sample, Asian and African population backgrounds showed differences for rs6788433 and rs76246107 (*PRR* 12 gene), rs10189330 rs11066301 (*PTPN* 11 gene). This observation, along with other previous studies [31,32] reinforces the need for the inclusion of race/ethnicity as a criterion in sarcopenia definitions since the genetic ancestry is a factor for an individual or a population to have different polymorphisms' frequencies associated with sarcopenia [33]. Although it is challenging, the use of mixed ethnicity in genetic studies can offer significant advantages and insights. There are three main points to be taken into consideration: 1. It is true that allele frequencies can vary significantly between populations. However, this variation is not necessarily a problem; rather, it can offer unique insights into how certain genetic variants affect health outcomes across different ethnic groups. In fact, studying individuals with mixed ethnicity allows us to observe the interaction of alleles from diverse backgrounds, which can lead to a better understanding of the genetic architecture of traits and diseases; 2. Imputation accuracy does depend on the similarity between the study population and the reference genome. However, for this analysis, we consider it more appropriate not to impute data and 3. Calling issues on microarrays can indeed arise when the study population is genetically diverse, as many arrays are designed based on data from specific populations (usually European). However, this challenge is not unique to mixed ethnicities—it affects any population that diverges significantly from the reference population used to design the array.

Our study has some limitations. Although our sample size was small for genetic studies (n = 712), we found statistically significant associations with twelve SNPs for sarcopenia. This is a cross-sectional study, so we cannot infer causality. We also do not have a replication cohort, but our results provide suggestive genetic pathways that future functional studies can focus on. Another limitation is that we applied the candidate gene approach, and therefore, it restricts the finding of hypothesis-free.

5. Conclusions

The present study identified, in a Brazilian population sample, 12 genetic variations significantly associated with ALMI that may potentially be involved with the pathophysiological mechanisms of sarcopenia. The identification of genetic biomarkers can contribute to the early diagnosis and prevention of sarcopenia. Ethnicity and race must be considered in sarcopenia evaluation. Sarcopenia is a relevant and eminent public health problem that affects many people during the aging process. With advances in genomic technology, identifying risk-related SNPs is a promising approach for diagnoses and precision-based therapies targeting age-related conditions.

Author contributions

SMAS, PFT and VA were responsible to conceptualization, data curation, formal analysis and writing the original draft. RDP, MLA and ST reviewed and edited the manuscript.

Conflicts of interest

The authors declare no conflict of interest as bellow:
Dr. da Silva has nothing to disclose.
Dr. Tempaku has nothing to disclose.
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Supplementary materials

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