

# Clinical, functional and inflammatory factors associated with muscle fatigue and self-perceived fatigue in elderly community-dwelling women

Fatores clínicos, funcionais e inflamatórios associados à fadiga muscular e à fadiga autopercebida em idosas da comunidade

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## Abstract

**Background:** Fatigue is a common and nonspecific symptom associated with chronic health problems in the elderly. The modifications and adaptations of the aging process associated with complex and multidimensional nature of fatigue favors the interaction of multiple factors in the genesis of this phenomenon. **Objectives:** To investigate the association of clinical, functional and inflammatory factors with muscle fatigue and self perceived fatigue in elderly women. **Methods:** Participated in the study one hundred and thirty five community elderly women, all sedentary, with a mean age of  $71.2 \pm 4.57$ . A structured questionnaire and functional testing were used to evaluate clinical and functional characteristics. Plasma concentrations of inflammatory mediators (IL-6 and sTNFR1) were measured by ELISA method. Muscle fatigue was measured by isokinetic dynamometer and self-perceived fatigue was measured by a visual analog scale. Statistical analysis was performed by multiple linear regression and Spearman correlation coefficient with statistical significance of 5%. **Results:** The regression models showed that the variables age, body mass index, physical activity level, functional capacity and peak torque were associated with muscle fatigue ( $R^2=0.216$ ,  $p<0.01$ ). Self-perceived fatigue was associated with number of comorbidities, depression, physical activity level, functional capacity, peak torque and perceived health ( $R^2=0.227$ ,  $p<0.01$ ). **Conclusion:** This study showed a psychophysical interaction of the fatigue, by identifying the main factors associated with muscle fatigue and self-perceived fatigue in elderly women. These findings demonstrate the importance of evaluation and treatment of modifiable factors in both muscle fatigue and self-perceived fatigue, seeking a better physical and functional performance of elders.

**Key words:** Muscle fatigue; self-perceived fatigue; aging; elderly.

## Resumo

**Contextualização:** A fadiga é um sintoma comum e inespecífico associado aos problemas crônicos de saúde nos idosos. As alterações e adaptações do processo de envelhecimento associadas à natureza complexa e multidimensional da fadiga favorecem a interação de múltiplos fatores na gênese desse fenômeno. **Objetivos:** Investigar a associação dos fatores clínicos, funcionais e inflamatórios com a fadiga muscular e a autopercebida em idosas. **Métodos:** Participaram 135 idosas sedentárias da comunidade, com média de idade de  $71,2 \pm 4,57$ . Questionário estruturado e teste funcional foram utilizados para avaliar as características clínicas e funcionais. As concentrações plasmáticas dos mediadores inflamatórios (IL-6 e sTNFR1) foram dosadas pelo método ELISA. A fadiga muscular foi mensurada pelo dinamômetro isocinético, e a fadiga autopercebida, pela Escala Visual Analógica (EVA). A análise estatística foi realizada pela regressão linear múltipla e pelo Coeficiente de Correlação de Spearman, com nível de significância de 5%. **Resultados:** Os modelos de regressão demonstraram que os fatores idade, índice de massa corporal (IMC), nível de atividade física, capacidade funcional e pico de torque foram associados à fadiga muscular ( $R^2=0,216$ ,  $p<0,01$ ). A fadiga autopercebida foi associada ao número de comorbidades, estado depressivo, nível de atividade física, capacidade funcional, pico de torque e saúde percebida ( $R^2=0,227$ ,  $p<0,01$ ). **Conclusão:** O presente estudo mostrou uma interação psicofísica da fadiga, identificando os principais fatores associados à fadiga muscular e à autopercebida em idosas. Esses achados demonstram a importância da avaliação e tratamento dos fatores modificáveis tanto na fadiga muscular quanto na autopercebida, buscando um melhor desempenho físico-funcional dos idosos.

**Palavras-chave:** fadiga muscular; fadiga autopercebida; envelhecimento; idosos.

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## Introduction ::::

Fatigue is a nonspecific symptom associated with chronic health problems and with functional deterioration, and its construct has a complex and multidimensional nature<sup>1</sup>. The word fatigue has been used to describe several physiological and psychological phenomena; therefore, it is frequent the misunderstanding and controversy in its definitions<sup>2</sup>. From the physiological perspective, fatigue is related to the functional failure of one or several organs. Whereas from a psychological perspective, it is associated to the conscious, subjective and individual state of reduced motivation, involving physical, mental and/or emotional alterations<sup>1</sup>. Ahsberg<sup>2</sup> in an operational division, distinguished three forms of fatigue: physiological, objective and self-perceived<sup>2</sup>.

Regarding physiological fatigue, the focus is the muscle and its capacity to generate and maintain muscle power<sup>3</sup>. Muscle fatigue can be defined as the reduction, induced by the capacity of the neuromuscular system to generate strength, work or power<sup>1,3,4</sup>. Its setup may be related to neurological, metabolic, electrophysiological, mechanical, subjective among others, which interfere in the synchronous functioning between the central nervous system (CNS) and the peripheral paths<sup>5,6</sup>.

Objective fatigue is related to a modified performance during the execution of a certain type of task<sup>2</sup>. Individual alterations in the performance might be influenced by the type of activity or work<sup>5</sup>. The performance of subjects at the work environment is the focus. In this context, fatigue represents a reduction in the performance, a loss of efficiency and/or a lack of interest in working<sup>2</sup>.

The self-perceived fatigue can be understood as a conscious and unpleasant symptom, encompassing sensations that involve the whole body<sup>1</sup>. It is a subjective symptom that can be influenced by internal or external features of the subject<sup>2,7</sup>. Fatigue sensation may be related to physical alterations and modifications to mental and emotional status. The context of this approach is multifactorial<sup>1,8</sup>. The conscious self-report of tiredness is the most important information for the evaluation of fatigue under the psychological and subjective perspective<sup>2</sup>.

The variety of descriptions on fatigue illustrates its diverse meanings, among which it is not always possible to obtain a clear differentiation. This multifactorial nature shall be considered in the assessment of the fatigue symptoms in the elderly. The neuromuscular alterations associated to sarcopenia produce quantitative and qualitative deficiencies on movements and muscle function, predisposing to significant impairment on functionality and fatigue symptoms<sup>9-11</sup>. Otherwise, the diversity of health problems that affects elderly people can also influence fatigue onset<sup>12</sup>.

The diverse alterations related to the aging process, as well as the multidimensional nature of fatigue create a propitious condition for the interaction among several factors in its manifestations in the elderly population<sup>12,13</sup>. Clinical, physical, functional, psycho-emotional, lifestyle, alterations in the concentration of inflammatory mediators, among others inherent to senescence and senility, may be associated to fatigue<sup>10,12-14</sup>. However, fatigue symptoms, considered under a multifactorial perspective, have been scarcely documented in elderly people. None comparative investigation was identified in the literature, with regards to the major factors associated to physical and self-perceived fatigue.

To investigate fatigue with emphasis in the multifactorial aspects will provide scientific advances for a better comprehension of these symptoms in the elderly people. It will also offer evidence for comprehension of the major mechanisms involved in this phenomena, supporting the understanding of the relations and interactions between fatigue symptoms and functionality and morbid-mortality. In this context, the purpose of the present study was to investigate the association of clinical, functional and inflammatory factors muscle and self-perceived fatigue in community-dwelling older adults.

## Methods ::::

This is an observational, cross-sectional study, approved by the Ethics Committee of Research of the Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil, under the protocol n° ETIC 321/07 – Amendment 01/08.

## Sample

The present study used a convenience sample composed of 135 sedentary, community-dwelling older women, recruited from the Center of Reference for the Elderly People of the UFMG; at the Centro Universitário de Belo Horizonte (UNIBH), Belo Horizonte, MG, Brazil; in the Network Studies on Frailty in Brazilian Older Adults - REDE FIBRA; from the waiting list of the Project Physical Education for the Third Age of the UFMG and through advertisements in local newspapers. All volunteers agreed to participate and signed a free informed consent.

The inclusion criteria were: being female, aged from 65 years-old or older, living in the community and walking without aid devices. Older women with sequel of neurologic diseases, history of recent fractures in the lower limbs, active neoplastic in the last five years, cognitive impairment detectable in the Mini-Mental State Exam<sup>15</sup>, acute inflammatory diseases and use of immune-reactive medication were excluded.

The sample size was based on a pilot study with 15 participants and from literature information<sup>16</sup>. A statistical power of 90% and  $\alpha$  value of 5% was previously defined. After the use of statistical tables of power, the minimal sample number was defined as 92 older women<sup>17</sup>.

## Measuring instruments

All participants were required to answer a structured multidimensional questionnaire for characterizing the sample with regards to their clinical and socio-demographic aspects, such as age, marital status, levels of education, number of comorbidities, body mass index (BMI) and perceived health. In order to quantify depressive status, the short version of the Geriatric Depressive Scale (GDS)<sup>18</sup>, the level of physical activity was assessed through the Human Activity Profile (HAP)<sup>19</sup> questionnaire. All the instruments were administered by previously trained examiners.

## Muscular fatigue

Muscular fatigue of knee extensors was assessed through an isokinetic dynamometer (*Biodex System 3 Pro*<sup>®</sup>). Participants performed 21 maximal repetitions of knee extension in an angular velocity of 180°/s and a range of motion (ROM) of 90°. The muscular fatigue index (MFI) represents the percentage of work (W) declined during the test and was calculated by the software of the isokinetic dynamometer based on the following equation:  $MFI = 100 - (W_{latter} \frac{1}{3} / W_{former} \frac{1}{3} \times 100)$ . Higher MFI indicate a higher level of muscular fatigue of the muscle assessed. The protocol used for the isokinetic dynamometer was administered by a single trained examiner. All procedures for test execution were performed following the manufacturer's recommendations<sup>20</sup>.

## Self-perceived fatigue

Tiredness or fatigue sensations reported by the participants for the execution of the usual daily activities was assessed by an Visual Analogue Scale for fatigue (VAS-F), with graduation in colors, ranging from light blue (minimal) to intense red (maximal), and a numerical scale ranging from 0 to 10 cm, which quantified the level of fatigue reported. The procedures for such assessment were standardized and administered by a single trained evaluator<sup>21</sup>.

## Functional capacity

The assessment of functional performance was performed through the sit-to-stand test. The time taken for each participant

to stand up and sit back down in a standardized chair for five times, with arms crossed on the trunk, was recorded. This test presents acceptable reliability and validity to assess functional performance among older adults<sup>22</sup>.

## Inflammatory mediators

Plasma concentrations of the inflammatory mediators interleucin-6 (IL-6) and soluble receptor of tumor necrosis factor  $\alpha$  (sTNFR1) were measured by the method *Enzyme-Linked Immuno Sorbent Assay* (ELISA). To dose IL-6 and sTNFR1, high sensibility kits were used (*Quantikine*<sup>®</sup>HS, *R&D Systems, Mineapolis, USA*). All the tests were performed according to recommendations from the manufacturers. Samples' reading was performed by a microplate reader adjusted for 490 nm and correction of wave length in 650 nm.

## Statistical analysis

To describe the sample characteristics, measures of frequency and central tendency were used. Analysis of normality distribution was performed by *Kolmogorov-Smirnov* test.

The association between the clinical, functional and inflammatory features (independent variables) with the type of fatigue (dependent variables) was determined by two models of multiple regression analysis: one for muscular fatigue and other for self-perceived fatigue. This model of analysis was performed because the dependent variables were continuous and the assumptions of the multiple linear regression (absence of multicollinearity among the independent variables, presence of direct linear relationship of the independent variables with the dependent ones and the normality of distribution from the model residues) were confirmed. The potential explanatory variables were selected according to statistical theoretical criteria and included in the regression models according to statistical criteria. First, the following explanative variables were considered: age, BMI, plasmatic concentrations of IL-6 and sTNFR1, levels of physical activity, functional capacity, and peak torque normalized by the participants' weight, depressive status, self-perceived health and number of comorbidities. There were included in the models of regression only the independent variables that significantly correlated with the outcome variables ( $p < 0.05$ ). Since the independent variables that significantly correlated with the dependent variable did not present normal distribution, the correlations of the explanative variables that were included in the regression model for muscular fatigue and self-perceived fatigue were assessed by the Spearman's Correlation Coefficient. For each regression model, by the *Backward elimination* method, All analyses were performed using the *Statistical Package for the Social Sciences*

(SPSS) for Windows (Version 15.0), and the level of significance adopted was 5%.

## Results

One hundred thirty-five old women participated in this study. They were sedentary, living in the community, with good functionality levels, and with absence of apparent inflammatory signs. The descriptive characteristics of the sample are shown in Tables 1 and 2.

The variables plasma concentrations of IL-6 (Rho=0.001; p=0.999) and sTNFR1 (Rho=0.23; p=0.798), number of comorbidities (Rho=-0.26; p=0.770), depressive state (Rho=-0.113; p=0.204) and perceived health (Rho=-0.074; p=0.431) did not correlate significantly with the variable muscle fatigue and were not included in the regression model. The final model demonstrated that the factors age, BMI, level of physical activity, functional capacity and peak torque explained 21.6% (R<sup>2</sup>=0.216, p<0.01) of muscle fatigue variability, and the peak torque was the variable that most explained the muscle fatigue (Table 3).

For the self-perceived fatigue, there was no significant correlation with the variables plasma levels of IL-6 (Rho=-0.790; p=0.370), sTNFR1 (Rho=0.149; p=0.090), age (Rho=0.017; p=0.847) and BMI (Rho=-0.070; p=0.425). These variables were not included in the regression model. The final model showed association of the self-perceived fatigue with the factors number of comorbidities, depressive state, levels of physical activity, functional capacity, peak torque and perceived health. These

**Table 1.** Descriptive characteristics of sample: continuous variables.

Variable	n	Mean	Standard Deviation	Median
Age (years)	135	71.29	±4.57	70.00
Level of education (years)	134	5.59	±3.88	4.00
Weight (kg)	135	68.37	±12.17	66.95
Height (cm)	135	154.77	±5.98	155.00
IL-6 (pg/ml)	132	3.56	±6.96	1.72
sTNFR1 (pg/ml)	132	1393.95	±503.07	1310.23
Comorbidities (n°)	134	2.93	±1.76	3.00
Functional capacity (seconds)				
Sit and stand up from a chair	135	15.08	±3.87	15.25
Peak torque (Nm)				
Right knee extensors	131	79.81	±19.39	80.70
Self-perceived fatigue				
EVA-F(score/10)	133	4.08	±2.61	3.90
Muscle fatigue (IMF in %)				
Right knee extensors	131	34.20	±10.92	36.10

IL-6=interleukin 6; sTNFR1=soluble receptor tumor necrosis factor α; VAS-F=visual analogue scale of fatigue; IMF=index of muscle fatigue.

variables explained 22.7% (R<sup>2</sup>=0.227, p<0.01) of the variability of subjective fatigue. Levels of physical activity and perceived health were the factors which most explained self-perceived fatigue (Table 3). The results from the present study also indicated a negative and significant correlation between self-perceived fatigue and muscular fatigue from knee extensors (Rho=-0.185; p<0.05).

## Discussion

In this exploratory investigation, there were analyzed the relationships between fatigue and muscular fatigue with the major clinic, functional and inflammatory factors in

**Table 2.** Descriptive characteristics of sample: categorical variables.

Variable	n	Frequency	Percentage
Marital status (score/4)	134		
Married/partner		45	33.6
Single		16	11.9
Divorced		12	9.0
Widowed		61	45.5
*Body mass index - BMI (kg/m <sup>2</sup> )	135		
Underweight (BMI <18.5)		2	1.48
Normal weight (18.5 ≤ BMI ≤ 24.9)		26	19.26
Overweight (25.0 ≤ BMI ≤ 29.9)		56	41.48
Obesity (BMI ≥ 30.0)		51	37.78
Class I (30.0 ≤ BMI ≤ 34.9)		38	28.15
Class II (35.0 ≤ BMI ≤ 39.9)		12	8.89
Class III (BMI ≥ 40.0)		1	0.74
Perceived health (score/3)	123		
Poor		6	4.9
More or less		57	46.3
Good		60	48.8
Life satisfaction (score/3)	123		
Little		3	2.4
More or less		41	33.3
Very		79	64.2
Depressive state (score GDS/15)	133		
0-3 points		67	50.37
4-6 points		44	33.08
7-9 points		18	13.53
10-15 points		4	3.01
†Physical activity level (score HAP/94)	134		
Inactive (AAS<53)		21	15.67
Moderately active (53 ≤ AAS ≤ 74)		76	56.72
Activity (AAS>74)		37	27.61
Dominance LL (score/2)	135		
Right		133	98.5
Left		2	1.5

GDS=geriatric depression scale; HAP=human activity profile; LL=lower limbs; BMI=body mass index, \* CUT off points for categories according to criteria of World Health Organization; † AAS=adjusted activity score.

community-dwelling older women. Demographic data indicate a growing in feminization of old age, justifying the relevance of the investigations involving old female population<sup>23</sup>.

The factors age, BMI, level of physical activity, functional capacity and peak torque presented significant association with muscle fatigue of knee extensors. Peak torque was the factor that best explained the variability of the muscle fatigue, remaining associated negatively and independently even after adjustment for the other explanatory variables. Peak torque represents the maximal muscle strength of an individual, reflecting the point of maximal muscle performance during a isokinetic test, besides of being the most frequently described parameter in isokinetic assessments of muscular performance<sup>24</sup>. Our results demonstrated that the increase on peak torque was associated to an increase on muscular fatigue. Katsiaras et al.<sup>16</sup>, assessing muscular fatigue of knee extensors in a sample of 1512 older adults, with age ranging from 70 to 79 years, good functionality, recruited from a cohort of the *Health ABC Study*, with 3075 participants, also found similar results regarding the variable peak torque and knee extensors muscular fatigue<sup>16</sup>. A plausible explanation for this association may be the increased use of the oxidative path for the production of adenosine triphosphate (ATP) during muscular contraction and strength generation by the older adults<sup>25,26</sup>. This

aerobic path presents more metabolic economy and lower fatigue rate when compared to the glycolytic/anaerobic metabolism, which is less used as a source of energy in muscle contraction of the elders<sup>25,27</sup>. The definition of muscle fatigue used in the present study, represented by the MFI, indicates the reduction of the capacity of the neuromuscular system to generate power over time and shall be considered for a better comprehension of the results. Neuromuscular alterations of the aging process cause decrease of the number of type II muscle fibers in relation to the type I fibers and, thus, muscular power production in the elders become more dependent of type I fibers, which are more resistant to fatigue, nevertheless produce less power than type II fibers. From this perspective, in this sample, it might be that those older women with higher muscle strength presented a greater proportion of type II fibers and, consequently, a higher fatigue rate, since, theoretically and proportionally, they had more type II fibers, which are stronger and less resistant to fatigue<sup>28</sup>. This argument is in accordance with the literature which indicate higher muscle fatigue rate in young adults, whom possess relatively higher muscle strength and higher proportion of type II fibers, when compared to older adults<sup>25-27</sup>.

Spearman's Correlation Coefficient indicated that, unexpectedly, there was a negative correlation of the features

**Table 3.** Relationship of muscle fatigue and self-perceived fatigue with clinical, functional and inflammatory.

Variable	Muscle fatigue (EXTD)				Self-perceived fatigue (EVA-F)			
	Sperman correlation		‡ Multivariate linear regression R <sup>2</sup> = .216		Sperman correlation		‡ Multivariate linear regression R <sup>2</sup> = .227	
	rho	p	β	p	rho	p	β	p
Age (years)	-.263* n=129	<.01	-.109	.20	.020 n=133	.85	-	-
IL-6 (pg/ml)	-.0001 n=126	.99	-	-	-.079 n=130	.37	-	-
sTNFR1 (pg/ml)	.023 n=126	.80	-	-	.149 n=130	.90	-	-
Comorbidities (n°)	-.026 n=128	.43	-	-	.184* n=132	<.05	-.036	.71
BMI (kg/m <sup>2</sup> )	-.223* n=129	<.05	-.072	.44	-.070 n=133	.43	-	-
Perceived health (score/3)	-.074 n=117	.43	-	-	-.252* n=122	<.01	-.153†	<.05
Peak torque normalized weight (Nm)	.429* n=129	<.01	.305†	<.01	-.186* n=129	<.05	.171	.12
Depressive state (score GDS/15)	-.113 n=128	.20	-	-	.377* n=133	<.01	.100	.25
Physical activity level (score PAH/94)	.287* n=128	<.01	.081	.43	-.379* n=133	<.01	-.407†	<.01
F.C. – Sit and stand up (seconds)	-.283* n=129	<.01	-.051	.58	.324* n=133	<.01	.126	.20

\* Significant correlation with the dependent variable; † significant independent association in the regression model adjusted for other variables; ‡ n=113 for all variables in the regression; BMI=body mass index; IL-6=interleukin 6; sTNFR1=soluble receptor tumor necrosis factor α; IMF=index of muscle fatigue; GDS=geriatric depression scale; HAP=human activity profile; F.C.=functional capacity; EXTD=right knee extensor muscles; VAS-F=visual analogue scale of fatigue.



age, BMI and functional capacity. In other words, the older the subjects were, the higher their BMI, the poorer their BMI as well as their levels of physical activity and the lower were their FMI. These variables are pointed in the literature as relevant aspects in the evaluations of physical and functional performances of the older adults and presented associations with the changes in muscular strength, reduction of mobility and functional decline<sup>12-14,29</sup>, but not with fatigue. In a first glance, the results from the present study seem discrepant from the remaining literature. The first impression would be that the older adults, obese, with low levels of physical activity and with poorer functional capacity, would have higher FMI, but the results from the present study evidenced the opposite situation. It is valuable to highlight that the results relative to muscle fatigue reflect the decline of muscle performance of the older women along the time of execution of the isokinetic test. The evidence consulted indicated an association between lower muscle strength with a functional decline<sup>28-30</sup>, but not with the increase on muscle fatigue among the elders.

These findings can be explained by the higher proportion of type I fibers in aged muscles, since they are more resistant to fatigue, but generate lower peak torque and, therefore, lower muscular strength<sup>28</sup>. Moreover, it should be noted that muscle function is complex and is associated with other variables<sup>6</sup>, in addition to the peak torque during isokinetic testing.

The results for self-perceived fatigue showed a significant association between higher perception of fatigue with the largest number of comorbidities, worse depression status, poorer health perception, lower levels of physical activity, poorer physical functioning and lower peak torque. Self-perceived health and level of physical activity were the factors that most explained the variation in self-perceived fatigue. These associations are in agreement with the literature, suggesting multifactorial relationships in self-perceived symptoms of fatigue in older adults<sup>12,14</sup>. In this sample, there was also an association between physical and emotional factors with the symptoms of self-perceived fatigue.

The results of this study are corroborated by the literature. Polur et al.<sup>12</sup> in a review of fatigue in the elderly population, observed an association of fatigue symptoms with chronic diseases, health problems, depressive symptoms, psychological problems and physical disability<sup>12</sup>. Avlund et al.<sup>30</sup> studying factors associated with tiredness in a sample of approximately 1000 elders observed associations between the number of comorbidities, muscle weakness, depression status, social status and pain with symptoms of tiredness<sup>30</sup>. Recent evidences indicated the association of self-perceived fatigue with poorer functional capacity, worse physical functioning, muscle weakness, changes in mobility, among others<sup>10,14</sup>.

The self-perceived fatigue was negatively associated with muscle fatigue in the older women evaluated. The findings of the literature on the subject are conflicting; Bautmans et al.<sup>21</sup> studying a sample of older adults, found negative and significant correlation of self-perceived fatigue with the manual muscle fatigue<sup>21</sup>. However, the same group of researchers, in another study in 2008, investigating a sample of elderly subjects, found no correlation between self-perceived fatigue and manual muscle fatigue<sup>31</sup>. The comparison of our results with the two studies of Bautmans et al.<sup>21,31</sup> was not possible due to the methodological differences. In this study we assessed the knee extensors using an isokinetic protocol of dynamic muscle contractions, while in the studies of Bautmans, a hand dynamometer and a protocol of isometric contraction of wrist's muscles were used<sup>21,31</sup>. The samples of the studies of Bautmans et al.<sup>21,31</sup> were varied; in one study, it was composed of community-dwelling older adults without inflammation<sup>21</sup> and, in the other, by institutionalized elderly affected by evident inflammatory process<sup>31</sup>. In both cases, no information was provided regarding the levels of physical activity; therefore, it may be a confounding factor in comparing the results. It is noteworthy that the sample studied in this study consisted of community-dwelling older women, sedentary, with good functionality and without evidence of inflammation processes.

The results of this study showed no associations between self-perceived fatigue and muscle fatigue with plasma IL-6 and sTNFR1 levels. The evidences from the literature are controversial. While there are reports of correlation of elevated levels of IL-6 with low levels of manual muscle fatigue<sup>21</sup>, there are evidence of correlation of high concentrations of IL-6 and TNF- $\alpha$  with worse resistance to muscle fatigue<sup>31</sup>. However, the interpretation of the results of previous studies and of this study regarding the release of inflammatory mediators should be cautious. It is necessary to consider the multiple factors and mechanisms responsible for the production and release of IL-6 and TNF- $\alpha$ , as well as its soluble receptor (sTNFR1). Studies have shown that the production and release of inflammatory mediators in the elderly is a complex process regulated by different mechanisms<sup>32,33</sup>.

Another important aspect of the results of this study is that the level of physical activity, functional capacity and peak torque were predictive variables for the two types of fatigue. Such data are particularly important if there were observed differences between the determinant factors for each of the studied fatigues. There is evidence that the mechanical principles related to the onset of muscle fatigue in older adults involve, mainly, physiological neuromuscular changes<sup>25</sup>, whereas for self-perceived fatigue, the mechanisms involved are more complex and influenced by multiple factors,

including physiological, psychological, individual and subjective factors<sup>12,14</sup>. This evidence support the hypothesis that, in elderly, healthy, community-dwelling women, the FMI of knee extensors are mainly a reflection of the deterioration of the physiological capacity of the neuromuscular system to maintain maximal contractions and are less associated with the subjective aspects. On the other hand, analyzing the characteristics of the variables associated with self-perceived fatigue, it is possible to suggest a psychophysical interaction to explain their subjective symptoms. In the elderly adults evaluated, there were influences from both physiological factors and subjective and psychological factors. However, to demonstrate these relationships in studies with humans seems to be a difficult task, considering the several factors that may be involved with the final outcome<sup>6</sup>.

Some limitations of this study should be considered. The possible bias in sample selection can compromise the interpretation and the generalisability of our results, thus limiting their external validity. The absent evaluation of the aspects related to metabolic muscle fatigue is another point that should be mentioned; since there is evidence that the metabolic changes of the muscles are the main determinant factors for the muscle fatigue<sup>25</sup>.

The lack of a multidimensional instrument for assessing self-perceived symptoms of fatigue, which is known to be affected by multiple factors<sup>1</sup>, may also have influenced the results.

This study provided a general and expanded overview on fatigue, investigating the main factors behind this symptom in

community-dwelling older adults. Maximal muscle strength, represented in this study for peak torque, was the predictive factor that best explained muscular fatigue, which also showed associations with physical activity level, functional capacity, age and BMI. Predictive factors of greatest impact on the self-perceived fatigue were the levels of physical activity and perceived health. In this sample, this type of fatigue was also associated with the factors functional capacity, peak torque, number of comorbidities and depression status.

These results support the evidence<sup>10,12,13</sup> that pointed for the multifactorial relationships in the onset of fatigue in the elderly. Physical therapists and other professionals in the field of rehabilitation should consider these aspects in clinical practice, being useful the combination of diverse factors for measuring and classifying fatigue in the elderly. Thus, the approach of fatigue symptoms in the elderly population, both in interventions and in evaluations, should consider the multifactorial nature and the psychophysical construct of the fatigue.

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