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FACULDADE DE CIÊNCIAS DA NUTRIÇÃO E ALIMENTAÇÃO
UNIVERSIDADE DO PORTO

SARCOPENIA, FRAILTY AND NUTRITIONAL STATUS IN OLDER PEOPLE

Sarcopenia, fragilidade e estado nutricional em pessoas idosas

Thesis presented to the *Faculdade de Ciências da Nutrição e Alimentação da Universidade do Porto*

Ph.D. in Clinical Nutrition

Ana Rita Sousa Santos

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Supervisor:
Prof. Teresa Maria de Serpa Pinto Freitas do Amaral
Associate professor at the
Faculdade Ciências da Nutrição e Alimentação da Universidade do Porto

To my family

"Passion for your work is a little bit of discovery, followed by a lot of development, and then a lifetime of deepening."

Angela Duckworth
Grit: The Power of Passion and Perseverance

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Abbreviations

ABSI	Body shape index
ASM	Appendicular skeletal muscle mass
BIA	Bioelectrical impedance analysis
BMI	Body mass index
BRI	Body roundness index
CC	Calf circumference
CI	Confidence interval
DXA	Dual-energy X-ray absorptiometry
EWGSOP	European Working Group on Sarcopenia in Older People
HGS	Handgrip strength
ICD	International Classification of Diseases
IGF-1	Insulin-like growth factor 1
MAMC	Mid-arm muscle circumference
MMSE	Mini-Mental State Examination
MNA-SF	Mini-Nutritional Assessment – Short Form
NPV	Negative predictive value
PPV	Positive predictive value
SE	Standard error
SMI	Skeletal muscle mass index
SMM	Skeletal muscle mass
SPPB	Short Physical Performance Battery
TSF	Triceps skinfold
TUG	Timed-Up and Go test
WC	Waist circumference
WHO	World Health Organization
1,25(OH)$_2$D	1,25-dihydroxyvitamin D
25(OH)D	25-hydroxyvitamin D

List of Publications

This thesis is based on the following papers:

I. **Sousa-Santos AR**, Amaral TF. Differences in handgrip strength protocols to identify sarcopenia and frailty - a systematic review. BMC Geriatr. 2017 Oct 16;17(1):238. doi: 10.1186/s12877-017-0625-y.

II. **Sousa-Santos AR**, Afonso C, Moreira P, Padrão P, Santos A, Borges N, Amaral TF. Weakness: The most frequent criterion among pre-frail and frail older Portuguese. Arch Gerontol Geriatr. 2018 Jan;74:162-168. doi: 10.1016/j.archger.2017.10.018.

III. **Sousa-Santos AR**, Afonso C, Santos A, Borges N, Moreira P, Padrão P, Fonseca I, Amaral TF. The association between 25(OH)D levels, frailty status and obesity indices in older adults. PLoS One. 2018 Aug 28;13(8):e0198650. doi: 10.1371/journal.pone.0198650.

IV. **Sousa-Santos AR**, Afonso C, Borges N, Santos A, Padrão P, Moreira P, Amaral TF. Sarcopenia and Undernutrition Among Portuguese Older Adults: Results From Nutrition UP 65 Study. Food Nutr Bull. 2018 Sep;39(3):487-492. doi: 10.1177/0379572118765801.

V. **Sousa-Santos AR**, Afonso C, Borges N, Santos A, Padrão P, Moreira P, Amaral TF. Factors associated with sarcopenia and undernutrition in older adults. Nutr Diet. 2019 Nov;76(5):604-612. doi: 10.1111/1747-0080.12542.

VI. **Sousa-Santos AR**, Afonso C, Borges N, Santos A, Padrão P, Moreira P, F Amaral T. Sarcopenia, physical frailty, undernutrition and obesity cooccurrence among Portuguese community-dwelling older adults: results from Nutrition UP 65 cross-sectional study. BMJ Open. 2020 Jun 15;10(6):e033661. doi: 10.1136/bmjopen-2019-033661.

VII. Afonso C, **Sousa-Santos AR**, Santos A, Borges N, Padrão P, Moreira P, Amaral TF. Frailty status is related to general and abdominal obesity in older adults. Nutr Res. 2021 Jan;85:21-30. doi: 10.1016/j.nutres.2020.10.009.

VIII. **Sousa-Santos AR**, Barros D, Montanha TL, Carvalho J, Amaral TF. Which is the best alternative to estimate muscle mass for sarcopenia diagnosis when DXA is

unavailable? Arch Gerontol Geriatr. 2021 Nov 1;97:104517. doi: 10.1016/j.archger.2021.104517.

Abstract

Population ageing is a global phenomenon, and its pace is much faster than in the past. The world's older population is increasing, and Portugal is no exception. Unfortunately, higher life expectancy does not necessarily mean an increased quality of life, and the growth in the numbers and proportions of older adults raise important health concerns.

Sarcopenia and frailty are two conditions often associated with ageing that share vast similarities, namely concerning its aetiologic factors and overall impact on health status and quality of life. Despite the growing interest and the enormous progress made in these areas, there are still some matters that require further investigation, such as the inconsistency in the criteria and procedures used to define sarcopenia and frailty, the frequency of these conditions in the Portuguese older population, and their association with other conditions related to nutritional status.

Hence, the present work aims to increase the knowledge on sarcopenia, frailty, and several conditions related to nutritional status among the Portuguese older population, particularly: to describe the frequency of sarcopenia, undernutrition and frailty, and their associated factors; to evaluate the association between frailty and several anthropometric indicators of body adiposity, and also with vitamin D levels; to investigate the coexistence of these health conditions among these individuals; to compile and critically review all the data regarding handgrip strength measurement for the diagnosis of sarcopenia and frailty; to elucidate which is the best alternative method to estimate muscle mass for sarcopenia diagnosis in older adults.

The studies comprised in chapters 2 and 3 included data from the Nutrition UP 65 Project, a cross-sectional study conducted in Portugal, which was based on a nationwide sample of 1500 older adults (≥65 years) representative of the Portuguese older population in terms of age, sex, education, and regional area. Data were collected between December 2015 and June 2016. In chapter 4.1, it is presented a systematic review that was carried out following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Statement). Finally, for chapter 4.2 a cross-sectional study was conducted on a convenience sample of older adults aged ≥65 years, or if they completed 65 years in the year of the evaluation, between November 2017 and February 2020.

The results of this thesis lead to the following conclusions: (a) sarcopenia frequency was low (4.4%) in this nationwide sample of Portuguese older adults. However, a large proportion (36%) of the individuals presented the primary parameter of sarcopenia diagnosis (low muscle strength). Moreover, a low frequency of undernutrition was observed in this sample however, together with undernutrition risk, it affected 16% of the older adults; (b) pre-frailty and frailty were highly prevalent among these Portuguese older adults. More than half were pre-frail and one-fifth was frail, and weakness was the criterion more frequently observed; (c) frailty and obesity were independently associated with lower 25-hydroxyvitamin D levels, and besides the commonly used obesity indicators (body mass index and waist circumference), body shape index and body roundness index showed an inverse association with serum 25-hydroxyvitamin D concentrations; (d) overweight, general and abdominal obesity rates were high among Portuguese older adults, and older adults with frailty were more likely to have general and abdominal obesity; (e) almost three out of five older adults presented at least one, and one-fifth had two or more of these health conditions (sarcopenia, physical frailty, undernutrition, and obesity). When all pre-conditions were considered, almost all older adults presented at least one of these pre-conditions or conditions; (f) it was found a high heterogeneity in handgrip strength protocols used by the studies to identify sarcopenia and frailty; (g) in a sample of 159 older adults, sarcopenia frequency showed a great variability depending on the method used to estimate muscle mass and the cut-off point applied. Bioelectrical impedance analysis was found to be a suitable alternative method to evaluate muscle mass for the diagnosis of sarcopenia, and calf circumference showed to be a valid indicator to rule in the presence of sarcopenia.

Overall, our findings suggest that some of these age-related and nutritional conditions are highly prevalent in Portuguese older adults and emphasise the need to screen these individuals. Moreover, the low coexistence between sarcopenia, physical frailty, undernutrition, and obesity found here, reinforces the need to assess them all individually during geriatric assessment. Furthermore, the enormous differences observed concerning sarcopenia and frailty diagnostic criteria may hamper the comparison with other studies.

Keywords: sarcopenia, frailty, nutritional status, obesity, undernutrition, vitamin D.

Resumo em português

O envelhecimento da população é um fenómeno global, e o ritmo do envelhecimento populacional é muito mais acelerado que no passado. A população idosa mundial está a aumentar, e Portugal não é exceção. Infelizmente, uma maior esperança de vida não é sinónimo de melhor qualidade de vida, e o aumento do número e proporção de pessoas idosas levanta questões importantes de saúde.

A sarcopenia e fragilidade são duas condições frequentemente associadas ao envelhecimento que partilham inúmeras similaridades, nomeadamente no que diz respeito aos seus fatores etiológicos e impacto no estado de saúde geral e qualidade de vida. Apesar do crescente interesse e enorme progresso observado nestas áreas, ainda há alguns aspetos que requerem uma investigação mais aprofundada, particularmente a inconsistência nos critérios e procedimentos usados para definir sarcopenia e fragilidade, a frequência destas condições na população idosa portuguesa e a sua associação com outras condições relacionadas com o estado nutricional.

Por conseguinte, o presente trabalho tem como objetivo o estudo da sarcopenia, fragilidade e de várias condições relacionadas com o estado nutricional na população idosa portuguesa, particularmente: descrever a frequência de sarcopenia, desnutrição e fragilidade e os seus fatores associados; avaliar a associação entre fragilidade e múltiplos indicadores de adiposidade corporal, e ainda com os níveis séricos de vitamina D; investigar a coexistência destas condições de saúde nestes indivíduos; reunir e analisar todos os dados relativos à medição da força de preensão da mão para o diagnóstico de sarcopenia e fragilidade; clarificar qual o melhor método alternativo para avaliar a massa muscular para o diagnóstico de sarcopenia em pessoas idosas.

Os estudos englobados nos capítulos 2 e 3 incluíram dados do Projeto *Nutrition UP 65*, que foi um estudo transversal realizado em Portugal, baseado numa amostra nacional de 1500 pessoas idosas (≥65 anos) representativa da população idosa portuguesa quanto à idade, sexo, escolaridade e área regional. Os dados foram recolhidos entre dezembro 2015 e junho de 2016. No capítulo 4.1 foi realizada uma revisão sistemática, seguindo as recomendações da *PRISMA Statement*. Finalmente, para o capítulo 4.2 foi realizado um estudo transversal na cidade do Porto, Portugal. Este estudo avaliou uma amostra de conveniência de pessoas idosas com idade ≥65 anos, ou que completassem 65 anos no ano da avaliação, entre novembro 2017 e fevereiro 2020.

Os resultados desta tese conduziram às seguintes conclusões: (a) a frequência de sarcopenia era baixa (4.4%) nesta amostra de pessoas idosas portuguesas. Contudo, uma grande proporção (36%) dos indivíduos apresentava o parâmetro primário do diagnóstico de sarcopenia (baixa força muscular). Além disso, observou-se uma baixa frequência de desnutrição nesta amostra, no entanto, quando considerada em conjunto com o risco de desnutrição afetou 16% dos indivíduos idosos; (b) a pré-fragilidade e fragilidade eram bastante prevalentes entre estes idosos portugueses. Mais de metade era pré-frágil e um quinto era frágil, e a fraqueza muscular foi o critério mais frequentemente observado; (c) a fragilidade e obesidade estavam independentemente associadas com menores níveis de 25-hidroxivitamina D, e para além dos indicadores de obesidade geralmente usados (índice de massa corporal e perímetro da cintura), o índice de forma corporal e o índice de redondeza corporal mostraram uma associação inversa com as concentrações séricas de 25-hidroxivitamina D; (d) as taxas de excesso de peso e obesidade abdominal e geral eram altas entre estas pessoas idosas portuguesas, e os indivíduos idosos com fragilidade apresentavam maiores chances de ter obesidade geral e abdominal; (e) quase três em cada cinco indivíduos idosos apresentavam pelo menos um, e um quinto apresentavam duas ou mais destas condições (sarcopenia, fragilidade física, desnutrição e obesidade). Quando consideradas todas as pré-condições, quase todos os indivíduos idosos apresentavam pelo menos uma destas pré-condições ou condições; (f) foi encontrada uma elevada heterogeneidade nos protocolos de força de preensão da mão usados pelos estudos para identificar sarcopenia e fragilidade; (g) numa amostra de 159 indivíduos idosos, a frequência de sarcopenia apresentou grande variabilidade dependendo do método utilizado para estimar a massa muscular e do ponto de corte aplicado. A impedância bioelétrica foi considerada um método alternativo adequado para avaliar a massa muscular para o diagnóstico de sarcopenia, e perímetro geminal mostrou-se um indicador válido para determinar a presença de sarcopenia.

Em suma, os nossos resultados sugerem que algumas destas condições nutricionais e relacionadas com a idade são bastante prevalentes em pessoas idosas portuguesas, e reforçam a necessidade de rastreio nestes indivíduos. Além disso, a baixa coexistência de sarcopenia, fragilidade física, desnutrição e obesidade aqui encontrada reforça a necessidade de avaliar estas condições individualmente durante a avaliação geriátrica. Além disso, as enormes diferenças observadas em relação aos critérios de diagnóstico de sarcopenia e fragilidade podem dificultar a comparação entre estudos.

Palavras-chave: sarcopenia, fragilidade, estado nutricional, obesidade, desnutrição, vitamina D.

Chapter 1

General introduction

1.1. Background

Population ageing is a global phenomenon, and its pace is much faster than in the past. In 2019, approximately 9% of people were aged 65 or older worldwide, and it is expected that the number of older adults could reach 1.5 billion (16%) by 2050 (Figure 1) [(1)]. Interestingly, the number of individuals above 80 years is growing at an even faster rate than the number above age 65 globally, and it is projected to nearly triple to 426 million, between 2019 and 2050 [(1)].

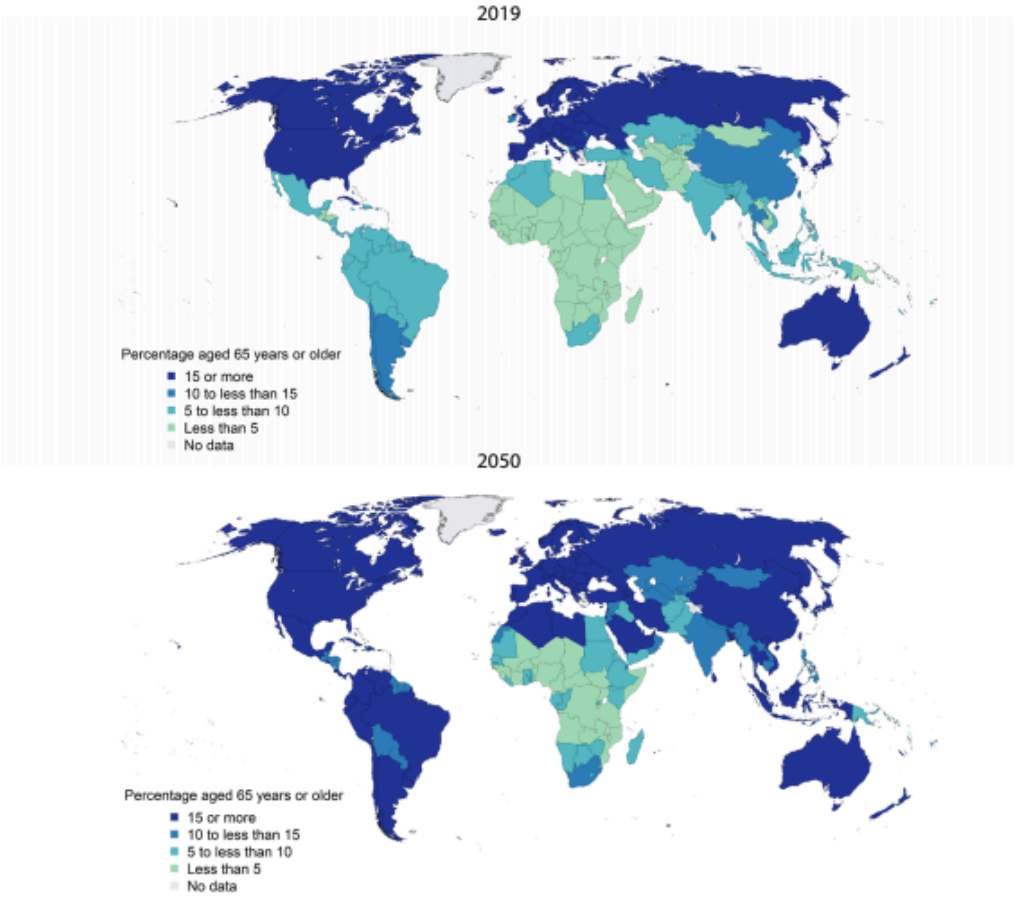

Figure 1. Global evolution of the percentage of the population aged 65 years or older, between 2019 and the projections for 2050. Source: United Nations, Department of Economic and Social Affairs, Population Division (2019), *Word Population Prospects 2019*.

The world's older population is increasing, and Portugal is no exception. In fact, the number of Portuguese people aged 65 years or older is projected to increase from 2.2 in 2018 to 3 million by 2080 [(2)]. Unfortunately, higher life expectancy does not necessarily mean an increased quality of life, and the growth in the numbers and proportions of older adults raise important health concerns. As a result of this fast demographic transition, the

number of age-associated health problems has been rising, and now the focus is on preventing and managing these conditions.

Geriatric syndromes are complex health states that emerge later in life and do not fall into discrete disease categories however, they appear to be better predictors of death than the presence or number of specific diseases [3].

Sarcopenia and frailty are two conditions often associated with ageing that share vast similarities, namely in its aetiologic factors and overall impact on health status and quality of life. Hence, given the world's progressive ageing trend, the growing number of sarcopenic and frail older adults poses major public health challenges for current healthcare systems and societies. In recent years, it has been observed an increasing interest in sarcopenia and frailty, with the exponential growth in the number of scientific publications in these areas [4,5].

The present thesis aims to investigate sarcopenia and frailty in older adults, namely by studying the measurements used in their diagnosis and to evaluate sarcopenia and frailty frequency in Portuguese older adults and their associated factors. Also, the impact of several conditions related to nutritional status often observed in older adults, such as undernutrition, obesity, and vitamin D deficiency, and its association with sarcopenia and frailty will also be explored. This may be important to uncover the Portuguese panorama regarding sarcopenia and frailty and identify potential risk factors. Furthermore, it is essential to understand how nutritional problems affect older adults in general, and the Portuguese older population, in particular, for the development of new strategies to prevent and manage these conditions and promote healthy ageing.

1.2. Ageing

Ageing is defined as the process of becoming older and results from an accumulation of complex changes over time, including physical, psychological, and social changes [6]. During the ageing process, there is a gradual accumulation of a wide variety of molecular and cellular damage [6]. Over time, this damage contributes to a gradual decrease in physiological reserves, an increased risk of many diseases, a general decline in the capacity of the individual, and ultimately, death [6].

Age-related changes in body composition and physical function are innumerous. Across the life cycle, there are variations in both muscle mass and strength (Figure 2). Indeed, a review intended to present the current knowledge regarding the decline in muscle mass and strength with advancing age estimated a rate of muscle mass loss ranging enormously from 8-49%, between the age of 18 and 80 years [7]. In more detail, these cross-sectional studies comparing young (18-45 years) and older (>65 years) samples reported median values of rate of muscle mass loss of 0.47% and 0.37% per year, for men and women, respectively [7]. Longitudinal data from older individuals between 70-79 years, showed a total thigh muscle area decrease of approximately 4.9%, in men and 3.2% in women, over a 5-year period [8]. Furthermore, it also observed that age-related decrease in strength was 2-5 times higher than the loss of muscle size [8]. A meta-analysis that included data from 114 publications showed a mean age-related decline of handgrip strength (HGS) in the general population between the ages of 25 and 95 years from 45.5 kg to 23.2 kg for males and from 27.1 kg to 12.8 kg for females [9]. As an indicator of muscle strength, HGS also varies similarly across the life course, it increases to a peak in early adult life, and is then followed by a period of broad maintenance prior to a decline with increasing age (Figure 2) [10].

Besides the decline in lean mass with age, there is also an initial increase in fat mass and then a decrease toward the end of the eighth decade of life [11]. Moreover, ageing is also associated with an increase in fatty infiltration of skeletal muscle regardless of body weight change or changes in the subcutaneous adipose tissue [8].

According to data from the Ageing Europe 2019 edition, older people were more likely to be obese, as 21.2% of the individuals between 65-74 years in the EU-28 were obese in 2017, whereas the average percentage for the adult population aged 16 years or more was 14.9% [12]. However, among the very old (≥75 years) the proportion of obese people was lower (15.8%) [12].

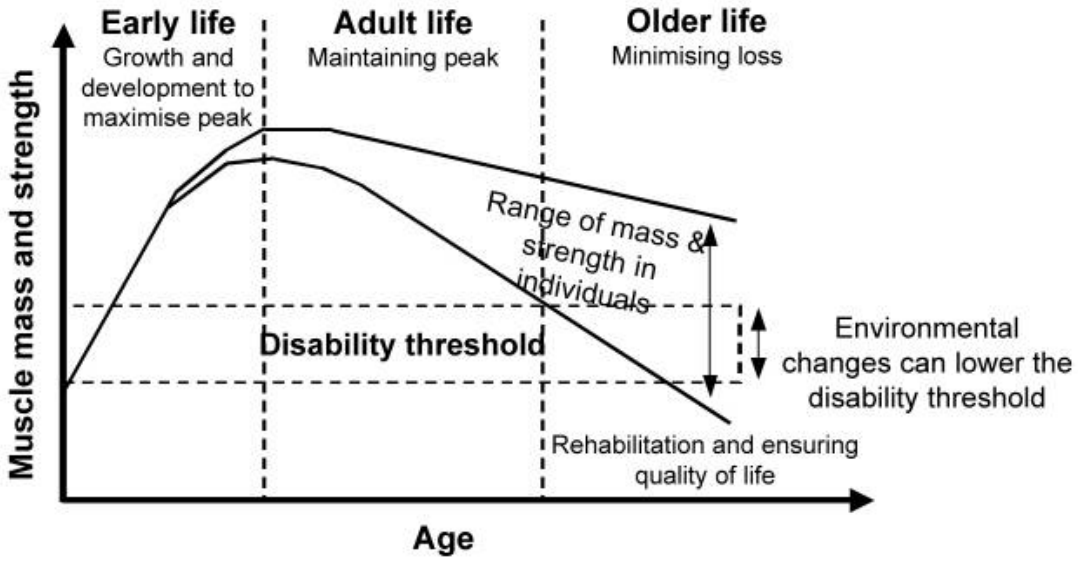

Figure 2. Muscle mass and strength along the life course. Source: Sayer *et al.* J Nutr Health Aging. Aug-Sep 2008;12(7):427-32. doi: 10.1007/BF02982703 *(Reproduced with permission of Springer Nature).*

1.3. Age-related health conditions

1.3.1. Sarcopenia

Definition and diagnosis

The term Sarcopenia derives from Greek words 'sarx', which means flesh, and 'penia', which means loss, and was firstly introduced in 1989, by Irwin Rosenberg, to define the age-related decrease of muscle mass [13]. Since then, sarcopenia definition has evolved, and several working groups have proposed definitions over the years [14–20]. In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) released a clinic definition and consensus diagnostic criteria for age-related sarcopenia [19]. Sarcopenia was then presented as a syndrome characterised by progressive and generalised loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life, and death. The diagnosis should consider the presence of low muscle mass and low muscle function (strength or performance) to define conceptual stages: 'presarcopenia', 'sarcopenia' and 'severe sarcopenia' [19]. The importance of sarcopenia as a geriatric condition led to further developments and, in 2016, sarcopenia was formally recognised as a muscle disease and was assigned with the International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM) code M62.84 [21].

Until very recently, the 2010 EWGSOP definition was the most widely adopted by the studies. However, in late 2018, the EWGSOP2 published an updated consensus paper [20]. In these guidelines, sarcopenia is presented as a progressive and generalised skeletal muscle disorder that is associated with an increased likelihood of adverse outcomes including falls, fractures, physical disability, and mortality [20]. Contrary to the initial EWGSOP consensus [19], these new recommendations suggest low muscle strength as a primary parameter, as it has proved to be stronger than muscle mass in predicting adverse clinical outcomes. Sarcopenia diagnosis is then confirmed by the presence of low muscle quantity and quality, and low physical performance is only used to ascertain sarcopenia severity [20]. Regarding sarcopenia diagnosis in clinical practice, the EWGSOP2 consensus also updated its algorithm for case-finding, diagnosis, and severity of sarcopenia (Figure 3). This EWGSOP2 definition is the only endorsed by a variety of international societies for clinical practice and research, such as the European Geriatric Medicine Society, the European Society for Clinical Nutrition and Metabolism, the

European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases, the International Osteoporosis Foundation, and the International Association of Gerontology and Geriatrics European Region [22].

The EWGSOP also suggested that sarcopenia could be categorised as acute or chronic depending on its duration. When sarcopenia occurs for less than 6 months is considered acute and chronic when it lasts 6 months or more [20]. Acute cases of sarcopenia are generally due to an acute illness or injury, whereas a chronic state is usually related to chronic and progressive conditions and increases the risk of mortality [20].

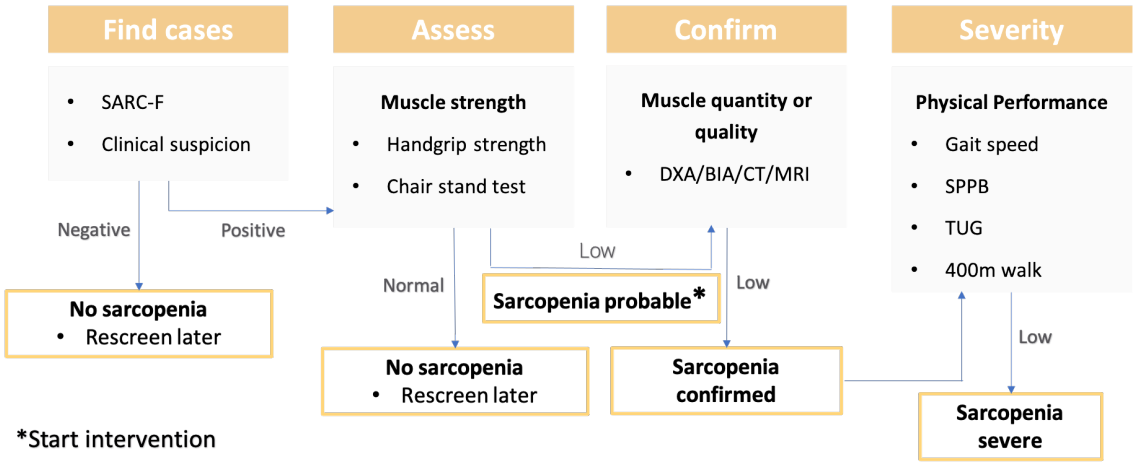

Figure 3. The EWGSOP2 algorithm for case-finding, diagnosis, and severity of sarcopenia in clinical practice. Adapted from Cruz-Jentoft *et al.* Age Ageing. 2019 Jan 1;48(1):16-31. doi: 10.1093/ageing/afy169 *(Reproduced with permission of Oxford University Press)*.

BIA, Bioelectrical impedance analysis; CT, Computed tomography; DXA, Dual-energy X-ray absorptiometry; MRI, Magnetic resonance imaging; SPPB, Short Physical Performance Battery; TUG, Timed-Up and Go test.

Prevalence

Among healthy adults aged 60 years or more, the estimated prevalence of sarcopenia in the world was 10% for both men (95% confidence interval (CI): 8-12%) and women (95% CI: 8-13%) [23]. Interestingly, a higher prevalence was observed when bioelectrical impedance analysis (BIA) was used to measure muscle mass when compared to dual-energy X-ray absorptiometry (DXA) (19% versus 10% in men and 20% versus 11% in women) [23]. Furthermore, the future prevalence of sarcopenia in Europe was estimated and the interpolated age- and gender-specific estimates retrieved from the Eurostat online database (28 European countries) were applied to population projections until 2045. Considering the reported prevalence estimates, sarcopenia prevalence was

between 11.1% and 20.2%, in 2016. When these rates were interpolated, the number of individuals with sarcopenia was estimated to dramatically increase between 63.8% and 72.4% by 2045, reaching prevalence rates ranging from 12.9% to 22.3% [24].

Results from a meta-analysis carried out in community-dwelling older adults revealed that sarcopenia prevalence was markedly dependent on the operationalised definition, ranging from 9.9 to 40.4% [25]. A lack of agreement between sarcopenia definitions was also found, whereas the 2010 European Working Group on Sarcopenia/Asian Working Group on Sarcopenia were among the definitions with the lowest prevalence estimates (12.9%, 95% CI: 9.9-15.9%) [25]. Furthermore, evidence also shows that sarcopenia is more prevalent in nursing-home older adults (38%), followed by the ones that are hospitalised (23%), and least prevalent among community-dwelling individuals (10%) [26]. Although sarcopenia prevalence has been evaluated by several studies worldwide, data concerning Portuguese older adults is still lacking.

Considering the evolution of sarcopenia definition from the 2010 EWGSOP consensus to the revised version in 2018, a large study developed in 2256 older adults that gathered data from eight cohorts found that sarcopenia prevalence using both definitions varied differently according to sex [27]. In men, it was observed a considerably lower prevalence with the EWGSOP2 (12.0% versus 31.9% with the EWGSOP), while for women sarcopenia prevalence was 4.9% and 6.1% according to EWGSOP and EWGSOP2, respectively [27]. These differences result, not only from the fact that low muscle strength is now considered the primary parameter of sarcopenia diagnosis but also from the updated cut-off points for HGS as muscle strength criterion, suggested in the EWGSOP2 consensus.

Aetiology

The aetiology of sarcopenia is not yet fully understood. In most cases among older adults, it is not possible to clearly define its aetiology, since sarcopenia has often multifactorial causes (Figure 4) [19]. Age-related or primary sarcopenia is identified when, besides the ageing process, there is no other evident cause for this muscle disorder [20]. On the other hand, the term secondary sarcopenia is applied when a specific cause is recognised other than (or in addition to) the ageing process, namely when sarcopenia is secondary to a systemic disease [20]. In fact, a recent meta-analysis that aimed to determine the prevalence of sarcopenia as a comorbid disease found that sarcopenia was highly

prevalent in individuals with cardiovascular and respiratory diseases, dementia, and diabetes mellitus [28].

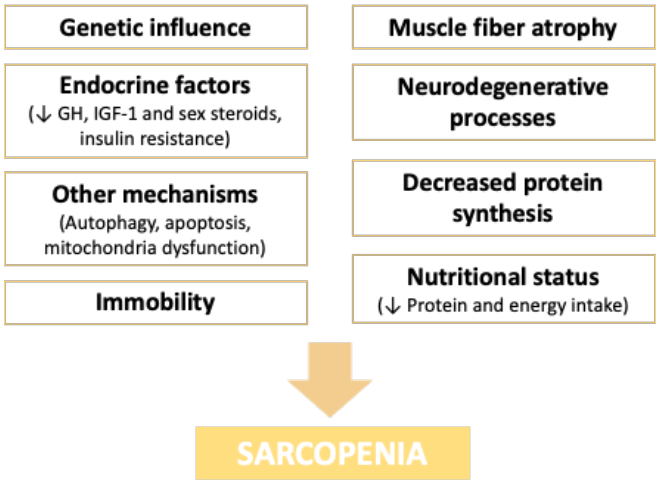

Figure 4. Pathophysiology of sarcopenia. Adapted from Ali *et al.* Gerontology. 2014;60(4):294-305. doi: 10.1159/000356760 *(Reproduced with permission of Karger Publishers).*

GH, Growth hormone; IGF-1, Insulin-like growth factor 1.

In the pathophysiology of sarcopenia, there is an age-related imbalance in the homeostasis of skeletal muscle. Although the aetiology has not been well-characterised, several mechanisms have been proposed. Regardless of the underlying mechanisms, there is an impairment in the rate of anabolic and catabolic pathways which progressively results in the loss of the skeletal muscle [22]. In more detail, sarcopenia is characterised by an atrophy of myofibres with a reduction in their amount and size, which predominantly affects type II (fast-twitch glycolytic) fibres [29,30]. Many underlying factors, such as the transition of muscle fibres from type II to type I with age, a decline in type II fibre satellite cells content [31], intramuscular and intermuscular fat infiltration (myosteatosis) [32], a reduction in the number of functioning motor units with an increase in the size of remaining/surviving motor units (by the remodeling of motor units through collateral re-innervation) [29,30] and mitochondrial dysfunction [33] are involved in the onset of sarcopenia.

Chronic inflammation is also a hallmark of ageing and is involved in the genesis of sarcopenia [34–36]. A chronic state of low-grade inflammation, characterised by increased levels of pro-inflammatory mediators, such as tumour necrosis factor α, interleukin 6, and C-reactive protein is a common manifestation in older adults [37]. In addition, there is evidence linking age-related hormonal changes to the loss of muscle.

The decline of several hormones [38], such as testosterone [39–41], growth hormone, and insulin-like growth factor 1 [42,43] may also play a key role in the development of sarcopenia. Moreover, sarcopenia can, in part, result from alterations in multiple physiological systems [44]. In more depth, the decline in muscle mass and function may result from dysregulations in the nervous, endocrine, and immune systems and is influenced by nutritional factors, level of physical activity, inflammation, and other disease states [44–46]. Indeed, pathology in these systems along with inflammation affects muscle homeostasis, exacerbates sarcopenia, and could eventually contribute to frailty [44].

Consequences

The presence of sarcopenia has a profound impact on older adults' health status and quality of life. Sarcopenia is a risk factor for falls [47,48], hospitalisation [47,49], and it is associated with worse quality of life [50], functional decline [47], and all-cause mortality [47,51,52]. Apart from the direct health consequences of sarcopenia, some studies suggest an associated economic burden to health care systems [53]. However, the financial impact of this disease needs to be further elucidated. In the United States, it was estimated that sarcopenia contribution to healthcare expenditures reached $18.5 billion, which represented about 1.5% of total healthcare expenditures in 2000 [54]. In Portugal, two studies conducted among hospitalised patients found that sarcopenic individuals had higher hospitalisation costs, compared with non-sarcopenic individuals [55,56].

1.3.2. Frailty

Definition and diagnosis

In the World report on ageing and health, the World Health Organization (WHO) defines frailty as a progressive age-related decline in physiological systems that results in decreased reserves of intrinsic capacity, which confers extreme vulnerability to stressors and increases the risk of a range of adverse health outcomes [57]. These stressors can be endogenous, such as chronic comorbidities, or exogenous, such as malnutrition or adverse life events [58]. This maladaptive response to stressors leads to a vicious cycle of functional decline [59].

Frailty is a complex syndrome [58], and currently, there is no consensus on its definition. Nonetheless, the physical frailty phenotype suggested by Fried *et al.* [60] is the most widely accepted and used definition and, therefore, the one adopted in the present work.

In 2001, Fried and colleagues introduced a phenotypical (rule-based) operational definition of frailty based on a large sample of community-dwelling older adults participating in the Cardiovascular Health Study [60], and this initiated considerable progress in understanding and exploring the pathophysiology of frailty. This frailty phenotype defined frailty as the display of three or more of five physiological deficits (muscle weakness, slow walking speed, unintentional weight loss, exhaustion, and low physical activity) [60]. Pre-frailty is identified when one or two of these criteria is present [60].

Findings from the Cardiovascular Health Study showed that frailty was independently associated with incident falls, disability, hospitalisation, and death [60]. Cross-sectional data on 8684 community-dwelling older adults have shown statistically significant differences in the level of social, psychological, and physical functioning between non-frail, pre-frail, and frail older adults, defined by Fried's frailty criteria [61]. Also, evidence suggests that frailty is a dynamic process and that older adults often transition between frailty states over time [62].

Although frailty is still considered a geriatric syndrome, the WHO has recently recognised the need for an ICD code for frailty, in the latest Clinical Consortium on Healthy Aging [63]. As a matter of fact, it was proposed to establish a working group to assess frailty and the ICD code question, and some progress in this regard may arise soon.

Prevalence

A systematic review that gathered cross-sectional data from community-based cohorts estimated that frailty prevalence in older adults ranged widely from 4.0-59.1%, depending on diagnostic criteria adopted by the studies and the characteristics of the studied sample [64]. Results also show that frailty prevalence increases with age and was higher in women [64]. Although it is usually evaluated in older individuals, evidence also denotes the presence of this syndrome under the age of 65 [65]. Later in 2018, another meta-analysis that published data reporting the prevalence of frailty in several European countries showed an overall estimate of 18% (95% CI: 15-21%). In a sub-analysis, a lower prevalence was observed for studies in the community (12%, 95% CI: 10-15%) in comparison with non-community-based studies (45%, 95% CI: 27-63%), $p<0.001$ [66]. However, when the authors narrowed the analysis to studies in the community adopting a physical phenotype, the prevalence was 12% (95% CI: 10-14%) versus 16% (95% CI: 7-29%) for all other definitions [66].

Evidence also suggests that frailty prevalence may be higher in Southern Europe, compared with the North [67]. In Portugal, evidence about physical frailty is scarce. A small study conducted among 50 centenarians, who lived in the Oporto Metropolitan Area, using the Fried frailty phenotype with some adaptations, revealed that 60% were frail and 36% pre-frail [68]. However, more information on frailty frequency among Portuguese older adults is needed. More recently, data from the Survey of Health, Aging and Retirement in Europe which used a modified definition of the Fried phenotype, estimated an overall prevalence of pre-frailty and frailty of 47.6% and 15.6% in Portuguese individuals aged ≥50 years, prevalence that increased with higher age [69].

Several health-related and sociodemographic factors, namely age, female gender, black race/color, cardiovascular diseases, number of comorbidities/diseases, functional incapacity, poor self-rated health, depressive symptoms, BMI, and smoking were found to be directly associated with frailty [70]. On the other hand, schooling, income, cognitive function, and alcohol use were identified as inverse associated factors [70]. Moreover, one other systematic review revealed that a wide range of biological, physical, sociodemographic, lifestyle and psychological factors show a longitudinal association with frailty and appear to play a significant role in the development of frailty [71]. Particularly, significant sociodemographic factors included older age and ethnic background, whereas significant physical factors included obesity and activities of daily living, and lastly significant psychological factors included depressive symptoms [71].

Aetiology

Frailty is a disorder of multiple inter-related physiological systems [45]. Although frailty is associated with advanced age, not all older individuals will become frail. Ageing is accompanied by a gradual physiological decline however, in frailty, this cumulative decline is accelerated and homeostatic mechanisms start failing (Figure 5) [45]. The multi-cause basis of frailty syndrome relies on the fact that these changes do not occur independently, but instead occur in a sequential, parallel, or synergistic manner to accelerate and accentuate frailty symptoms [72,73]. However, it is yet to be determined which processes might trigger the cascade of the multisystem frailty development. It is known that between these biological processes exist close bidirectional interrelationships, namely those involving inflammation, immune, and endocrine changes [73]. Furthermore, findings from a cross-sectional study among older women revealed that the likelihood of frailty increases nonlinearly in relationship to the number of physiological systems (hematological, inflammatory, endocrine, adiposity, neuromuscular, and micronutrients) at abnormal levels, and the number of abnormal systems is more predictive than the individual abnormal system, supporting the theories that aggregate loss of complexity in multiple physiological systems with ageing is an important cause of frailty [74]. This relationship between measures from these six different physiological systems and frailty was non-linear and independent of age and comorbidity [74].

Several body systems, such as the nervous system, endocrine system, immune system, and skeletal muscle are hypothesised to be physiological underpinnings of frailty and, along with enhanced inflammation, contribute to this multisystem dysregulation [44,73]. Evidence suggests that frailty may arise when age- and disease-related structural, physiological, and functional alterations in the brain, and decreased brain reserve in the stress response accumulate to an extent that causes cognitive decline [73]. In this way, it seems to exist a link between cognitive functioning, namely the importance of the central nervous system to the maintenance of stress adaptability, and physical functioning in the development of frailty [73]. Furthermore, the endocrine system also appears to be crucial in the pathogenesis of frailty, essentially through a dysregulation of glucocorticoid secretion, insulin-like growth factor signalling, and androgen production, which disturb body homeostasis and consequently reduce the adaptability to stressors and increase the risk of frailty [73,75]. Indeed, it was found that deficiency in multiple anabolic hormones was a stronger predictor of frailty status in women, supporting the theory of generalised

hormonal dysregulation and frailty [76]. Also, evidence suggests that vitamin D and insulin resistance are potentially involved in the genesis of frailty [73,75].

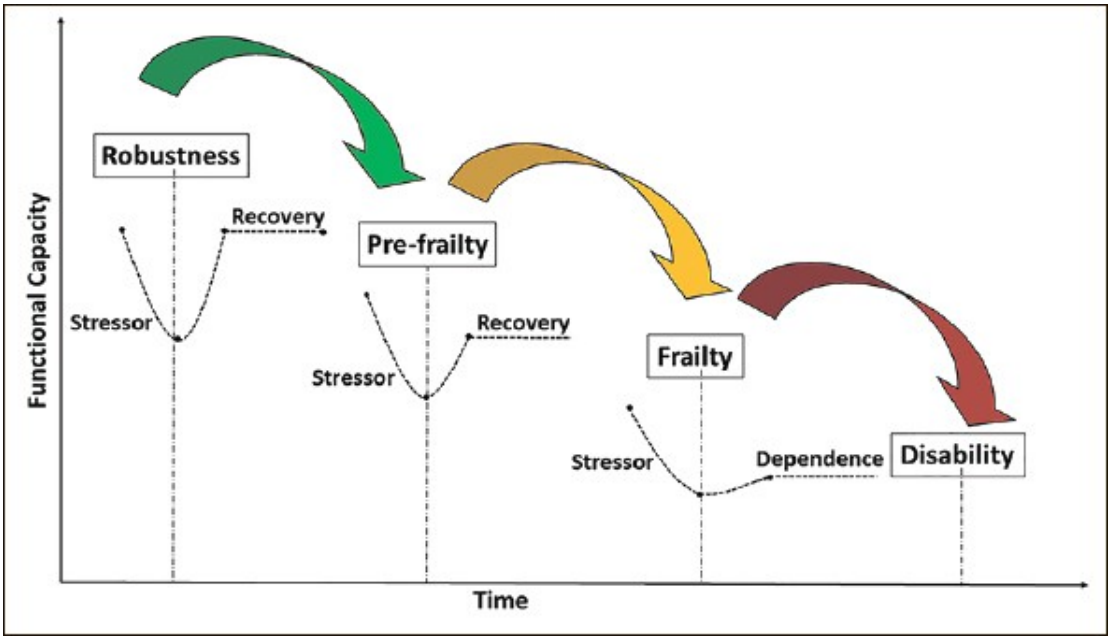

Figure 5. The cascade of functional decline in older adults from independence, through to frailty and disability (in the absence of intervention). Source: Dent, *et al.* J Nutr Health Aging 2019;23(9):771-787. doi: 10.1007/s12603-019-1273-z.

The effects of ageing on the immune system are extensive [77,78] however, evidence suggests that immune system changes observed in frailty are above and beyond the age-related immune senescent remodelling [78]. In frailty, immune dysregulation is characterised by heightened inflammation and alterations in the innate and adaptive immune systems, particularly in the T-cell compartment and potential B-cell function and regulation [78]. The senescent immune system may perform appropriately in homeostasis, but fail to respond to stressors, which eventually could contribute to the development of frailty [45,73]. Interactions between these systems and inflammatory cytokines are thought to play a role in the genesis of frailty. Chronic molecular and cellular damage may arise from failure to tightly regulate inflammatory response and consequently accelerating the biologic mechanisms that ultimately contribute to frailty [45]. A meta-analysis that examined the cross-sectional association between inflammation and frailty found that pre-frailty and frailty are associated with higher inflammatory parameters levels, in particular C-reactive protein and interleukin 6 [79]. Although previous findings from longitudinal studies present conflicting results regarding the association between higher inflammatory levels and the onset of frailty [80–82], a more recent prospective cohort study

with a follow-up period of 24 years, showed that systemic inflammation (measured by circulating inflammatory markers) during midlife was associated with late-life frailty [83].

As previously mentioned, sarcopenia is recognised as a contributor to the development of frailty, hence its aetiologic factors are also implicated in the genesis of frailty [20,44]. Other factors such as oxidative stress and metabolic imbalances, namely low serum concentrations of micronutrients, altered enzyme activities, and the accumulation of metabolic end products have also been pointed out to have a potential role in the pathogenesis of frailty [73].

Consequences

The impact of frailty in older adults has been extensively revised in the literature. Frailty has been suggested as a predictor of disabilities [84], falls [85,86], fractures [86,87], cognitive disorders [88], loss of activities of daily living [86], poor quality of life [89], hospitalisation [86,90] and even mortality [86,91,92] in older adults.

1.3.3. Sarcopenia and frailty: the same or different?

Sarcopenia and frailty were both first introduced as geriatric syndromes [60]. However the term sarcopenia has evolved in recent years, and nowadays it is considered a specific disease [21]. Even though there is considerable overlap between sarcopenia and physical frailty since both include handgrip strength and gait speed as diagnostic measurements in their definition [19,20,60], they are still distinct [20]. Sarcopenia is a clinical hallmark of the development of frailty, but frailty is more multifaceted than sarcopenia alone (Figure 6) [20,44,93]. Yet, despite continued research efforts, the aetiology of sarcopenia and frailty are complex and not yet fully understood.

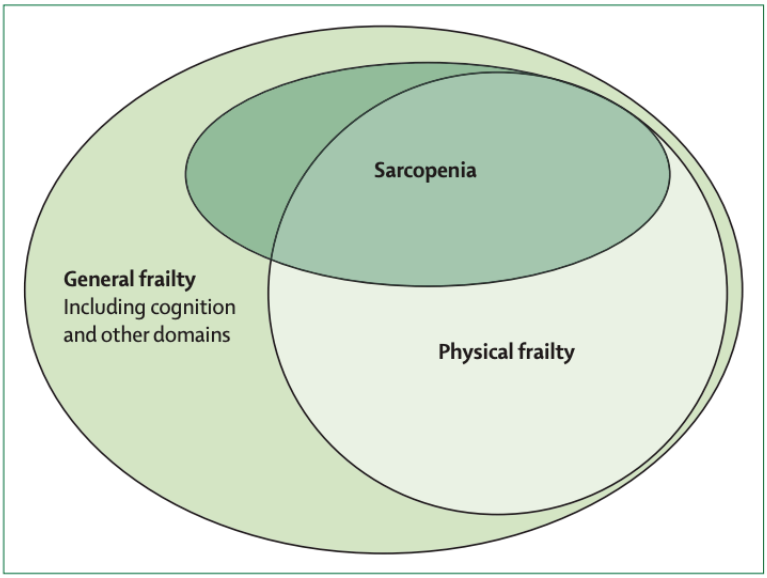

Figure 6. The diagnostic overlap between sarcopenia and frailty. Source: Cruz-Jentoft *et al.* Lancet. 2019 Jun 29;393(10191):2636-2646. doi: 10.1016/S0140-6736(19)31138-9 (*Reproduced with permission of Elsevier*).

Although sarcopenia and frailty have been extensively studied worldwide, data on Portuguese older adults is still lacking, and little is known about their frequency in the Portuguese older population. Also, there is a need to increase the knowledge about the factors potentially associated with these age-related conditions among these older adults.

1.4. Age-related health conditions and nutritional status

While the presence of multiple chronic diseases is frequently evaluated in older adults, the coexistence of sarcopenia and frailty, and other conditions related to nutritional status are often overlooked and data, especially in the community setting, is limited.

1.4.1. Sarcopenia and nutritional status

Sarcopenia and undernutrition

Older adults have a higher risk of suffering from undernutrition. Among these, undernutrition commonly manifests as weight loss [94]. Several risk factors, such as age, frailty in institutionalised individuals, excessive polypharmacy, general health decline (including physical function and cognition), loss of interest in life, basal oral dysphagia and signs of impaired efficacy of swallowing, and institutionalisation have been identified as contributors to the development of undernutrition over time [95].

Undernutrition leads to serious consequences, namely among older people. It has been associated with poor quality of life [96], higher health care costs [97], functional decline [98], prolonged length of hospital stay [99], and even mortality [98,100]. In Portugal, undernutrition screening is mandatory in the hospital setting [101]. However, data in community-dwelling older adults is lacking.

The Mini-Nutritional Assessment (MNA) is recommended for undernutrition screening [102,103]. The Short Form (MNA-SF) is a well-validated tool and appears to be the most appropriate tool to assess undernutrition risk in the community-dwelling older population [102]. The worldwide prevalence of undernutrition according to the MNA was estimated to be 5% (standard error (SE): 0.1) and 4.3% (SE: 0.1) in the community for MNA and MNA-SF, respectively. However, the prevalence was estimated to be higher among institutionalised older adults (18% (SE: 0.3) for MNA, and 22% (SE: 0.4) for MNA-SF) [103].

Undernutrition is also a key etiologic factor for sarcopenia. Undernutrition and sarcopenia are present in parallel in many cases among older individuals. In fact, a meta-analysis of cross-sectional studies found undernutrition as an independent associated factor of EWGSOP-defined sarcopenia in older nursing home residents however, undernutrition risk was not [104]. In a longitudinal study during a four-year follow-up, undernutrition was found to be a strong predictor of sarcopenia and severe

sarcopenia [105]. Indeed, low muscle mass has been proposed as a criterion for undernutrition diagnosis [106].

Sarcopenic obesity

Even though a positive association between obesity and muscle mass has been reported in the literature, evidence also indicates that obesity is associated with substantial impairment of muscle quality, which adversely affects muscle function [107].

Sarcopenic obesity is a condition that results from the presence of sarcopenia accompanied by excess adiposity (obesity) [108], which can pose individuals at risk of synergistic complications from both sarcopenia and obesity [109]. As expected, sarcopenic obesity frequency is highly variable depending on the definition applied [110]. One of the major limitations concerning sarcopenic obesity evaluation is in its diagnostic criteria since sarcopenic obesity definition is based on the individual definitions of sarcopenia and obesity, and currently lacks consensus [111]. Literature on the subject has shown a high heterogeneity in the criteria used to identify sarcopenic obesity, which compromises the interpretation of the results regarding its association with poor health outcomes [108].

1.4.2. Frailty and nutritional status

Frailty and Undernutrition

Frailty and undernutrition are frequently interrelated. Indeed, a meta-analysis showed that the prevalence of undernutrition (mainly identified using MNA) was significantly associated with the prevalence of physical frailty in community-dwelling older adults [112]. Nevertheless, it was also highlighted that despite being related, they are not interchangeable geriatric conditions, since 68% of the undernourished older adults were physically frail, whereas only 8.4% of the physically frail individuals were undernourished [112]. Furthermore, supporting the importance of nutritional status on frailty syndrome, a systematic review aimed to examine the nutritional determinants of frailty in older adults recognised the importance of both quantitative (energy intake) and qualitative (nutrient quality) factors of nutrition in the development of frailty syndrome in older adults [113].

Recently, it was estimated that the prevalence of undernutrition among frail older adults (outpatients and home care) was higher than the observed for community-dwelling individuals (11% (SE: 0.2) and 11.0% (SE: 0.3) versus 5% (SE: 0.1) and 4.3% (SE: 0.1) for MNA and MNA-SF, respectively) [103].

Frailty and obesity

The prevalence of overweight and obesity is increasing among older adults [12]. Ageing is also associated with body fat redistribution and an increase in visceral fat [114]. The use of body mass index (BMI) in older adults is often questioned and current recommendations for obesity diagnosis do not include specific guidelines for these individuals [115]. Therefore, the use of other anthropometric indicators of body adiposity, such as waist circumference (WC), body roundness index (BRI), and body shape index (ABSI) may provide more information about older adults' adiposity level and should be explored.

Several longitudinal studies evaluated the association between increased adiposity and the development of frailty [116–118]. Although some methodologic considerations should be pointed out, particularly the use of self-reported weight and height [116,118] and modified versions of frailty phenotype [116,118]. Midlife pre-obesity and obesity were found to have a predictive role in the development of frailty over two decades later [116–118],

suggesting that the development of frailty may start earlier in adulthood and that obesity is one of the underlying risk factors for frailty.

As mentioned earlier, evidence suggests inflammation as a potential link between obesity and frailty. Indeed, a meta-analysis of cross-sectional data revealed an association between inflammatory parameters, such as C-reactive protein and interleukin 6, and frailty status [79]. However, a scoping review of intervention trials highlighted the lack of studies demonstrating a link between total fat mass, systemic inflammation, oxidative stress and damage to muscle tissue, and changes in strength and physiologic function [119]. Consequently, even though there is evidence suggesting a possible link between frailty and obesity, the mechanisms involved are still not well-clarified.

The link between frailty, vitamin D, and obesity

Vitamin D is a fat-soluble vitamin and pro-steroid hormone. The two major forms are ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3), synthetised from their pro-vitamins, ergosterol (which is a plant and fungal sterol) and 7-dehydrocholesterol, the immediate precursor in the cholesterol biosynthetic pathway, respectively. Human skin, when exposed to sunlight by the action of ultraviolet-B produces previtamin D_3 from photolysis of 7-dehydrocholesterol [120]. The optimum wavelengths for this process to occur is between 295-300 nm [121]. Readily, this compound undergoes a nonenzymatic thermal isomerisation to form vitamin D_3 [120]. Several factors regulate the cutaneous production of previtamin D_3, namely age [122], use of sunscreen [123], latitude, and season of the year [124]. Sunlight exposure can also induce the formation of two other biologically inert photoisomers, lumisterol and tachysterol [125]. Conversely, vitamin D_3 can also suffer photodegradation by the action of solar ultraviolet radiation into a variety of photoproducts, including 5,6-trans-vitamin D_3, suprasterol I, and suprasterol II [126]. Alternatively, both forms vitamin D_2 and vitamin D_3, can be derived from dietary sources, such as plants and fungi (e.g. mushrooms), and fatty fish, respectively [127,128].

Vitamin D is then transported to the target organ, by the bloodstream mainly bonded to carrier proteins, the vitamin D binding protein [129]. In the liver, it is converted to 25-hydroxyvitamin D (25(OH)D) by cytochrome P450 enzymes, including the most relevant yet identified, CYP2R1 [130,131]. 25(OH)D enters the bloodstream and is then transported to the kidneys bounded to vitamin D binding protein [132], and it is finally converted to its active form 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), by a 1α-hydroxylase

(CYP27B1) [130,133]. This step is highly regulated primarily by three hormones, such as parathyroid hormone, fibroblast growth factor 23, and $1,25(OH)_2D$ itself. [128,133]. The catabolism of 25(OH)D, and $1,25(OH)_2D$ is performed by CYP24A1 and results in the biologically inactive calcitroic acid excreted by the bile or in 1,25-26,23 lactone, which has a substantial affinity for the vitamin D receptor and, therefore, has biological activity [127,128]. Vitamin D receptor is widely distributed in the human tissues, namely the skeletal muscle [134,135]. The hormonally active form $1,25(OH)_2D$ interacts with vitamin D receptor, which triggers multiple biological responses through genomic and non-genomic mechanisms [135]. Beyond its actions in the regulation of calcium and phosphorus metabolism, $1,25(OH)_2D$ seems to interact in multiple systems in the human body [136]. Vitamin D appears to be particularly important for skeletal muscle growth and homeostasis, mediated by the binding of $1,25(OH)_2D$ to the vitamin D receptor [137].

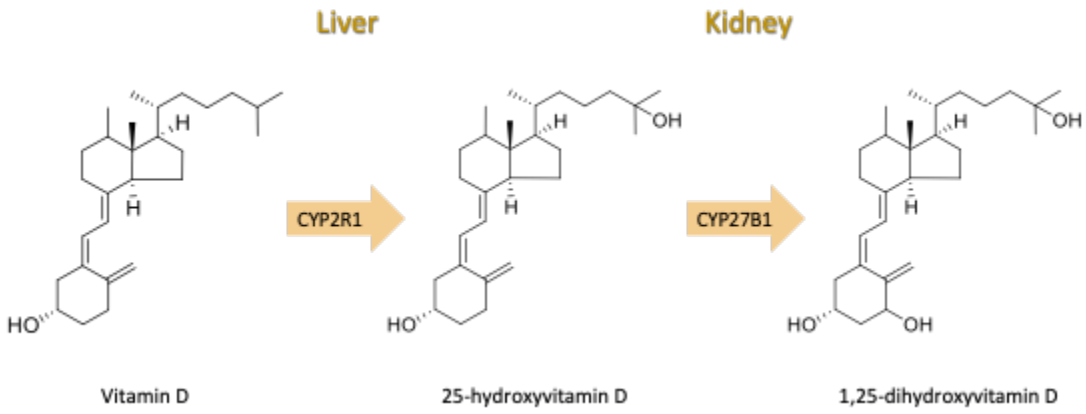

Figure 6. Vitamin D metabolism: steps involved in the activation of Vitamin D.

Ageing may have a negative impact on vitamin D metabolism since there is an age-dependent decrease in epidermal stores of provitamin D_3 (7-dehydrocholesterol) [122], and an impaired ability of the ageing kidney to synthesise $1,25(OH)_2D$ [138]. Moreover, older age was significantly associated with decreased vitamin D receptor expression [139].

Regarding the association between serum 25(OH)D and frailty, a meta-analysis of prospective cohort studies showed that when compared to the highest level of 25(OH)D, there was a significant association between frailty and the lowest levels of 25(OH)D [140]. Moreover, a dose-response meta-analysis that examined data with serum 25(OH)D concentrations ranging from 12.5 to 95 nmol/L, demonstrated a statistically significant inverse linear association between serum 25(OH)D levels and the risk of frailty [141]. Also supporting these findings, a meta-analysis intended to evaluate the association between

circulating levels of 25(OH)D and walking speed, found that usual walking speed was slower among participants with hypovitaminosis D [142]. Evidence suggests alterations in hormones involved in the vitamin D axis in frailty since higher levels of parathyroid hormone and fibroblast growth factor 23 have been linked to frailty [143–145].

The association between excessive body weight and 25(OH)D levels is well-documented [146]. Several hypotheses have been suggested to explain this association. Besides the fact that obese individuals are generally less exposed to sunlight [147], inadequate levels of vitamin D in obese individuals may be related to the sequestration of vitamin D by fat tissue, because adipose tissue acts as a reservoir for vitamin D [148]. Furthermore, it was hypothesised that lower vitamin D levels in obesity may be related to a simple volumetric dilution due to a higher volume of distribution of 25(OH)D in the adipose tissue [149]. On the other side, it is still unclear if low 25(OH)D levels may contribute to weight gain [150]. In fact, evidence based on a bi-directional genetic approach suggests that a higher BMI leads to lower 25(OH)D, while any effects of lower 25(OH)D increasing BMI are likely to be small [151].

Information regarding anthropometric indices, such as BRI and ABSI is lacking in general and is particularly scarce concerning the association between advanced age, frailty, and vitamin D status. Understanding if these indicators of body adiposity are associated with frailty and vitamin D status, and if these results confer any advantage for their current use (over the pre-existent measures of adiposity) is a crucial step towards their implementation.

1.5. Diagnostic measurements for sarcopenia and frailty

1.5.1. Muscle strength assessment

Handgrip strength (HGS)

Handgrip strength is the most widely used method to evaluate muscle strength and is recommended for the diagnosis of sarcopenia and frailty [19,20,60,152,153]. It shows a good correlation with knee extension strength [154] and is a good marker of physical function [155,156]. Low HGS is associated with incident outcomes of falls, mobility limitation, hip fracture, and mortality [157]. Furthermore, HGS has been associated with a wide range of health conditions, namely chronic cardiometabolic diseases, neural morbidities, functional declines, and mobility limitations [158].

Handgrip strength is simple and inexpensive and is usually the preferred measure to evaluate overall muscle strength, namely by clinicians [20,159]. Several protocols have been suggested for its evaluation [160–162], yet there is a large variability in the procedures used by the studies [162].

The inconsistency in the criteria and procedures used to define sarcopenia and frailty, namely in the evaluation of HGS, creates a tremendous difficulty in the comparability among the studies. Therefore, identify and evaluate these differences is important to understand the whole picture and to progress in sarcopenia and frailty research.

1.5.2. Evaluation of muscle mass

Assessment and management of sarcopenia is still a challenge nowadays. The gold standards to evaluate muscle mass are magnetic resonance imaging (MRI) and computed tomography (CT). MRI and CT estimate muscle quantity and quality, because they allow us to assess fat infiltration in muscle [163]. However, these methods are very expensive, not portable or easily accessible, and require specialised professionals, which make their use for estimating muscle mass almost exclusively for research purposes [152]. Moreover, MRI and CT lack specific cut-off points for muscle mass evaluation, recommended by scientific societies [20]. Even though DXA only assesses muscle quantity, it is recommended as the reference method to evaluate muscle mass for sarcopenia diagnosis [20]. Other alternative methods have also been suggested, such as BIA and anthropometry.

An international survey aimed to assess the tools used for the diagnosis of sarcopenia in clinical practice revealed that 53.3% of the clinicians stated that they assessed muscle mass in their daily practice [159]. Among these practitioners, the most reported tools used were calf circumference (CC) (57.5%) and DXA (45.9%), whereas BIA was only used by 22.6% [159]. Despite current recommendations from scientific societies, anthropometry still plays a major role as a diagnostic tool in daily practice.

Besides the limitations associated with each method, older adults pose a greater challenge for body composition assessment over adults in general, not only due to the mobility issues often present, but also due to the changes inherent to the ageing process, that can affect the accuracy of the estimates [20].

Dual-energy X-ray absorptiometry (DXA)

Dual-energy X-ray absorptiometry is a low-dose radiation technique, that can easily provide several body composition indices in a few minutes [164,165]. When compared with CT or MRI, it is relatively cheap however, it is not portable, has limited availability, and is unable to quantify fatty infiltration of skeletal muscle and consequently evaluate muscle quality [163,164].

The basic principle of DXA is based on the notion that when a beam of X-rays is passed through a complex material it is attenuated based on the intensity of energy and composition and thickness of the material [164–167]. Low-density materials (i.e., soft tissues) allow more photons to pass through and thus attenuate the X-ray beam less than high-density materials such as bone. At two different energy levels (high and low), DXA

distinguishes bone from soft tissue (lean mass + fat mass) and lean soft tissue mass from fat mass, in locations where the bone is absent. Therefore, DXA is capable to define the composition of the human body by indirectly discriminating three different compartments [164–167]. The precision of DXA body composition measures is better for lean mass than for fat mass, with a reported coefficient of variation of ~1.0% for the precision of whole-body lean mass measurements [168]. Since DXA does not differentiate between water and bone-free lean tissue and it assumes a uniform fat-free mass hydration value of 73% and electrolyte constancy, lean body mass measured by DXA may be overestimated in the elderly, who have been shown to have extracellular fluid accumulation [167].

In a recent article including position statements of the Sarcopenia Definition and Outcomes Consortium about sarcopenia definition, the use of DXA for sarcopenia diagnosis has been challenged [153]. The panel position was based on evidence suggesting that lean mass measured by DXA had limited utility as a predictor of adverse health-related outcomes such as mobility limitation, falls, ADL disability, and mortality in community-dwelling older adults [153,157]. Several explanations were suggested for the lack of association observed, in fact, DXA does not estimate muscle mass directly (it measures lean mass), and lean mass measured by DXA includes not only muscle mass but also water and fibrotic tissue [157]. Moreover, DXA does not estimate muscle quality. Despite the previously mentioned drawbacks inherent to other more accurate measures of skeletal muscle mass, these are likely related to poor outcomes in older people [169].

Despite the growing interest and the enormous progress made in these areas, there are still some matters that require further investigation. Since there is little consensus on the best alternative measure to evaluate muscle mass for sarcopenia diagnosis, the study of the agreement of several muscle mass methods in the same sample of older adults will help to clarify this subject.

Bioelectrical impedance analysis (BIA)

Bioelectrical impedance analysis is a practical tool to evaluate muscle mass because it is easy to use, portable, relatively inexpensive, non-invasive, and safe technique [164]. However, several factors or measurement conditions can limit the use of BIA and, therefore, affect the validity of its measurements [170,171]. Furthermore, BIA is not recommended for individuals at extremes of BMI ranges or with alterations in the hydration status [171]. These limitations are the reason why societies such as the Society

of Sarcopenia, Cachexia and Wasting Disorders have discouraged the use of BIA for the assessment of sarcopenia [172].

The principles of BIA for estimating body composition are based on the assumption that the human body is composed of cylindrical-shaped ionic conductors (trunk and limbs) with homogeneous composition, and the resistance of a length of homogeneous conductive material of uniform cross-sectional area is proportional to its length and inversely proportional to its cross-sectional area [173,174]. Moreover, it is assumed that fat-free mass contains all the water and conducting electrolytes in the body and that fat-free mass hydration is constant [173].

Impedance (Z) is the opposition to the flow of an alternating current and reflects different electrical properties of tissues [174,175]. This term is used to describe the combination of two parameters: resistance (R) which is caused by intra and extracellular fluid, and reactance (Xc) which is caused by the capacitance of the cell membrane [174,175]. Most BIA analysers operate at 50-kHz (single-frequency BIA) however, some devices operate at multiple frequencies (multi-frequency BIA) [174,175]. At a frequency of 50 kHz, the current passes through both intra and extracellular fluid, although the proportion depends from tissue to tissue [174]. The parameters measured by BIA are then used to estimate body composition using prediction equations.

Bioelectrical impedance analysis can be a useful tool for sarcopenia diagnosis however, there is a lack of standardisation of its use for assessing muscularity by the studies since BIA equations and cut-off values are population and device-specific [176]. Interestingly, a higher prevalence of sarcopenia has been reported when muscle mass was estimated by BIA [23]. Notwithstanding, there is still the need to clarify if BIA can be alternatively used for sarcopenia diagnosis when the recommended methods are unavailable.

Anthropometry

Anthropometric measurements are simple, portable, inexpensive, non-invasive, and easy to use tools for the clinical evaluation of sarcopenia, when the recommended methods are not accessible [177–179]. However, age-related changes in fat distribution and the loss of skin elasticity affect their accuracy and precision in older adults [163].

Mid-arm muscle circumference (MAMC) and CC have been suggested as methods to assess muscle mass for sarcopenia diagnosis [180,181]. MAMC was found to be

associated with better functional performance and survival among community-dwelling old-old individuals [182]. Moreover, it was observed that older individuals identified with sarcopenia using MAMC as muscle mass measure had a higher risk of incident falls during a follow-up period of 2 years compared to non-sarcopenic [180].

Concerning CC, in a large study with older women aged 70 years and older, it was found a correlation between CC and appendicular skeletal muscle mass (ASM) by DXA of r=0.63 [181]. Moreover, CC value below 31 cm was not a good screening tool to detect low muscle mass using the cut-off for ASM/height^2 <5.45 kg/m^2 as reference (sensitivity 44.3%, specificity 91.4%) [181]. On the other hand, women with CC <31 cm were more likely to experience disability in activities of daily living and some difficulty with physical function [181]. More recently, a large study showed that this measure was highly correlated with ASM evaluated by DXA, namely in individuals aged ≥60 years (r=0.79 for males and 0.74 for females) [183], suggesting that CC might be used as a marker of muscle mass.

While, the EWGSOP defends that anthropometry is not a good method to assess muscle mass [19,20], the advantages of these measures make them attractive when there is limited access to the recommended assessment tools [152,159]. In fact, CC is a simple measure to be collected and might be useful particularly in older people and clinical settings. Despite the above-mentioned limitations, namely concerning their use among older people, it is important to understand if anthropometry can be used as a surrogate indicator of muscle mass for sarcopenia diagnosis.

1.6. The Nutrition UP 65 Project

Health inequalities across the life course are largely responsible for the significant proportion of the diversity in older age. Public health policy must be designed to address and reduce this issue [3].

The Nutrition UP 65 Project [184] was a cross-sectional study conducted in Portugal, created with the goal of reducing nutritional inequalities in the Portuguese older population, namely by improving the knowledge on Portuguese older adults' nutritional status and focus on the empowerment of health professionals on dealing with older adults' nutritional status. Using a random sampling approach, a cluster sample of 1500 older adults (≥65 years), which was representative of the older Portuguese population in terms of age, sex, education, and regional area was selected. The study sample was composed of 95% of community-dwelling older adults and 5% of individuals institutionalised in retirement homes.

Briefly, data from the 2011 national census showed that the number of Portuguese residents was 10,562,178 and that 2,010,064 (19%) were aged ≥65 years [185]. Then, a study sample of 1500 older adults equivalent to 0.075% of the Portuguese older population was defined. In each stratum of the regional area, the number of subjects was ascertained considering the population structure in terms of sex, age, and education level (please see multimedia appendix 1 of the Nutrition UP 65 study protocol) [184]. In this regard, three or more town councils with >250 inhabitants were randomly selected from each regional area, and potential participants were contacted via home approach, telephone, or via institutions such as town councils and parish centres. Potential participants were invited to participate in the study if they fulfilled the requirements, and recruitment took place until the number of individuals of the pre-defined sample was reached. Subjects presenting any condition that precluded the collection of venous blood samples or urine (e.g., dementia or urinary incontinence) were not included.

Data for this study were collected between December 2015 and June 2016. Sociodemographic data and information regarding cognitive status, lifestyle, nutritional and functional status were collected. An interview was conducted by eight previously trained registered nutritionists, and a structured questionnaire was used to obtain information regarding demographic data (namely sex, date of birth, marital status, and education), cognitive performance, current and former professional occupation, lifestyle practices, health status and clinical history, nutritional status, cohabitation, skin

phenotype (evaluated by the Fitzpatrick classification), and household income. Further information regarding the Nutrition UP 65 study variables can be found described in detail in the corresponding paper or in the Nutrition UP 65 study protocol article [184].

The Nutrition UP 65 study was conducted according to the guidelines established by the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the department of Ciências Sociais e Saúde (Social Sciences and Health) from the Faculdade de Medicina da Universidade do Porto (PCEDCSS – FMUP 15/2015) and by the Portuguese National Commission of Data Protection (9427/2015).

1.7. Aims

Theoretical framework

This work aims to increase the knowledge about older adults' health status, with a special focus on two emerging health conditions, sarcopenia and frailty, and to investigate their association with other nutrition-related problems. Therefore, the objectives of the present work were outlined over chapters 2, 3, 4, and 5.

Chapter 2: Sarcopenia, frailty and nutritional status in the Portuguese older population

2.1. To describe the occurrence of sarcopenia and undernutrition in Portuguese older adults from the Nutrition UP 65 study.

2.2. To describe sarcopenia frequency using the 2018 EWGSOP2 guidelines, to investigate the factors associated with sarcopenia and undernutrition, and also to evaluate the coexistence of both conditions among older adults.

2.3. To present the frequency of frailty in a sample of Portuguese aged 65 years or older, and to evaluate its associated factors. Also, to increase the knowledge on the contribution of the different criteria for the diagnosis of frailty.

Chapter 3: The link between sarcopenia, frailty and conditions related to nutritional status

3.1. To evaluate the association between serum 25(OH)D concentrations, frailty, and obesity. In addition, to explore the association of other obesity indicators, such as WC, BRI, and ABSI with vitamin D status.

3.2. To examine the association between frailty status and indicators of body adiposity, such as BMI and WC. Moreover, to study the link between each frailty criterion and these indicators.

3.3. To elucidate the coexistence of sarcopenia, physical frailty, undernutrition, and obesity, and to evaluate the factors associated with the co-occurrence of these conditions in a large sample of the Portuguese older population.

Chapter 4: Muscle strength and muscle mass measurements to identify sarcopenia and frailty

4.1. To gather all the relevant studies that measure HGS and to identify the differences between the protocols used. To this end, the proposed systematic review will answer the following questions:

a. Which dynamometer was used for measuring HGS?
b. Which hand was used?
c. What was the individual's posture?
d. What was the arm position?
e. Which handle position was used?
f. How long did the HGS measurement take?
g. How long were the intervals between the measurements?

4.2. To explore the agreement of BIA and anthropometry with the reference method (DXA) in the diagnosis of sarcopenia in older adults, and to elucidate what is the best alternative measure to assess muscle mass. In addition, to investigate the impact of the use of several cut-off points for low muscle mass identification in sarcopenia diagnosis.

Chapter 5: Summarising discussion, concluding remarks, and future challenges

5.1. To discuss and provide an overall picture of the results presented in the previous chapters, as well as the strengths and limitations of the present work.

5.2. To debate about the future challenges and public health perspective.

Chapter 2

Sarcopenia, frailty and nutritional status in the Portuguese older population

2.1.

Sousa-Santos AR, Afonso C, Borges N, Santos A, Padrão P, Moreira P, Amaral TF. **Sarcopenia and undernutrition among Portuguese older adults: results from Nutrition UP 65 study.** Food Nutr Bull. 2018 Sep;39(3):487-492. doi: 10.1177/0379572118765801.

2.2.

Sousa-Santos AR, Afonso C, Borges N, Santos A, Padrão P, Moreira P, Amaral TF. **Factors associated with sarcopenia and undernutrition in older adults.** Nutr Diet. 2019 Nov;76(5):604-612. doi: 10.1111/1747-0080.12542.

2.3.

Sousa-Santos AR, Afonso C, Moreira P, Padrão P, Santos A, Borges N, Amaral TF. **Weakness: The most frequent criterion among pre-frail and frail older Portuguese.** Arch Gerontol Geriatr. 2018 Jan;74:162-168. doi: 10.1016/j.archger.2017.10.018.

2.1.

Sarcopenia and undernutrition among Portuguese older adults: results from Nutrition UP 65 study.

Sousa-Santos AR, Afonso C, Borges N, Santos A, Padrão P, Moreira P, Amaral TF.
Food Nutr Bull. 2018 Sep;39(3):487-492.
doi: 10.1177/0379572118765801.

Abstract

Background: Although undernutrition and sarcopenia are common among older adults and both result in worse health outcomes, data concerning the burden of these conditions in Portuguese community-dwelling older adults are scarce.

Objective: The aim of this study was to firstly describe the occurrence of sarcopenia and undernutrition among a nationwide community-dwelling sample of older adults.

Methods: Using a cross-sectional analysis, 1493 Portuguese older adults age ≥65 years from the Nutrition UP 65 study were evaluated. Sarcopenia was defined according to the European Working Group on Sarcopenia in Older People, and undernutrition status was evaluated by Mini-Nutritional Assessment – Short Form.

Results: Sarcopenia frequency was 11.6%, and of these, 4.4% were classified with severe sarcopenia. Furthermore, 0.8% presented sarcopenic obesity. Undernutrition frequency was 1.3%, and 14.7% of the older adults were classified as being at undernutrition risk.

Conclusion: Sarcopenia is present in one-tenth of the sample. This frequency taken together with undernutrition data warrants further study and preventive measures.

Keywords: sarcopenia, undernutrition, muscle mass, handgrip strength, gait speed.

Introduction

Age decline in physical performance and especially in muscle strength were shown to be significantly higher than the decline in muscle mass. Moreover, the onset of this decline can occur earlier, between the age of 40 and 50 [1,2]. Sarcopenia can be identified as the presence of low muscle mass plus low muscle function (strength or performance) with a risk of adverse outcomes such as physical disability, poor quality of life, and death [3]. Sarcopenia has multifactorial causes, namely, lack of exercise, endocrine dysfunction, chronic diseases, inflammation, insulin resistance, and nutritional deficiencies [4].

The aging process involves a deterioration in some functions that can result in reduced appetite, difficulty in chewing, inflammation of the gums, and a poor diet quality, which can negatively impact nutritional status [4]. Undernutrition status is associated with a decline in muscle mass, impaired muscle function, decreased bone mass, immune dysfunction, anemia, reduced cognitive function, and even higher mortality [5,6]. In Portugal, the frequency of sarcopenia and undernutrition was estimated in adult day care center facilities and in hospitalized older adults [7,8]; however, results regarding the community are still inexistent.

Therefore, it is important to acknowledge the frequency of these conditions in the community. The purpose of this study was to evaluate the occurrence of sarcopenia and undernutrition in Portuguese older adults from the Nutrition UP 65 study.

Materials and Methods

The present study is based on data from a cross-sectional observational study conducted in Portugal. A detailed description of the methods was published previously [9]. Briefly, the Nutrition UP 65 included a cluster sample of 1500 older Portuguese, ≥65 years old, representative of the Portuguese older population in terms of age, sex, education, and regional area. In each regional area, 3 or more town councils with >250 inhabitants were randomly selected, and potential community-dwelling participants were contacted via home approach, telephone, or via institutions, such as town councils and parish centers. Individuals presenting any condition that precluded the collection of venous blood samples or urine (eg, dementia or urinary incontinence) were excluded from the study. Individuals with missing values for triceps skinfold thickness and physical performance measures, which did not enable sarcopenia classification (n=7), were

excluded from the present analysis, and a total of 1493 older adults were included in this study. Muscle mass was estimated, as suggested by Landi et al [10], by the mid-arm muscle circumference (MAMC), calculated using the following formula: MAMC = mid-arm circumference − 3.14 × triceps skinfold thickness.

A calibrated Jamar® Plus+ Digital Hand Dynamometer (Sammons Preston Inc, Bolingbrook, Illinois) was used to assess muscle strength. Nondominant handgrip strength (HGS) was measured with individuals sitting in a chair without an arm rest, with their shoulders adducted, their elbows flexed 90°, and their forearms in neutral position, as recommended by the American Society of Hand Therapists [11]. Each participant performed 3 measurements with a 1-minute pause between measurements and the higher value was used for the analysis. When the individual was unable to perform the measurement with the nondominant hand, the dominant hand was used. Gait speed was quantified over a distance of 4.6 m. Participants were asked to walk at usual pace in an unobstructed corridor and walking time in seconds was recorded by a chronometer (School electronic stopwatch, Dive049, Topgim, Portugal).

Sarcopenia was identified using the European Working Group on Sarcopenia in Older People (EWGSOP) criteria as the presence of low muscle mass plus low muscle strength (measured by HGS) or low physical performance (measured by usual gait speed) [3]. Low muscle mass was classified as MAMC less than 21.1 cm or 19.2 cm in men or women, respectively [10]. Low muscle strength was classified as grip strength <20 kg in women and <30 kg in men, and a gait speed of ≤0.8 m/s identified participants with poorer physical performance [3]. Individuals who were unable to perform gait speed test due to mobility or balance limitations (n=29) were considered to have this criterion. Sarcopenic obesity was diagnosed by the coexistence of both sarcopenia using the EWGSOP criteria and obesity, identified by World Health Organization body mass index (BMI) classification.

The Portuguese version of the Mini-Nutritional Assessment® – Short Form (MNA-SF) was applied. A participant scoring ≤7 out of 14 points was classified as undernourished, one who scores between 8 and 11 was at risk of undernutrition, and one who scores between 12 and 14 points was considered well-nourished [12].

Ethics

This research was conducted according to the guidelines established by the Declaration of Helsinki, and the study protocol was approved by the ethics committee of the Department of Ciências Sociais e Saúde (Social Sciences and Health) from the Faculdade de Medicina da Universidade do Porto (PCEDCSS – FMUP 15/2015) and by the Portuguese National Commission of Data Protection (9427/2015). All study participants (or 2 representatives if the participant was deemed to be cognitively impaired) signed an informed consent form.

Statistical Analyses

All statistical analyses were performed using IBM SPSS Statistics 23 (SPSS, Inc, an IBM Company, Chicago, Illinois). Descriptive analyses were conducted to show the characteristics of the study sample according to sex, and comparison between the groups was conducted using χ^2 test or Fisher's exact test. Confidence intervals were computed at 95%, and statistical significance was defined by $p<0.05$.

Results

The main characteristics of the 1493 participants are presented in Table 1. Age ranged from 65 to 100 years, and the median age was 74.0 (interquartile range: 11.0) years. Women represented 59.7% of the sample. Regarding sarcopenia status, 108 were classified as sarcopenic (7.2%) and 66 as severely sarcopenic (4.4%), resulting in a total frequency of 11.6% of this syndrome. Sarcopenic obesity was present in 0.8% of the older adults (n=12).

Table 1. Characteristics of participants, according to sex.

	N (%)		
	Women	**Men**	***p*-value**
Age (years)			
65-75	468 (53.9)	382 (61.1)	0.006[a]
>75	400 (46.1)	243 (38.9)	
Residence			
Home	817 (94.1)	607 (97.1)	0.007[a]
Care home	51 (5.9)	18 (2.9)	
Education level (years of schooling)			
0	151 (17.4)	60 (9.6)	<0.001[a]
1-4	596 (68.7)	430 (68.8)	
5-12	87 (10.0)	101 (16.2)	
>12	34 (3.9)	34 (5.4)	
Marital status[b]			
Single/Divorced/Widower	560 (64.5)	233 (37.3)	<0.001[a]
Married/Common-law marriage	308 (35.5)	391 (62.7)	
Self-perception of health status[b]			
Very good/Good	231 (26.7)	246 (39.4)	<0.001[a]
Fair	435 (50.3)	295 (47.2)	
Poor/ Very poor	198 (22.9)	84 (13.4)	
Smoking status			
Nonsmoker	856 (98.6)	569 (91.0)	<0.001[a]
Smoker	12 (1.4)	56 (9.0)	
Alcohol consumption[b]			
None	540 (62.4)	193 (30.9)	<0.001[a]
Moderate (W: ≤1/day; M: ≤2/day)	262 (30.3)	342 (54.7)	
Excessive (W: >1/day; M: >2/day)	64 (7.4)	90 (14.4)	
MAMC			
W: <19.2 cm; M: <21.1 cm	772 (88.9)	529 (84.6)	0.014[a]
W: ≥19.2 cm; M: ≥21.1 cm	96 (11.1)	96 (15.6)	
HGS			
W: <20 kgf; M: <30 kgf	300 (34.6)	313 (50.1)	<0.001[a]
W: ≥20 kgf; M: ≥30 kgf	567 (65.4)	312 (49.9)	
Gait speed			
<0.8m/s	416 (49.2)	195 (31.8)	<0.001[a]
≥0.8m/s	430 (50.8)	419 (68.2)	
Sarcopenia status			
Not sarcopenic	779 (89.7)	540 (86.4)	0.135[a]
Sarcopenia	56 (6.5)	52 (8.3)	
Severe sarcopenia	33 (3.8)	33 (5.3)	
Sarcopenic obesity[c]	7 (0.8)	5 (0.8)	0.991[a]
BMI[c]			
<19 kg/m^2	2 (0.2)	1 (0.2)	0.148[d]
19.1-21 kg/m^2	11 (1.3)	9 (1.5)	
21.1-23 kg/m^2	56 (6.6)	24 (4.0)	
>23 kg/m^2	781 (91.9)	572 (94.4)	
Weight loss			
No weight loss	664 (76.5)	492 (78.8)	0.076[a]
1-3 kg	74 (8.5)	65 (10.4)	
> 3 kg	49 (5.6)	28 (4.5)	
Does not know	81 (9.3)	39 (6.3)	
Undernutrition status (MNA-SF)			
Not undernourished	708 (81.6)	546 (87.4)	0.008[a]
Undernutrition risk	149 (17.2)	71 (11.4)	
Undernutrition	11 (1.3)	8 (1.3)	

W, Women; M, Men; MAMC, Mid-arm muscle circumference; HGS, Handgrip stregth; BMI, Body mass index; MNA-SF, Mini-Nutritional Assessment – Short Form.

[a] Chi-square test.

[b] Information was not obtained: marital status n=1 (0.1%); self-perception of health status n=4 (0.2%); alcohol consumption n=2 (0.2%); HGS: n=1 (0.1%); gait speed: n=33 (2.2%); weight loss, n=1 (0.1%).

[c] Missing cases due to the absence of measured and estimated weight: n=1 (0.1%).

[d] Fisher's exact test.

Concerning undernutrition status, evaluated by the MNA-SF, 19 (1.3%) older adults were classified as undernourished and 220 (14.7%) at undernutrition risk. Women and men differed in all the studied characteristics, except for sarcopenia status (p=0.135), sarcopenic obesity (p=0.991), BMI (p=0.148), and weight loss (p=0.076). The frequency of each criterion which was used to diagnose sarcopenia was evaluated. Low muscle mass was present in 12.9% of all older adults. Higher frequencies were observed for low handgrip strength and low gait speed criteria, respectively, the first 58.9% and the second 56.9%.

Discussion

This study describes the burden of sarcopenia and undernutrition in a nationwide sample of community-dwelling older adults. Sarcopenia occurrence (11.6%) is within the values previously described in a systematic review that estimated the prevalence of sarcopenia in studies conducted in community-dwelling older adults (1%-29%) [13]. However, it should be referred that sarcopenia prevalence is highly dependent on the applied diagnostic criteria [14]. Even though the EWGSOP definition was used in all studies included in this systematic review, methodologic differences can be noted, because MAMC was applied in only 2 studies to estimate muscle mass [10,15]. In the latter studies, the frequency of sarcopenia was considerably higher than the current one and this may be due to the fact that their samples were also older. Despite not being recommended [3], anthropometric measures are easily applied in large population surveys and clinical practice, due to its simplicity [16]. Furthermore, there is lack of data comparing MAMC with the gold standard for assessing muscle mass in the identification of sarcopenia.

The HGS values within Nutrition UP 65 study have been previously discussed [17]. Similarly, a high frequency of low gait speed (56.9%) was observed in this study, but a much lower frequency of low muscle mass was present (12.9%). These results are in line with previous longitudinal research where these indicators were evaluated during the life course. Indeed, muscle strength and physical performance suffer a greater decline than muscle mass and this decline may start as early as middle age [1,2].

Undernutrition status values can vary significantly in accordance with inclusion criteria and the assessment tool chosen by the studies. When the MNA-SF was applied to older adults in the community setting, undernutrition and undernutrition risk were estimated to range from 8% to 29.6% [18]. In a Portuguese city, higher frequencies of

undernutrition and undernutrition risk were observed comparing with the present study (2.1% and 31.8% vs 1.3% and 14.7%, respectively), notwithstanding the sample of that study included individuals of day care center facilities who are expected to have greater decline in nutrition status [7].

Some weaknesses can be discussed. First, from the initial sample, 7 individuals were excluded from this study, and also the database has some missing values. Second, in order to be included, participants (or 2 representatives if the participant was deemed to be cognitively impaired) had to sign an informed consent form, which may have created a participation bias and led to a lower frequency of the conditions in this study. Additionally, low muscle mass criterion was measured by means of MAMC, which may underestimate the older adults at risk of sarcopenia and hamper the comparison with previous studies which used bioelectrical impedance analysis (BIA) or dual-energy X-ray absorptiometry (DXA). In contrast, this study has several strengths. It was the first to advance knowledge on the frequency of sarcopenia and undernutrition in the Portuguese community-dwelling older adults. Additionally, undernutrition status was evaluated using MNA-SF, which is a well-recognized tool to assess nutritional status.

In conclusion, sarcopenia is present in approximately one-tenth of Portuguese older adults included in this sample (11.6%). Moreover, 16% were undernourished or at risk of undernutrition. These results are of major relevance to plan public health interventions.

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2.2.

Factors associated with sarcopenia and undernutrition in older adults.

Sousa-Santos AR, Afonso C, Borges N, Santos A, Padrão P, Moreira P, Amaral TF.
Nutr Diet. 2019 Nov;76(5):604-612.
doi: 10.1111/1747-0080.12542.

Abstract

Aim: The aim of this study was to describe sarcopenia frequency, to identify the factors associated with sarcopenia and undernutrition, and to evaluate their coexistence.

Methods: A total of 1500 Portuguese older adults aged ≥65 years from the Nutrition UP 65 study were evaluated using a cross-sectional analysis. Sarcopenia was defined according to the European Working Group on Sarcopenia in Older People (EWGSOP)2 guidelines (2018), using anthropometric measures. Undernutrition status was evaluated by Mini-Nutritional Assessment – Short Form.

Results: Sarcopenia frequency was 4.4% (n=66). Sarcopenia coexists with undernutrition or undernutrition risk in 1.5% of this sample. In the multivariate analysis, sarcopenia was directly associated with age >75 years (odds ratio (OR): 2.14; 95% confidence interval (CI): 1.19-3.84), undernutrition or undernutrition risk (OR: 1.86; 95% CI: 1.01-3.43) and inversely associated with male gender (OR: 0.52; 95% CI: 0.29-0.97), overweight (OR: 0.24; 95% CI: 0.13-0.42) or obesity (OR: 0.02; 95% CI: 0.01-0.09) and moderate alcohol consumption (OR: 0.47; 95% CI: 0.24-0.90). Undernutrition or undernutrition risk was associated with a poor or very poor self-perception of health status (OR: 3.53; 95% CI: 2.32-5.37), a low physical activity level (OR: 1.74; 95% CI: 1.23-2.47), sarcopenia (OR: 1.85; 95% CI: 1.02-3.36), and being overweight (OR: 0.40; 95% CI: 0.27-0.59) or obese (OR: 0.43; 95% CI: 0.28-0.65).

Conclusions: The majority of the older adults presented low muscle strength (probable sarcopenia), but only a small number had concomitantly low muscle quantity or quality (sarcopenia). Coexistence between these conditions is low which reinforces the need to assess them both individually during geriatric assessment.

Keywords: gait speed, handgrip strength, muscle mass, sarcopenia, undernutrition.

Introduction

Sarcopenia and undernutrition are conditions frequently related with ageing and represent a major threat to older adults' health [1]. An increased interest in sarcopenia has been observed over the years, and this geriatric disorder is already recognised by the International Classification of Disease, Tenth Revision, Clinical Modification [2]. In 2010, sarcopenia was presented as a geriatric syndrome characterised by the age-related decline in muscle mass and function (strength and performance) [3]. In late 2018, the European Working Group on Sarcopenia in older people (EWGSOP)2 published an updated operational definition of sarcopenia [4]. Sarcopenia is defined as 'a progressive and generalised skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability, and mortality'. Contrary to the initial EWGSOP consensus [3], these new guidelines indicate low muscle strength as a primary parameter, as it has proved to be stronger than muscle mass in predicting adverse outcomes. Sarcopenia diagnosis is then confirmed by the presence of low muscle quantity and quality, and low physical performance is then used to identify sarcopenia severity [4]. The term undernutrition has also evolved and, based in its aetiology, the International Guideline Consensus Committee proposed the following three sub-types: starvation related, chronic disease-related and acute disease- or injury-related [5]. Regarding undernutrition assessment, the Mini-Nutritional Assessment – Short Form (MNA-SF) has been shown to be a rapid and reliable way of assessing undernutrition and undernutrition risk in the community [6,7]. In 2012, a new term to define the occurrence of both sarcopenia and undernutrition was suggested, the malnutrition sarcopenia syndrome [8]. This syndrome was recently pointed out as a prognostic indicator for long-term mortality in hospitalised older patients [9]. Sarcopenia and undernutrition are both associated with higher care costs [10,11] and several adverse health outcomes, namely poor quality of life [12,13] prolonged length of stay in hospital [11,14,15] and mortality [11,16,17]. Routine undernutrition identification is increasing in the clinical practice, but sarcopenia remains poorly identified. To delineate the geriatric assessment, it is essential to know if the same individuals are at higher risk of both sarcopenia and undernutrition and if these conditions share similar risk factors. Indeed, if they share similar associated factors, this may be helpful to choose the best strategy for their management among older adults. As both conditions are preventable, early intervention may promote healthier ageing by improving older adults' quality of life and health status. If these potentially modifiable

risk factors differ between sarcopenia and undernutrition, independent evaluation of each condition during geriatric screening and assessment will be relevant. Therefore, the purpose of the present study is to present the results of sarcopenia frequency using the updated guidelines, to investigate the factors associated with sarcopenia and undernutrition and also to evaluate coexistence of both conditions among older adults.

Methods

Data from Nutrition UP 65 cross-sectional observational study was used. A cluster sample of 1500 older adults aged ≥65 years, representative of the Portuguese older population in terms of age, sex, education and regional area. In each regional area, three or more town councils with >250 inhabitants were randomly selected, and potential community-dwelling participants were contacted via home approach, telephone or via institutions, such as town councils and parish centres. Individuals presenting any condition that precluded the collection of venous blood samples or urine (e.g. dementia or urinary incontinence) were not included. Data collection took place between December 2015 and June 2016. Trained registered nutritionists applied a structured questionnaire and collected all anthropometric data. Besides demographic data, information about lifestyle practices, self-perception of health status, cognitive function and undernutrition status were gathered. Demographic data, lifestyle practices, such as smoking and alcohol consumption, and self-perception of health status were self-reported and ascertained with questions from the National Health Survey questionnaire [18]. A full description of the methods was published elsewhere [19]. This manuscript was prepared in accordance with the STROBE statement.

Anthropometric measurements

Anthropometric measurements were collected following standard procedures [20]. Intra- and inter-rater observer errors were calculated and ranged from 0.05 to 0.34% and 0.19 to 1.48%, respectively. Standing height was obtained with a calibrated stadiometer (SECA 213, SECA GmbH, Hamburg, Germany) with 0.1 cm resolution. Body weight (in kilograms) was measured with a calibrated portable electronic scale (SECA 803, SECA GmbH) with 0.1 kg resolution, with the participants wearing light clothes. When it was not possible to weigh a patient, for the same reasons that prevented standing height measurement, body weight was estimated from mid-upper arm (MAMC) and calf

circumferences [21]. MAMC and waist circumferences were measured with a metal tape (Lufkin W606 PM, Lufkin, Sparks, MD, USA) with 0.1 cm resolution. Triceps skinfold thickness was obtained using a Holtain Tanner/Whitehouse (Holtain, Ltd., Crosswell, UK) skinfold calliper, with 0.2 mm resolution. Muscle mass was estimated, as suggested by Landi et al. [22], using MAMC, calculated according to the formula suggested by Jelliffe [23].

Muscle strength and function

A calibrated Jamar Plus+ Digital Hand Dynamometer (Sammons Preston Inc., Bolingbrook, IL, USA) was used to assess muscle strength. Nondominant hand grip strength (HGS) was measured with individuals sitting in a chair without arm rest, with their shoulders adducted, their elbows flexed 90º and their forearms in neutral position, as recommended by the American Society of Hand Therapists [24]. Each participant performed three measurements with a one-minute pause between them, and the highest value was used for the analysis. When the individual was unable to perform the measurement with the non-dominant hand, the dominant hand was used.

Gait speed was quantified over a distance of 4.6 m. Participants were asked to walk at usual pace along an unobstructed corridor and walking time in seconds was recorded by a chronometer (School electronic stopwatch, Dive049, Topgim, Portugal).

Sarcopenia status

Sarcopenia was identified using the EWGSOP2 guidelines, as the presence of low muscle strength measured by HGS, plus low muscle quantity and quality [4]. Low muscle strength was classified as grip strength <16 kgf in women and <27 kgf in men. Low muscle quantity and quality was classified as calf circumference <31 cm, and also by MAMC <21.1 and 19.2 cm in men and women, respectively [3,22]. Sarcopenia severity was further determined by low physical performance as measured by usual gait speed [4]. A gait speed of ≤0.8 m/second identified subjects with poorer physical performance [4].

Of the 1500 older adults included, it was only possible to assess sarcopenia using MAMC criterion in 1495, because of missing data. Despite not being mentioned in the updated consensus, MAMC criterion was mentioned previously as a measure to estimate muscle mass [3,22]. Therefore, sarcopenia frequency was also studied using this measure and the agreement between definitions.

Undernutrition status

The Portuguese version of the MNASF was applied. The MNA-SF consists of six questions targeting food intake, weight loss, physical and mental status, and anthropometry through body mass index (BMI) or calf circumference assessment. A participant scoring ≤7 out of 14 points was classified as undernourished, one that scores between 8 and 11 is at risk of undernutrition and one scoring between 12 and 14 points was considered wellnourished [27].

Cognitive function

Cognitive performance was assessed with the Portuguese version of the Mini-Mental State Examination (MMSE). Individuals were classified as cognitive impaired using the following criteria: individuals with no education, ≤15 points; 1–11 years of years of school completed, ≤22 points; and >11 years of school completed, ≤27 points [28].

Physical activity

The short form of the International Physical Activity Questionnaire was used to assess physical activity [29]. Information regarding how much time the individuals spent walking or hiking, sitting, in moderate and vigorous activities, in the previous seven days, was collected. Low physical activity was defined as <383 and <270 kcal/week, for men and women, respectively [30].

Body mass index

BMI was calculated as (weight (kg)/height^2 (m)), and categories were defined according to World Health Organization as underweight for BMI below 18.5 kg/m^2, as normal weight for BMI between 18.5 and 24.9 kg/m^2, as overweight for BMI between 25.0 and 29.9 kg/m^2 and as obese for BMI of 30.0 kg/m^2 or above [31]. Because of the small number of underweight individuals (n=4), they were included in the reference group (normal weight). The BMI categories suggested by Lipschitz were also used for descriptive analysis [32].

Ethics

This research was conducted according to the guidelines established by the Declaration of Helsinki and the study protocol was approved by the ethics committee of the 'Department of "Ciências Sociais e Saúde (Social Sciences and Health) from the Faculdade de Medicina da Universidade do Porto" (PCEDCSS – FMUP 15/2015) and by the Portuguese National Commission of Data Protection (9427/2015)'. All study participants (or two representatives if the participant was deemed to be cognitively impaired) signed an informed consent form.

Statistical analyses

Descriptive analyses were conducted to show the characteristics of the study sample according to sarcopenia and undernutrition status. Results were expressed as number of participants (percentage). Differences between the groups were evaluated using chi-square test or Fisher's exact test. Because of the low number of undernourished individuals identified in this sample, undernutrition and undernutrition risk were analysed as a single group. Also, sarcopenic and severe sarcopenic individuals were included in same category (sarcopenia). Agreement between sarcopenia definitions, using calf circumference or MAMC to estimate muscle quantity and quality, was evaluated through Cohen's kappa coefficient (κ), in 1495 older adults.

In order to handle missing data for the variables alcohol consumption (n=2), BMI (n=4), marital status (n=1) and self-perception of health status (n=4), multiple imputation was performed using a Markov Chain Monte Carlo approach, with five imputation data sets and 10 iterations. Afterwards, bivariate and multivariate logistic regressions were conducted using sarcopenia and undernutrition status as dependent variables. Odds ratios (OR) with 95% confidence intervals (CI) were calculated as measures of association. Sex, age, residential status, regional area, educational level, marital status, self-perception of health status, smoking status, alcohol consumption, BMI classification, physical activity level, sarcopenia (or undernutrition status) and cognitive function were variables included in the models.

Confidence intervals were defined at 95% and statistical significance was set at a $p<0.05$. All statistical analyses were performed using IBM SPSS Statistics 23 (SPSS, Inc., an IBM Company, Chicago, IL, USA).

Results

A total of 1500 individuals were included in the present study. Women represented 58.1% of the sample and the median age was 74 years (age range: 65–100 years). Using the new algorithm released by EWGSOP2, a large proportion (n=538, 36%) of the sample had the primary parameter of sarcopenia (low muscle strength). However, considering the combined presence of low muscle strength and low muscle quantity or quality, 4.4% (n=66) were identified with sarcopenia, of which 21 (1.4%) presented a severe state.

When MAMC criterion was used, in a sub-sample of 1495 older adults, a slightly higher number (n=93, 6.2%) was identified with sarcopenia. Furthermore, when the agreement between both approaches was explored, and a fair agreement (k=0.336; $p<0.001$) was observed, as only 29 older adults (1.9%) were considered sarcopenic using both calf circumference and MAMC criteria (Table S1, Supporting Information).

Table 1. Characteristics of participants, regarding sarcopenia and undernutrition status[1].

	Not sarcopenic 1434 (95.6)	**Sarcopenia** 66 (4.4)	***p*-value**	**Not undernourished** 1259 (84.0)	**Undernutrition risk/ Undernourished** 240 (16.1)	***p*-value**
Sex						
Women	825 (57.5)	47 (71.2)	0.028[2]	710 (56.4)	162 (67.2)	0.002[2]
Men	609 (42.5)	19 (28.8)		549 (43.6)	79 (32.8)	
Age						
65-75 years	831 (57.9)	22 (33.3)	<0.001[2]	731 (58.1)	122 (50.6)	0.033[2]
>75 years	603 (42.1)	44 (66.7)		528 (41.9)	119 (49.4)	
Regional Area						
North/Centre/Lisbon	1192 (83.1)	53 (80.3)	0.671[3]	1043 (82.8)	202 (83.8)	0.929[2]
Alentejo/Algarve	190 (13.2)	11 (16.7)		170 (13.5)	31 (12.9)	
Madeira/Azores	52 (3.6)	2 (3.0)		46 (3.7)	8 (3.3)	
Residence						
Home	1371 (95.6)	57 (86.4)	0.001[2]	1206 (95.8)	222 (92.1)	0.015[2]
Care home	63 (4.4)	9 (13.6)		53 (4.2)	19 (7.9)	
Education level						
Without education	197 (13.7)	15 (22.7)	0.093[2]	164 (13.0)	48 (19.9)	0.013[2]
1-4 years	988 (68.9)	43 (65.2)		872 (69.3)	159 (66.0)	
≥5 years	249 (17.4)	8 (12.1)		223 (17.7)	34 (14.1)	
Marital status						
Single/Divorced/Widower	753 (52.5)	44 (66.7)	0.025[2]	641 (51.0)	156 (64.7)	<0.001[2]
Married/Common-law marriage	680 (47.5)	22 (33.3)		617 (49.0)	85 (35.3)	
Self-perception health status						
Very good/Good	455 (31.8)	24 (36.4)	0.739[2]	429 (34.2)	50 (20.8)	<0.001[2]
Fair	702 (49.1)	30 (45.5)		632 (50.3)	100 (41.7)	
Poor/Very poor	273 (19.1)	12 (18.2)		195 (15.5)	90 (37.5)	
Cognitive function						
Not impaired	1346 (93.9)	55 (83.3)	0.001[2]	1189 (94.4)	212 (88.0)	<0.001[2]
Impaired	88 (6.1)	11 (16.7)		70 (5.6)	29 (12.0)	
Smoking status						
Non-smoker	1372 (95.7)	60 (90.9)	0.069[2]	1204 (95.6)	228 (94.6)	0.483[2]
Smoker	62 (4.3)	6 (9.1)		55 (4.4)	13 (5.4)	
Alcohol consumption						
None	691 (48.3)	48 (72.7)	<0.001[3]	595 (47.3)	144 (59.8)	0.002[2]
Moderate (W≤1/day; M≤2/day)	591 (41.3)	14 (21.2)		527 (41.9)	78 (32.4)	
Excessive (W>1/day; M>2/day)	150 (10.5)	4 (6.1)		135 (10.7)	19 (7.9)	
Physical Activity						
Not low	1192 (83.1)	46 (69.7)	0.005[2]	1069 (84.9)	169 (70.1)	<0.001[2]
Low	242 (16.9)	20 (30.3)		190 (15.1)	72 (29.9)	
BMI (WHO)						
<25.0 kg/m^2	214 (15.0)	38 (58.5)	<0.001[3]	184 (14.6)	68 (28.5)	<0.001[2]
25.0-29.9 kg/m^2	636 (44.4)	25 (38.5)		578 (46.0)	83 (34.7)	
≥30.0 kg/m^2	581 (40.6)	2 (3.1)		495 (39.4)	88 (36.8)	
BMI (Lipschitz)						
<22.0 kg/m^2	44 (3.2)	15 (23.1)	<0.001[2]	33 (2.7)	26 (11.4)	<0.001[2]
22.0-27.0 kg/m^2	367 (26.4)	38 (58.5)		337 (27.5)	68 (29.7)	
>27.0 kg/m^2	978 (70.4)	12 (18.5)		855 (69.8)	135 (59.0)	
Undernutrition status						
Not undernourished	1216 (84.8)	43 (65.2)	<0.001[2]	-	-	-
Undernutrition risk/Undernourished	218 (15.2)	23 (34.8)		-	-	

BMI, body mass index; M, men; W, women; WHO, World Health Organization.
Data before multiple imputation. Missing data: Marital status: n=1 (0.1%), Self-perception of health status: n=4 (0.3%), Alcohol consumption: n=2 (0.1%), BMI: n=4 (0.3%).
Chi-square test.
Fisher's exact test.

The characteristics of the study participants regarding sarcopenia and undernutrition status are displayed in Table 1. Sarcopenic individuals were more likely to be women (p=0.028), over 75 years (p<0.001), live in a care home (p=0.001), being single, divorced or widower (p=0.025), not drinking alcohol (p<0.001), have a low physical activity level (p=0.005), placed in a lower BMI category (p<0.001), being undernourished or at undernutrition risk (p<0.001) and cognitively impaired (p=0.001). When comparing not undernourished versus undernourished or at undernutrition risk individuals, statistically significant differences were found for all study variables, except for regional area (p=0.929) and smoking status (p=0.483) (Table 1). Results characteristics of study participants according to sarcopenia using MAMC criterion are displayed in Table S2.

The coexistence of sarcopenia and undernutrition status is displayed in Figure 1. In this sample, sarcopenia and undernutrition or undernutrition risk coexisted in 23 older adults (1.5%). When MAMC criterion was used in sarcopenia definition, coexistence was observed in 18 (1.2%) of the 1495 individuals evaluated (data not shown).

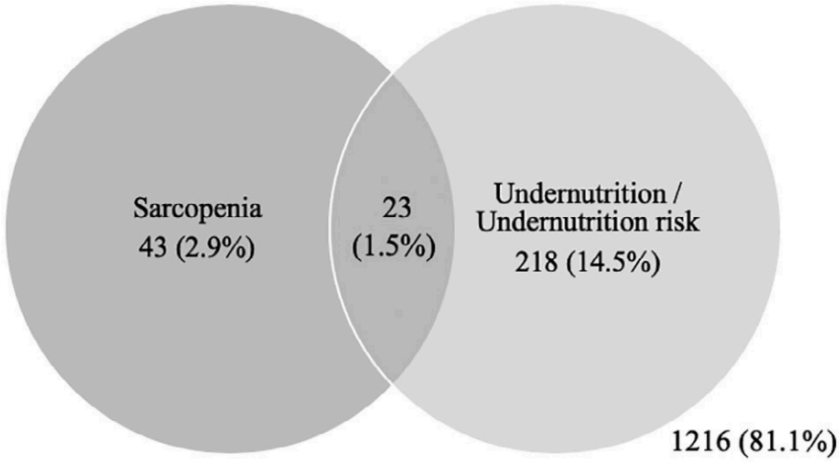

Figure 1. Sarcopenia and undernutrition or undernutrition risk coexistence.

The results of the bivariate and multivariate logistic regression analyses after multiple imputation, regarding sarcopenia and undernutrition or undernutrition risk, are presented in Tables 2 and 3. In the adjusted model, sarcopenia was directly associated with age >75 years (OR: 2.14; 95% CI: 1.19-3.84) and undernutrition or undernutrition risk (OR: 1.86; 95% CI: 1.01-3.43), and inversely associated with male gender (OR: 0.52; 95% CI: 0.29-0.97), moderate alcohol consumption (OR: 0.47; 95% CI: 0.24-0.90), BMI

between 25.0 and 29.9 kg/m2 (OR: 0.24; 95% CI: 0.13-0.42) and BMI ≥30.0 kg/m2 (OR: 0.02; 95% CI: 0.01-0.09) (Table 2).

Table 2. Results from the bivariate and multivariate logistic regression analysis, regarding sarcopenia status.

	Sarcopenia			
	Unadjusted		Adjusted	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Sex				
Women	1		1	
Men	0.55 (0.32-0.94)	0.030	0.52 (0.29-0.97)	0.038
Age				
65-75 years	1		1	
>75 years	2.76 (1.64-4.65)	<0.001	2.14 (1.19-3.84)	0.011
Regional area				
North/Centre/Lisbon	1		1	
Alentejo/Algarve	1.35 (0.69-2.64)	0.380	1.25 (0.59-2.63)	0.566
Madeira/Azores	0.90 (0.21-3.78)	0.882	1.22 (0.27-5.51)	0.800
Education level				
Without education	1		1	
1-4 years	0.57 (0.31-1.05)	0.071	0.68 (0.34-1.35)	0.268
≥5 years	0.42 (0.18-1.02)	0.054	0.49 (0.18-1.30)	0.153
Marital status				
Single/Divorced/Widower	1		1	
Married/Common-law marriage	0.55 (0.33-0.93)	0.026	0.99 (0.54-1.82)	0.984
Self-perception of health status				
Very good/Good	1		1	
Fair	0.81 (0.47-1.40)	0.450	0.73 (0.40-1.34)	0.311
Poor/Very poor	0.83 (0.41-1.69)	0.611	0.52 (0.23-1.16)	0.110
Alcohol consumption				
None	1		1	
Moderate (W≤1/day; M≤2/day)	0.35 (0.19-0.65)	0.001	0.47 (0.24-0.90)	0.024
Excessive (W>1/day; M>2/day)	0.40 (0.14-1.12)	0.081	0.75 (0.24-2.31)	0.610
Physical Activity				
Not low	1		1	
Low	2.14 (1.24-3.69)	0.006	1.71 (0.92-3.18)	0.093
BMI (WHO)				
<25.0 kg/m^2	1		1	
25.0-29.9 kg/m^2	0.23 (0.13-0.39)	<0.001	0.24 (0.13-0.42)	<0.001
≥30.0 kg/m^2	0.02 (0.01-0.08)	<0.001	0.02 (0.01-0.09)	<0.001
Undernutrition status				
Not undernourished	1		1	
Undernutrition risk/ Undernutrition	2.98 (1.76-5.05)	<0.001	1.86 (1.01-3.43)	0.046

BMI, body mass index; CI, confidence interval; M, men; OR, odds ratio; W, women; WHO, World Health Organization.

The results of multivariate logistic regression showed that when MAMC was used to estimate muscle quantity and quality, sarcopenia was directly associated with male gender (OR: 1.92; 95% CI: 1.18-3.13), and age >75 years (OR: 3.20; 95% CI: 1.94-5.29). Otherwise, it was inversely associated with moderate alcohol consumption (OR: 0.42;

95% CI: 0.24-0.72), BMI between 25.0 and 29.9 kg/m^2 (OR: 0.38; 95% CI: 0.24-0.62) and BMI ≥30.0 kg/m^2 (OR: 0.03; 95% CI: 0.01-0.10) (Table S3).

Moreover, in the adjusted model, undernutrition or undernutrition risk was significantly associated with poor or very poor self-perception of their health status (OR: 3.53; 95% CI: 2.32-5.37), BMI between 25.0 and 29.9 kg/m^2 (OR: 0.40; 95% CI: 0.27-0.59) and ≥30.0 kg/m^2 (OR: 0.43; 95% CI: 0.28-0.65), a low physical activity level (OR: 1.74; 95% CI: 1.23-2.47) and sarcopenia (OR: 1.85; 95% CI: 1.02-3.36) (Table 3).

The results of the regression analyses showed that a higher BMI was inversely associated with both sarcopenia and undernutrition. Also, despite the low coexistence between both conditions, a significant association between sarcopenia and undernutrition was found.

Table 3. Results from the bivariate and multivariate logistic regression analysis, regarding undernutrition status.

	Undernutrition risk/Undernutrition			
	Unadjusted		Adjusted	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Sex				
Women	1		1	
Men	0.63 (0.47-0.84)	0.002	0.78 (0.56-1.09)	0.151
Age				
65-75 years	1		1	
>75 years	1.35 (1.02-1.78)	0.033	0.86 (0.62-1.18)	0.351
Residence				
Home	1		1	
Care home	1.95 (1.13-3.35)	0.016	1.23 (0.68-2.24)	0.499
Education level				
Without education	1		1	
1-4 years	0.62 (0.43-0.90)	0.011	0.76 (0.51-1.13)	0.174
≥5 years	0.52 (0.32-0.85)	0.008	0.77 (0.45-1.33)	0.352
Marital status				
Single/Divorced/Widower	1		1	
Married/Common-law marriage	0.57 (0.43-0.75)	<0.001	0.75 (0.54-1.04)	0.084
Self-perception of health status				
Very good/Good	1		1	
Fair	1.36 (0.95-1.95)	0.093	1.38 (0.95-2.02)	0.093
Poor/Very poor	3.96 (2.69-5.82)	<0.001	3.53 (2.32-5.37)	<0.001
Cognitive function				
Not impaired	1		1	
Impaired	2.32 (1.47-3.67)	<0.001	1.62 (0.98-2.69)	0.061
Smoking status				
Non-smoker	1		1	
Smoker	1.25 (0.67-2.32)	0.484	1.10 (0.54-2.24)	0.787
Alcohol consumption				
None	1		1	
Moderate (W≤1/day; M≤2/day)	0.61 (0.45-0.83)	0.001	0.93 (0.67-1.31)	0.688
Excessive (W>1/day; M>2/day)	0.58 (0.35-0.97)	0.038	1.07 (0.61-1.88)	0.814
Physical Activity				
Not low	1		1	
Low	2.40 (1.75-3.29)	<0.001	1.74 (1.23-2.47)	0.002
BMI (WHO)				
<25.0 kg/m^2	1		1	
25.0-29.9 kg/m^2	0.39 (0.27-0.56)	<0.001	0.40 (0.27-0.59)	<0.001
≥30.0 kg/m^2	0.48 (0.34-0.69)	<0.001	0.43 (0.28-0.65)	<0.001
Sarcopenia				
Not sarcopenic	1		1	
Sarcopenia	2.98 (1.76-5.05)	<0.001	1.85 (1.02-3.36)	0.043

BMI, body mass index; CI, confidence interval; M, men; OR, odds ratio; W, women; WHO, World Health Organization.

Discussion

In the present study, it was shown that sarcopenia was directly associated with age >75 and undernutrition or undernutrition risk and inversely associated with male gender, moderate alcohol consumption and a higher BMI, when calf circumference was used to

estimate muscle quality and quantity. Results also revealed that older adults who were undernourished or at undernutrition risk had increased odds of having poor or very poor self-perception of their health status, low physical activity level and sarcopenia, and decreased odds of being overweight or obese. The majority of the older adults included in the present study presented low muscle strength, but only a small number had concomitantly low muscle quantity or quality.

Nevertheless, it is important to advance with the possibility that the use of these revised guidelines may identify a larger number of individuals in which sarcopenia is probable, while a lower number of individuals are diagnosed as sarcopenic. This is because of the fact that the sarcopenia definition was updated (low physical performance is no longer used to define sarcopenia, and is only used to classify its severity), but also because low muscle strength cutoff points were also updated. Although anthropometric measures are not recommended for sarcopenia diagnosis [4], it is important to recognise that this condition is a geriatric disorder and the presence of medical devices and prothesis is common among older adults, which calls into question the use of the recommended methods to evaluate muscle quantity and quality, and strengthens the use of alternative measures in these cases, such as anthropometry.

In contrast to what was observed in the majority of the studies included in a systematic review [33], gender was associated with sarcopenia, nevertheless we have found contradictory results depending on the method used to assess muscle quantity and quality. On the other hand, age was positively associated with sarcopenia status, corroborating the results of previous studies that reported increasing prevalence of sarcopenia with increasing age [33]. As observed in a recent meta-analysis [34], a moderate alcohol intake was inversely associated with sarcopenia. A possible explanation could be that older adults who consume a moderate amount of alcohol regularly may also have better overall health.

Previously, BMI has been indicated as a strong predictor of skeletal muscle mass in women and men [35]. In agreement with previous data, an inverse association between higher BMI categories and sarcopenia was identified in the present study, and this association was stronger for obesity. This may be because of the fact that obese individuals, besides the larger amount of fat mass can also have higher lean mass, which can mask the inadequate muscle mass for their size [36]. As expected, a similar association was observed for undernutrition or undernutrition risk, as a higher BMI was associated with a lower risk. However, it is important to consider that BMI may be a suboptimal

indicator of adiposity among older adults, as body composition is altered during ageing, where increased in adiposity levels and decrease in muscle mass is observed [37].

A systematic review based on longitudinal data, that highlighted the risk factors for undernutrition in older adults found that higher age, poor self-perception of health status and cognitive decline were significantly associated with undernutrition status [38]. However, age was not associated to a higher risk of undernutrition in the present study. On the other hand, similar results were found for self-perception of health status, which are also in line with previous data in a small sample of Portuguese older adults [39]. In addition, in agreement with previous data [40,41], undernutrition or undernutrition risk was directly associated with low physical activity, which is expected because mobility is evaluated during undernutrition assessment.

The association between undernutrition status and frailty has already been addressed [42]; however, results concerning the association between undernutrition and sarcopenia still need to be further elucidated. Low handgrip strength has been recognised as an indicator of both sarcopenia and undernutrition status [3,43]. While some research conducted in the community revealed an association between sarcopenia and undernutrition [44-48], this was only partially confirmed in the present study. A systematic review which intended to gather the results regarding this association, found a high heterogeneity between the criteria used to diagnose these conditions, which made it difficult to draw conclusions [48]. Supporting this, in the present study, association between sarcopenia and undernutrition or undernutrition risk was only found when calf circumference was used to estimate muscle quantity and quality. This may be because of the fact that calf circumference can also be used as criterion to evaluate undernutrition status in MNA-SF, when BMI is unavailable. Therefore, it is important to acknowledge that this association is highly dependent on the chosen diagnostic criteria.

Nevertheless, only 1.5% of the older adults were identified with both sarcopenia and undernutrition. Compared with previous data from individuals of day care centre facilities [49], a lower coexistence was found in the present study (6.8 vs 1.5%), however a higher frequency of sarcopenia and undernutrition was also previously observed in older adults from day care centre facilities [49]. The low coexistence observed here is an important finding and suggests that sarcopenia and undernutrition are not interchangeable conditions.

Moreover, when we compare the factors associated with both conditions, only overweight and obesity were identified. All this reinforces the need to identify both conditions when assessing nutritional status in the geriatric care.

The present study has several strengths and some limitations. It is the first to explore the associated factors of sarcopenia and undernutrition in the same older adult population. In addition, sarcopenia was defined according to the new revised EWGSOP2 definition and undernutrition status was evaluated using MNA-SF, which is a reliable tool to assess nutritional status [6,7]. The present study has the limitation inherent to a cross-sectional design, therefore we were unable to determine cause-effect relationships. Second, muscle mass was evaluated using calf circumference and MAMC over dual-energy X-ray absorptiometry, recommended by the EWGSOP2, which could underestimate sarcopenia frequency. Third, during gait speed evaluation, a distance of 4.6 m was used, instead of 4 m suggested by EWGSOP2. Although the velocity would theoretically be the same, we cannot exclude the possibility that this longer distance can result in slightly slower or faster walking speeds, and therefore influence the frequency of sarcopenia severity. Also, the low number of sarcopenic and undernourished individuals in this sample may hinder the existence of possible associations.

In conclusion, the majority of the older adults included in the present study presented low muscle strength (probable sarcopenia), but only a small number had concomitantly low muscle quantity or quality (sarcopenia). Also, the present study shows that a higher BMI is inversely associated with both sarcopenia and undernutrition. Plus, an association between sarcopenia and undernutrition was only found when calf circumference was used to estimate muscle quantity and quality, not MAMC. However, the coexistence between these conditions is low which reinforces the need to assess them both individually during geriatric assessment.

Supplemental material

Supplemental material for this article can be found online:

https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1111%2F1747-0080.12542&file=ndi12542-sup-0001-TableS1-S3.docx

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2.3.

Weakness: The most frequent criterion among pre-frail and frail older Portuguese.

Sousa-Santos AR, Afonso C, Moreira P, Padrão P, Santos A, Borges N, Amaral TF.
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Abstract

Aim: In Portugal, the burden of pre-frailty and frailty in community-dwelling older adults is still unknown. The purpose of this study is to estimate the frequency of frailty in a Portuguese sample with ≥65 years and to evaluate its associated factors. We also intend to identify which criterion has more impact on the diagnosis of frailty.

Methods: 1457 older adults with ≥65 years from the Nutrition UP 65 study were evaluated in a cross-sectional analysis. Frailty was identified according to Fried et al. by the presence of three or more of the following factors: unintentional weight loss, self-reported exhaustion, slowness, weakness and low physical activity. Pre-frailty was defined as the presence of one or two of these criteria. The association between individuals' characteristics and frailty status was analysed through logistic regression analysis.

Results: The frequency of pre-frailty and frailty is 54.3% and 21.5%, respectively. In older adults classified as pre-frail or frail, 76.7% presented weakness and 48.6% exhaustion. In multivariate analyses, frailty was associated with age >75, lower education level, being single, divorced or widower, being professionally inactive, poor self-perception of health status, not drinking alcohol, being obese and undernourished or at undernutrition risk.

Conclusion: This condition is very prevalent in Portuguese older adults, one fifth are frail whereas half are pre-frail. Weakness identified by low handgrip strength is the most prevalent criterion in pre-frail and frail Portuguese older adults.

Keywords: exhaustion, frailty, physical activity, walking time, weakness, weight loss.

Introduction

Frailty is a common clinical syndrome in older adults. It is characterised by multisystem dysregulations, leading to a loss of dynamic homeostasis, decreased physiologic reserve and increased vulnerability for poor health outcomes, such as falls, incident disability, hospitalization, and mortality [1,2].

Several methodologies have been proposed to identify frailty [3-5]. Fried's frailty scale has been the most extensively tested for its validity and is the most widely used instrument in frailty research [6]. Fried et al. suggested that individuals should be classified as normal, pre-frail or frail based on the following factors: unintended weight loss, exhaustion, weakness, slow walking speed and low physical activity. Frailty was considered as the presence of three or more of these characteristics and pre-frailty when one or two characteristics were present [3]. Older adults categorised according to this definition, showed differences in the level of social, psychological and physical functioning between the three stages [7].

In a systematic review where the prevalence of pre-frailty and frailty reported by studies in the community in older adults with 65 years or older was pooled, the average prevalence of pre-frailty was 41.6% and frailty of 10.7% [8]. Frailty numbers ranged substantially from 4% to 59.1% between the analysed studies. Nevertheless, when only studies using Fried's definition were analysed, frailty prevalence ranged from 4% to 17% [8].

To our knowledge, only one study in Portugal has reported the frequency of pre-frailty (44%) and frailty (56%) among 50 institutionalized older adults using Fried's criteria [9]. Thus, the burden of this condition among Portuguese older adults living in the community is still unknown. This is of major relevance because the proportion of older people in Portugal is increasing [10] and, consequently, the number of individuals at risk of frailty.

Using data from the Nutrition UP 65 study, we aim to identify the frequency of frailty in a sample of Portuguese with 65 years or older, and to evaluate its associated factors. We also intend to evaluate the contribution of the different criteria for the diagnosis of frailty.

Methods

This study used data from the Nutrition UP 65 study which is a cross-sectional observational study conducted in Portugal. Details regarding the recruitment, selection and measures were outlined elsewhere [11]. Briefly, Nutrition UP 65 included a sample of 1500 Portuguese with ≥65 years old, representative of the Portuguese older population in terms of age, sex, education and regional area. Individuals presenting any condition that precluded the collection of venous blood samples or urine (eg, dementia or urinary incontinence) were excluded from the study. For the current analysis, 43 individuals were excluded due to incomplete data regarding frailty assessment. Therefore, a total of 1457 older adults were included.

Data collection

Data were collected between December 2015 and June 2016 and information on each subject was gathered by means of an interview conducted by previously trained registered nutritionists, also responsible for anthropometric and functional data collection. Demographic data, cohabitation, professional occupation, lifestyle practices, health status and clinical history, cognitive performance, and nutritional status data were collected using a structured questionnaire. Lifestyle practices included current tobacco use and number of alcoholic drinks daily. Chronic diseases were evaluated by the presence of asthma; chronic bronchitis, chronic obstructive pulmonary disease, or emphysema; myocardial infarction or chronic consequences of myocardial infarction; coronary heart disease or angina pectoris; hypertension; stroke or chronic consequences of a stroke; arthrosis; lumbar pain or other chronic lumbar problems; neck pain or other chronic neck problems; diabetes; hepatic cirrhosis; allergies; chronic renal disease, including renal failure; urinary incontinence or bladder control problems; depression; other disease, diagnosed in the past year. The variable was categorised as: absence of chronic diseases; presence of 1 chronic disease; or presence of 2 or more chronic diseases [12].

Cognitive and nutritional assessment

Cognitive performance was assessed by the Portuguese version of the Mini-Mental State Examination. The cut-off scores for cognitive impairment are as follows: individuals with no education, ≤15 points; 1 to 11 years of school completed,

≤22 points; and >11 years of school completed, ≤27 points [13]. The Portuguese version of the Mini-Nutritional Assessment® – Short Form (MNA-SF) was also applied. A participant scoring ≤7 out of 14 points was classified as undernourished, one that scores between 8 and 11 is at risk of undernutrition and one scoring between 12 and 14 points was considered well-nourished [14].

Anthropometric measurements

Anthropometric measurements were collected following standard procedures [15]. Intra and inter-rater observer error was calculated and ranged from 0.05 to 0.34% and 0.19 to 1.48%, respectively. Standing height was obtained with a calibrated stadiometer (SECA 213, SECA GmbH, Hamburg, Germany), with 0.1 cm resolution. For participants with visible kyphosis or when it was impossible to measure standing height due to participant's paralysis or due to mobility or balance limitations, height was obtained indirectly from non-dominant hand length [16], measured with a calibrated paquimeter (Fervi Equipment, Vignola, Italy), with 0.1 centimeter resolution. Body weight (in kilograms) was measured with a calibrated portable electronic scale (SECA 803, SECA GmbH, Hamburg, Germany) with 0.1 kg resolution, with the participants wearing light clothes. When it was not possible to weigh a patient, body weight was estimated from mid-upper arm and calf circumferences [17]. Mid upper arm, waist and calf circumferences were measured with a metal tape measure (Lufkin W606 PM, Lufkin, Sparks, Maryland, USA), with 0.1 cm resolution. Triceps skinfold thickness was obtained using a Holtain Tanner/Whitehouse (Holtain, Ltd., Crosswell, United Kingdom) skinfold calliper, with 0.2 mm resolution.

Muscle strength and function

Non-dominant hand grip strength (HGS) was measured with a calibrated Jamar Plus Digital Hand Dynamometer (Sammons Preston Inc., Bolingbrook, Illinois, USA), with 0.1 kgf resolution. Individuals were asked to sit in a chair without arm rest, with their shoulders adducted, their elbows flexed 90° and their forearms in neutral position, as recommended by the American Society of Hand Therapists [18]. Each participant performed three measurements with a one minute pause between them and the higher value, recorded in kilogram-force (kgf), was used for the analysis. When the individual was unable to perform the measurement with the non-dominant hand, the dominant hand was used.

Walking time was measured over a distance of 4.6 m with a chronometer (School electronic stopwatch, Dive049, Topgim, Portugal) and walking time in seconds was recorded. Participants were asked to walk at their usual pace in an unobstructed corridor. Those unable to walk due to mobility or balance limitations were considered frail for this criterion (n=28).

Self-reported exhaustion and physical activity levels

Self-reported exhaustion was measured using two items from the Center for Epidemiologic Studies Depression Scale (CES-D) [19]. The following two statements were read: "I felt that everything I did was an effort" and "In the last week I could not get going." The exhaustion criterion was considered present if a participant answered "a moderate amount of the time" or "most of the time" to the question: "How often in the last week did you feel this way?".

Physical activity was assessed by the short form of the International Physical Activity Questionnaire [20]. Information regarding the previous seven days, namely on how many days and how much time the participant spent: walking or hiking (at home or at work, moving from place to place, for recreation or sport), sitting (at a desk, visiting friends, reading, studying or watching television), moderate activities (carrying light objects, hunting, carpentry, gardening, cycling at a normal pace or tennis in pairs) and vigorous activities, namely lifting heavy objects, agriculture, digging, aerobics, swimming, playing football and cycling at a fast pace was gathered.

A weighted estimate of total physical activity (MET-minutes per week) from all reported activities per week was obtained through the sum of the duration of the activity × frequency per week × MET intensity of each activity domain included in the questionnaire, which was then converted to kilocalories expended per week [20].

Frailty status

Frailty, according to Fried *et al.* frailty phenotype, encompasses the assessment of the five following criteria: shrinking: evaluated by self-reported unintentional weight loss (>4.5 kg lost unintentionally in prior year); weakness: evaluated as low HGS adjusted for gender and BMI [Men: ≤29 kgf (BMI ≤24 kg/m^2), ≤30 kgf (BMI 24.1–26 kg/m^2), ≤30 kgf (BMI 26.1–28 kg/m^2), ≤32 kgf (BMI >28 kg/m^2)/Women: ≤17 kgf (BMI ≤23 kg/m^2), ≤17.3 kgf (BMI 23.1–26 kg/m^2), ≤18 kgf (BMI 26.1–29 kg/m^2), ≤21 kgf (BMI >29 kg/m^2)]; poor endurance and energy: evaluated as self-reported

exhaustion; slowness: walking time measurement adjusted for gender and standing height; and low physical activity: kilocalories expended per week, adjusted for gender (men <383 kcals/week and women <270 kcals/week). If one or two of these criteria were present, the individual was characterized as pre-frail. Frailty was defined as the presence of three or more criteria [3].

Ethics

This research was conducted according to the guidelines established by the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of the department of "Ciências Sociais e Saúde" (Social Sciences and Health) from the "Faculdade de Medicina da Universidade do Porto" (PCEDCSS – FMUP 15/2015) and by the Portuguese National Commission of Data Protection (9427/2015). All study participants signed an informed consent form.

Statistical analyses

Statistical analyses were performed with IBM SPSS Statistics 23 (SPSS, Inc, an IBM Company, Chicago, IL). Descriptive analyses were conducted to show the characteristics of the study sample according to frailty status. Kolmogorov-Smirnov test was used to evaluate the normality of the distribution for quantitative variables and results were presented as median and interquartile range (IQR) for non-normal data. For categorical variables, results were expressed as number of participants (percentage). Included and excluded individuals were compared using Chi-square test or Fisher's exact test. Prevalence of each individual frailty criteria was also estimated according with frailty status.

A logistic regression was carried out and the crude and adjusted odds ratios (OR) and their respective 95% confidence intervals (CI) were calculated as measures of association in two different models, with pre-frailty and frailty as dependent variables. Gender, age, interviewer, regional area, residential status, marital status, professional status, smoking status, alcohol consumption, self-assessed health status, cognitive function, BMI classification and undernutrition status were variables included in the models. Unanswered questions or missing values for marital status (n=1), professional status (n=5), alcohol consumption (n=2), self-assessed health status (n=4) and BMI classification (n=3), were included in the reference groups. Regarding BMI classification,

underweight individuals were also included in the reference group due to its small number (n=3).

Confidence intervals were computed at 95% and statistical significance was defined by $p<0.05$.

Results

The 1457 participants evaluated were aged 65–100 years old, in which 57.0% were between 65 and 75 years, and 57.8% were women. Excluded individuals did not differ from included individuals in all the studied characteristics, except for regional area (p=0.005), BMI (p=0.033) and alcohol consumption (p=0.012), where excluded individuals were more likely to be underweight or have normal weight and not drinking alcohol (Supplementary Table 1). However, even without statistically significant differences, excluded individuals were more frequently women and also more frequently classified as cognitively impaired, as undernourished or at undernutrition risk.

The characteristics of the study sample by frailty status are presented in Table 1. Frequency of pre-frailty and frailty according to Fried's criteria was 54.3% and 21.5%, respectively. More than one third of older adults were obese, according with BMI (38.9%) and pre-frail and frail individuals were more likely to be in this category. Almost 83% of the participants had low education level (≤4 years of schooling). In addition, the majority of the individuals reported having chronic diseases (97.3%), and 31.8% considered their health status as good or very good.

Table 1. Characteristics of study participants, according to frailty status*.

	N (%)		
	Normal	**Pre-frailty**	**Frailty**
	353 (24.2)	**791 (54.3)**	**313 (21.5)**
Gender			
Women	164 (46.5)	462 (58.4)	216 (69.0)
Men	189 (53.5)	329 (41.6)	97 (31.0)
Age (years), median (IQR)	70.0 (6.0)	74.0 (10.0)	80.0 (10.0)
Age			
65-75 years	286 (81.0)	448 (56.6)	97 (31.0)
>75 years	67 (19.0)	343 (43.4)	216 (69.0)
Regional Area			
North	121 (34.3)	238 (30.1)	98 (31.3)
Centre	92 (26.1)	202 (25.5)	90 (28.8)
Lisbon	84 (23.8)	208 (26.3)	85 (27.2)
Alentejo	41 (11.6)	67 (8.5)	21 (6.7)
Algarve	6 (1.7)	38 (4.8)	14 (4.5)
Madeira	9 (2.5)	18 (2.3)	1 (0.3)
Azores	0 (0.0)	20 (2.5)	4 (1.3)
Residence			
Home	348 (98.6)	757 (95.7)	280 (89.5)
Care home	5 (1.4)	34 (4.3)	33 (10.5)
Education level			
Without education	15 (4.2)	113 (14.3)	78 (24.9)
1-4 years	232 (65.7)	555 (70.2)	213 (68.1)
5-12 years	72 (20.4)	94 (11.9)	18 (5.8)
Higher education	34 (9.6)	29 (3.7)	4 (1.3)
Marital status			
Single	23 (6.5)	57 (7.2)	30 (9.6)
Married or common-law marriage	229 (64.8)	371 (46.9)	83 (26.5)
Divorced	25 (7.1)	62 (7.8)	27 (8.6)
Widower	76 (21.5)	300 (37.9)	173 (55.3)
Professional status			
Active	15 (4.3)	13 (1.6)	2 (0.6)
Not active	337 (95.7)	776 (98.4)	309 (99.4)
Smoking status			
Non-smoker	334 (94.6)	757 (95.7)	300 (95.8)
Smoker	19 (5.4)	34 (4.3)	13 (4.2)
Alcohol consumption			
None	92 (26.1)	410 (52.0)	209 (66.8)
Moderate (W: ≤1/day; M: ≤2/day)	211 (59.8)	300 (38.0)	86 (27.5)
Excessive (W: >1/day; M: >2/day)	50 (14.2)	79 (10.0)	18 (5.8)
Cognitive function (MMSE)			
Normal	346 (98.0)	745 (94.2)	272 (86.9)
Impaired	7 (2.0)	46 (5.8)	41 (13.1)
Self-perception of health status			
Very good	34 (9.7)	24 (3.0)	9 (2.9)
Good	141 (40.1)	219 (27.8)	36 (11.5)
Fair	164 (46.6)	406 (51.5)	145 (46.5)
Poor	12 (3.4)	121 (15.3)	92 (29.5)
Very poor	1 (0.3)	19 (2.4)	30 (9.6)
Self-reported chronic diseases (number)			
None	11 (3.1)	20 (2.5)	1 (0.3)
1	38 (10.8)	65 (8.3)	17 (5.4)
≥2	303 (86.1)	700 (89.2)	294 (94.2)
Undernutrition status (MNA-SF)			
Not undernourished	334 (94.6)	683 (86.3)	210 (67.1)
Undernutrition risk	19 (5.4)	103 (13.0)	90 (28.8)
Undernutrition	0 (0.0)	5 (0.6)	13 (4.2)

IQR, Interquartile range; W, Women; M, Men; MMSE, Mini-Mental State Examination; MNA-SF, Mini-Nutritional Assessment – Short Form.
*Column percentages may not add to 100% due to rounding. Information was not obtained: Marital status n=1 (0.1%); Professional status n=5 (0.3%); Alcohol consumption n=2 (0.1%); Self-perception of health status n=4 (0.2%); Self-reported chronic diseases n=8 (0.5).

Results regarding anthropometric, functional and physical activity measures are presented in Table 2. BMI distribution by frailty status varied according to gender. Higher BMI values were observed in frail women ($p \leq 0.001$). Frail men presented and lower calf and mid-arm muscle circumferences values ($p \leq 0.001$).

Table 2. Anthropometric, functional and physical activity measures[†].

	Normal	Pre-frailty	Frailty	*p*-value
BMI (kg/m^2), median (IQR)				
Women	27.7 (5.0)	29.7 (6.7)	30.4 (7.2)	<0.001[a]
Men	27.9 (4.3)	28.5 (5.2)	28.4 (7.6)	0.387[a]
BMI classification (WHO), n (%)				
Underweight/Normal weight	73 (20.7)	114 (14.4)	53 (17.1)	<0.001[b]
Overweight	187 (53.0)	355 (44.9)	105 (33.9)	
Obesity	93 (26.3)	322 (40.7)	152 (49.0)	
MAMC (cm), median (IQR)				
Women	22.2 (3.2)	22.6 (4.0)	22.4 (3.9)	0.269[a]
Men	25.6 (3.5)	24.4 (4.0)	23.4 (3.0)	<0.001[a]
Waist circumference, n (%)				
Women: ≤ 80cm, men: ≤ 94cm	63 (17.8)	88 (11.1)	29 (9.6)	<0.001[b]
Women: 81-88cm, men: 95-102cm	105 (29.7)	157 (19.8)	42 (14.0)	
Women: > 88cm, men: > 102cm	185 (52.4)	546 (69.0)	230 (76.4)	
Calf circumference (cm), median (IQR)				
Women	35.5 (4.1)	35.5 (4.2)	35.2 (5.1)	0.847[a]
Men	37.0 (4.0)	35.8 (4.5)	35.0 (4.4)	<0.001[a]
Maximal HGS (kgf), median (IQR)				
Women	23.0 (4.9)	17.4 (5.8)	14.5 (5.6)	<0.001[a]
Men	37.8 (8.9)	27.6 (8.7)	21.4 (8.4)	<0.001[a]
Walking time (s), median (IQR)				
Women	4.2 (1.4)	5.5 (2.6)	8.9 (4.5)	<0.001[a]
Men	4.1 (1.4)	5.1 (2.3)	8.3 (5.8)	<0.001[a]
Physical activity (MET·min·wk-1), median (IQR)				
Women	2826.0 (4432.0)	1636.5 (2444.0)	146.0 (600.0)	<0.001[a]
Men	2772.0 (3235.0)	1729.5 (4013.0)	219.0 (796.0)	<0.001[a]

BMI, Body mass index; IQR, Interquartile range; WHO, World Health Organization; MAMC, Mid-arm muscle circumference; HGS, Handgrip strength; MET, Metabolic equivalent.
[†] Column percentages may not add to 100% due to rounding. Missing cases: BMI n=3 (0.2%), Waist circumference n=12 (0.8%), Walking time n=46 (3.2%).
[a] Kruskal-Wallis test.
[b] Qui-square test.

Concerning the functional measures included in frailty criteria (HGS, walking time and physical activity), lower values were observed across frailty stages for both men and women (Table 2), with men generally performing better than women for all tests (data not shown).

The results of logistic regression are displayed in Table 3. In this multivariate analysis, frailty was associated with age >75 (OR: 7.33, CI: 4.14-12.97), higher education

level (OR: 0.03, CI: 0.01-0.15), being married or in common-law marriage (OR: 0.51, CI: 0.29-0.88), being professionally inactive (OR: 6.67, CI: 1.13-39.32), poor or very poor self-perception of health status (OR: 12.56, CI: 5.18-30.47), moderate alcohol consumption (OR: 0.23, CI: 0.13-0.42), obesity (OR: 5.24, CI: 2.35-11.68) and being undernourished or at undernutrition risk (OR: 16.30, CI: 6.71-39.56). Pre-frailty was also associated with most of these variables, marital and professional status.

Table 3. Results from the bivariate and multivariate logistic regression analyses, regarding pre-frailty and frailty status.

	Pre-frailty				Frailty			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	OR (CI 95%)	*p*-value	OR (CI 95%)	*p*-value	OR (CI 95%)	*p*-value	OR (CI 95%)	*p*-value
Gender								
Women	1		1		1		1	
Men	0.62 (0.48-0.80)	<0.001	0.93 (0.68-1.28)	0.657	0.39 (0.28-0.54)	<0.001	0.64 (0.36-1.13)	0.124
Age								
65-75 years	1		1		1		1	
>75 years	3.27 (2.42-4.42)	<0.001	2.66 (1.87-3.77)	<0.001	9.51 (6.65-13.60)	<0.001	7.33 (4.14-12.97)	<0.001
Residence								
Home	1		1		1		1	
Care home	3.13 (1.21-8.06)	0.018	1.95 (0.67-5.72)	0.222	8.20 (3.16-21.29)	<0.001	3.52 (0.91-13.58)	0.068
Education level								
Without education	1		1		1		1	
1-4 years	0.32 (0.18-0.56)	<0.001	0.58 (0.32-1.07)	0.080	0.18 (0.10-0.32)	<0.001	0.31 (0.13-0.73)	0.008
5-7 years	0.17 (0.09-0.32)	<0.001	0.33 (0.17-0.66)	0.002	0.05 (0.02-0.10)	<0.001	0.09 (0.03-0.29)	<0.001
Higher education	0.11 (0.05-0.24)	<0.001	0.20 (0.09-0.46)	<0.001	0.02 (0.01-0.07)	<0.001	0.03 (0.01-0.15)	<0.001
Marital status								
Single, divorced or widower	1		1		1		1	
Married or common-law marriage	0.48 (0.37-0.62)	<0.001	0.83 (0.60-1.14)	0.239	0.20 (0.14-0.27)	<0.001	0.51 (0.29-0.88)	0.016
Professional status								
Active	1		1		1		1	
Not active	2.46 (1.20-5.03)	0.014	2.10 (0.89-4.94)	0.090	3.67 (1.21-11.09)	0.021	6.67 (1.13-39.32)	0.036
Smoking status								
Non-smoker	1		1		1		1	
Smoker	0.79 (0.44-1.40)	0.421	1.46 (0.77-2.77)	0.253	0.76 (0.37-1.57)	0.460	1.43 (0.42-4.85)	0.565
Alcohol consumption								
None	1		1		1		1	
Moderate (W: ≤1/day; M: ≤2/day)	0.32 (0.24-0.42)	<0.001	0.42 (0.30-0.59)	<0.001	0.18 (0.13-0.26)	<0.001	0.23 (0.13-0.42)	<0.001
Excessive (W: >1/day; M: >2/day)	0.35 (0.23-0.54)	<0.001	0.51 (0.31-0.83)	0.007	0.16 (0.09-0.29)	<0.001	0.14 (0.05-0.43)	0.001
Cognitive function (MMSE)								
Normal	1		1		1		1	
Impaired	3.05 (1.36-6.83)	0.007	2.08 (0.83-5.20)	0.117	7.45 (3.29-16.87)	<0.001	2.62 (0.71-9.64)	0.148
Self-perception of health status								
Very good or good	1		1		1		1	
Fair	1.78 (1.36-2.32)	<0.001	1.71 (1.26-2.32)	0.001	3.38 (2.28-5.02)	<0.001	2.20 (1.21-4.00)	0.010
Poor or very poor	7.74 (4.24-14.10)	<0.001	4.89 (2.58-9.27)	<0.001	35.91 (18.60-69.30)	<0.001	12.56 (5.18-30.47)	<0.001
BMI classification (WHO)								
Underweight/ Normal weight	1		1		1		1	
Overweight	1.22 (0.86-1.71)	0.265	1.64 (1.10-2.45)	0.016	0.73 (0.48-1.12)	0.148	1.38 (0.66-2.92)	0.394
Obesity	2.22 (1.53-3.22)	<0.001	2.70 (1.75-4.15)	<0.001	2.13 (1.38-3.29)	0.001	5.24 (2.35-11.68)	<0.001
Undernutrition status (MNA-SF)								
Not undernourished	1		1		1		1	
Undernutrition or undernutrition risk	2.78 (1.68-4.61)	<0.001	2.69 (1.53-4.75)	0.001	8.62 (5.13-14.49)	<0.001	16.30 (6.71-39.56)	<0.001

OR, Odds ratio; CI, Confidence interval; W, Women; M, Men; MMSE, Mini-Mental State Examination; BMI, Body mass index; WHO, World Health Organization; MNA-SF, Mini-Nutritional Assessment – Short Form.

Figure 1 shows the distribution of the five criteria: weakness assessed by HGS, exhaustion, walking time, physical activity and unintentional weight loss, according to frailty status. Weakness was by far the most prevalent criterion in the total number of older adults with pre-frailty or frailty (76.7%), followed by exhaustion (48.6%). Unintentional weight loss was only reported in 10.3% of the participants with these conditions.

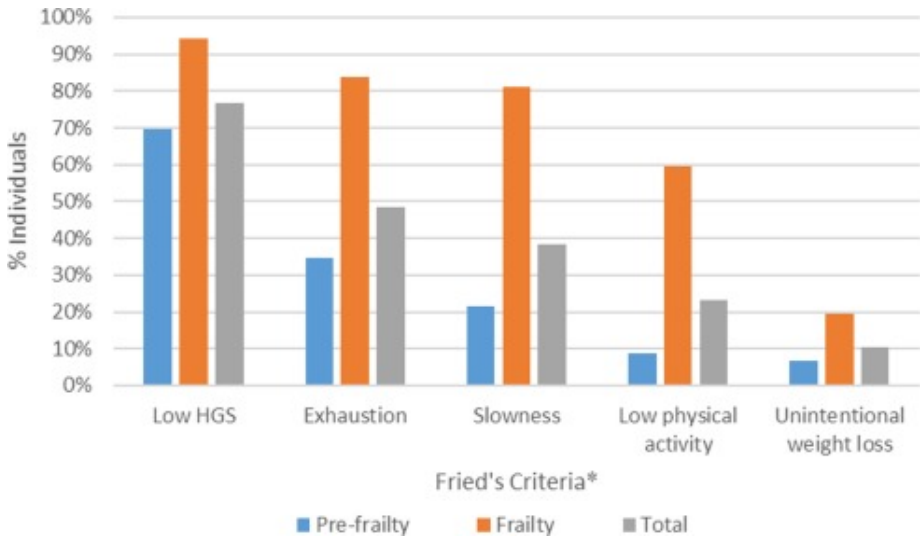

Figure 1. Distribution of the five frailty criteria among pre-frail and frail older adults.

HGS, Handgrip strength. * Cut-off points: HGS – Men: ≤29 kgf (BMI ≤24 kg/m^2), ≤30 kgf (BMI 24.1–26 kg/m^2), ≤30 kgf (BMI 26.1–28 kg/m^2), ≤32 kgf (BMI >28 kg/m^2) / Women: ≤17 kgf (BMI ≤23 kg/m^2), ≤17.3 kgf (BMI 23.1–26 kg/m^2), ≤18 kgf (BMI 26.1–29 kg/m^2), ≤21 kgf (BMI >29 kg/m^2); Exhaustion – Modified 10-item CES-D ("I felt that everything I did was an effort'' ≥3 days in the past week or "I could not get 'going'" ≥3 days in the past week); Slowness: Men: ≥7 seconds (height ≤173 cm), ≥6 seconds (heigh >173 cm) / Women: ≥7 seconds (height ≤159 cm), ≥6 seconds (height >159 cm); Low physical activity – Men <383 kcals/week / Women <270 kcals/week; Unintentional weight loss: >4.5 kg lost unintentionally in prior year.

Discussion

According with Fried's frailty scale, pre-frailty and frailty are very frequent in Portuguese older adults. Almost three quarters of the individuals presented at least one frailty criterion, and older individuals were more likely to be affected. Moreover, these individuals showed more frequently low HGS, over other criteria. Several factors, such as being professionally inactive, having poor or very poor self-assessed health status, obesity and being undernourished or at undernutrition risk were associated with worse frailty status.

The frequency of pre-frailty (54.3%) and frailty 21.5%) was higher compared with the original report in the Cardiovascular Health Study (6.9%) [(3)]. In Europe, the frequency

of frailty and of pre-frailty was evaluated in ten different countries and it was found that southern European countries presented a higher frequency of frailty and pre-frailty, indicating the possibility of an existing north-south gradient [21]. Although Portugal was not included in this study, based in the cultural similarities, a comparable frequency of frailty and pre-frailty to that observed in other southern European countries was expected. When our results were compared with those from these countries, frailty frequency (21.5%) was lower than in Spain (27.3%) and in Italy (23%) but higher than in Greece (14.7%) [21]. However, pre-frailty frequency was higher (54.3%) compared to the previously reported in Spain (50.3%), Italy (45.6%) and Greece (44.9%) [21]. Similarly, results from FRADEA study (Spain) have shown a high frequency of pre-frailty (48.5%) and frailty (21.3%), but they also included a larger number of institutionalized older adults (21.3% versus 4.9% in our sample) [22], which has been associated with worsen frailty status [23,24]. On the other hand, data from the InCHIANTI study, in Italy, reported much lower values 37.8% and 6.5% for pre-frailty and frailty, respectively [25]. Analogous results were observed in Toledo study for healthy ageing [26] and FRALLE survey [27], in Spain, in which frailty prevalence was 8.4% in the first, and 9.6% in the second. Pre-frailty values were slightly higher for the two latest studies (41.8% and 47%) [26,27].

Even though Fried's frailty definition was used in the aforementioned studies, variations in the results may be the result of the differences within the frailty criteria used. Namely in the SHARE study, which reported higher frequencies when compared with other studies conducted in the same areas. In these, operationalization of the criteria was different from the Cardiovascular Health Study, except for weakness, which can explain the contradictory results across studies. Nevertheless, the present study reveals much higher frequencies of pre-frailty and frailty even when compared with results from studies with fewer differences in the used criteria [3,25,26].

Due to the higher frequency of this syndrome among Portuguese older adults, the prevalence of each frailty criterion is expected to be much higher, than the previously found in other studies. In the present study, a higher prevalence of weakness among pre-frail and frail older adults was observed and exhaustion was the second most prevalent criterion. In contrast, other studies reported larger prevalence of exhaustion over weakness with similar patterns in the three less prevalent criteria presented [21,28]. In the Cardiovascular Health Study, low activity was the most prevalent criterion, followed by slowness and weakness in second. Weight loss was the less frequent criterion, as observed in the present study [3]. Nevertheless, in the InCHIANTI study, different patterns

were observed in the first three more prevalent criteria, slowness was the first, weakness the second, and exhaustion the third [25]. Results concerning the onset of frailty showed that weakness was the most common first manifestation, despite the significant heterogeneity in the initial manifestations of frailty, with early development of weight loss or exhaustion predicting more rapid onset of the frailty syndrome [29]. While the cross-sectional nature of present study does not allow us to establish temporal inferences, weakness was still the most prevalent criterion in the pre-frail participants.

This study extends the findings of others, showing that frailty prevalence increased with age, which may be associated to the physiologic changes inherently associated with the ageing process. Nevertheless, the expected positive association between female gender and frailty status was not observed, even though women were in a higher number in the present study [8]. Additionally, a moderate and an excessive alcohol consumption was inversely associated with frailty status. Comparable results were reported by a systematic review aimed to study the relationship between alcohol consumption and frailty risk [30]. However, the possibility of reverse causality has been pointed out, in which the reduction in alcohol consumption starts when individuals become more frail [30].

Present results show that a lower educational level was also associated with higher frequency of pre-frailty and frailty. One possible explanation to this association may be the fact that individuals with more education have more access to information and better healthy behavior awareness, and also a higher socioeconomic status. Considering Portugal background, these were the individuals with a privileged access to education. Although in the Cardiovascular Health study, differences regarding education level were not found [31], similar results reported by several other studies are in line with our findings [32-34]. Plus, in the Longitudinal Aging Study Amsterdam (LASA), it was observed that low education level was associated with frailty, but although the prevalence of frailty increased over time, the rate of increase did not vary across education levels [32].

In the NHANES study, frailty prevalence was highest among obese followed by overweight participants [35]. Even though, present data showed that overweight status was only associated with pre-frailty, whereas obesity was positively associated with both pre-frailty and frailty. These results are in line with data from Women Health and Aging study [36]. For each BMI category, a similar pattern to the one described for all categories concerning the prevalence of frailty criteria was observed [36]. In this sample, overweight and obese people have lower physical activity levels and higher levels of exhaustion,

which can explain this association as physical activity and exhaustion are both criteria used to determine frailty status. Additionally, professionally inactive people were also more physical inactive (data not shown).

The results regarding the association of pre-frailty and frailty with undernutrition status demonstrated that frail older adults are also more likely to be undernourished or at undernutrition risk. Indeed, the close association between these syndromes was previously highlighted [37]. It is worth noting that questions about weight loss and mobility are included in the MNA-SF and are similar to some frailty criteria.

This study has some strengths. It used data from a nationwide sample of the Portuguese older adult population. Although forty-three individuals were excluded, when included and excluded individuals were compared, differences between them were only observed regarding the regional area, BMI and alcohol consumption. Even though, the possibility that the lack of statistical significance is related with the low number of excluded individuals and a consequence of type II error cannot be ruled out.

The cross-sectional design of this study is a limitation, as we are unable to determine the direction of the associations established. Fried's criteria to evaluate frailty status was adopted, however the International Physical Activity Questionnaire was chosen instead of the Minnesota Leisure Time Activities Questionnaire. The latter was used in the proposed definition to assess physical activity levels, which can lead to variations in the results. However, studies about this matter are still lacking.

Conclusion

This condition is very prevalent in Portuguese older adults, one fifth are frail whereas half are pre-frail. Nevertheless, comparison with other studies is hampered by the differences between them. Age >75, being professionally inactive, poor self-perception of health status, being obese and undernourished or at undernutrition risk increased frailty risk, whereas a higher education level, being married or living together and alcohol consumption were associated with a decreased frailty risk. Pre-frail and frail Portuguese older adults manifest low HGS as the most prevalent criterion, over other frailty criteria.

Supplemental material

Supplemental material for this article can be found online:

https://ars.els-cdn.com/content/image/1-s2.0-S0167494317300389-mmc1.docx

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Chapter 3

The link between sarcopenia, frailty and conditions related to nutritional status

3.1.

Sousa-Santos AR, Afonso C, Santos A, Borges N, Moreira P, Padrão P, Fonseca I, Amaral TF. **The association between 25(OH)D levels, frailty status and obesity indices in older adults.** PLoS One. 2018 Aug 28;13(8):e0198650. doi: 10.1371/journal.pone.0198650.

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3.1.

The association between 25(OH)D levels, frailty status and obesity indices in older adults.

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Abstract

Background: Vitamin D deficiency is common in older adults and has been linked with frailty and obesity, but it remains to be studied whether frail obese older adults are at higher risk of vitamin D deficiency. Therefore, the aim of this study is to explore the association between frailty, obesity indices and serum 25(OH)D concentrations.

Methods: 1447 individuals with 65 years or older, participating in a cross-sectional study (Nutrition UP 65) were included. Frailty, according to Fried *et al*., body mass index (BMI), waist circumference (WC), body roundness index (BRI) and body shape index (ABSI) were evaluated. A stepwise multinomial logistic regression was carried out to quantify the association between 25(OH)D quartiles and independent variables.

Results: Median 25(OH)D levels were lower in individuals presenting both frailty and obesity (p<0.001). In the multivariate analysis, pre-frailty (OR: 2.65; 95% CI: 1.63-4.33) and frailty (OR: 3.77; 95% CI: 2.08-6.83) were associated with increased odds of lower 25(OH)D serum levels (first quartile). Regarding obesity indices, the highest categories of BMI (OR: 1.74; 95% CI: 1.06-2.86), WC (OR: 3.46; 95% CI: 1.95-6.15), BRI (OR: 4.35; 95% CI: 2.60-7.29) and ABSI (OR: 3.17 95% CI: 1.86-5.38) were directly associated with lower 25(OH)D serum levels (first quartile).

Conclusions: A positive association between frailty or obesity and lower vitamin D levels was found. Moreover, besides BMI and WC, other indicators of body adiposity, such as BRI and ABSI, were associated with lower 25(OH)D serum concentrations.

Keywords: frailty, vitamin D, obesity, waist circumference.

Introduction

Vitamin D is fat-soluble vitamin mainly obtained from sun exposure of the skin and in lesser amounts from diet and supplements [1-3]. It is stored mainly in adipose tissue and muscle and, to a lesser extent, in other tissues [4]. Vitamin D deficiency is a public health problem of growing concern [5-7], common in older adults [5,7,8] and it has been linked to adverse health outcomes such as falls [9], poorer cognitive function [10] and cancer [11]. 25(OH)D concentrations decrease with age, due to a reduction in cutaneous vitamin D synthesis [12], and to the possible decline in the ability of the kidney to synthesize $1,25(OH)_2D$ [4].

Despite the well-known consequences of vitamin D deficiency in bone health [13], this hormone seems to also have a key-role in skeletal muscle [14], namely influencing its function and performance [14,15]. Frailty increases with age and its prevalence in the community ranges from 4.0-59.1%, depending on the definition adopted [16]. It is associated with an increased risk of adverse health outcomes, such as falls, disability, hospitalization and even mortality [17]. Evidence has shown a link between frailty and vitamin D status, with frailty being associated with lower levels of serum 25(OH)D [18]. However, the impact of vitamin D deficiency in frailty status in later life is still unknown.

Obesity has also increased appreciably worldwide and older adults are no exception [19]. Several meta-analyses reported a significant association with lower serum 25(OH)D concentrations [20-22], although the mechanisms underlying this association are not yet fully understood. Furthermore, obesity has also been positively associated with frailty status in older adults [23,24], but it remains to be studied whether frail obese older adults are at higher risk of vitamin D deficiency and if the presence of these conditions could simultaneously lead to worse health outcomes. According to the previously described in literature, obese older adults may be predisposed to vitamin D deficiency, which is in turn associated with worse physical function and frailty [18,25]. Conversely, frailty may impact the amount of sun exposure and, consequently, predispose to vitamin D deficiency. Even though several studies have evaluated the association of frailty status and obesity on vitamin D levels separately [18,20,21], to our knowledge, literature regarding the study of all three conditions is absent. It will be relevant to know if frail obese older adults are more likely to present low vitamin D levels. Besides body mass index (BMI), other obesity indicators such as waist circumference (WC), body roundness index (BRI) and body shape index (ABSI) may be used [26,27]. While previous studies have established

a link between several indices and vitamin D status, such as BMI and WC [28,29], data regarding BRI and ABSI is lacking. Thus, we hypothesized that these indices may be associated with vitamin D levels, as higher values may denote worse vitamin D status.

Frailty, obesity and vitamin D deficiency are potentially preventable or treatable. Early interventions in these conditions may lead to an improvement in health status and quality of life during the course of aging [30]. So, it is important to elucidate the association between these conditions to target the individuals at risk. Therefore, the aim of this study is to evaluate the association between serum 25(OH)D concentrations, frailty and obesity, but also to examine if there is an interaction effect between frailty and obesity on 25(OH)D levels. In addition, the association of other obesity indicators, such as WC, BRI and ABSI, with vitamin D status will also be explored.

Materials and methods

The study sample included individuals enrolled in the Nutrition UP 65 study, a cross-sectional observational study conducted in Portugal. As described in detail previously [31], a cluster sample of 1500 individuals with 65 years or older, representative of the Portuguese older population in terms of age, sex, education and regional area was selected. In each regional area, three or more town councils with >250 inhabitants were randomly selected, and potential community-dwelling participants were contacted via home approach, telephone or via institutions such as town councils and parish centres. Individuals presenting any condition that precluded the collection of venous blood samples or urine (*eg*, dementia or urinary incontinence) were not included.

Data were gathered between December 2015 and June 2016. A structured questionnaire was applied by interview, conducted by eight trained registered nutritionists and anthropometric data were also collected. From the initial sample, forty-six individuals could not be assessed regarding frailty status (n=43) and body mass index (n=4) due to missing data and were therefore excluded from the present analysis. Additionally, seven older adults were also excluded due to missing data regarding the covariates.

Anthropometric and functional measurements

Anthropometric measurements were collected following standard procedures [32]. A calibrated stadiometer (SECA 213, SECA GmbH, Hamburg, Germany) with 0.1 cm resolution was used to measure standing height. Body weight (in kilograms) was

measured with a calibrated portable electronic scale (SECA 803, SECA GmbH, Hamburg, Germany) with 0.1 kg resolution, with the participants wearing light clothes. When it was not possible to measure standing height or weigh a participant, height was obtained indirectly from non-dominant hand length [32], measured with a calibrated caliper (Fervi Equipment) with 0.1 centimeter resolution and body weight was estimated from mid-upper arm and calf circumferences [33]. Mid-upper arm, waist and calf circumferences were measured with a metal tape (Lufkin W606 PM, Lufkin®, Sparks, Maryland, USA), with 0.1 cm resolution. Triceps skinfold thickness was obtained using a Holtain Tanner/Whitehouse (Holtain, Ltd., Crosswell, United Kingdom) skinfold caliper, with 0.2 mm resolution.

Hand grip strength (HGS) was measured in the non-dominant hand with a calibrated Jamar Plus Digital Hand Dynamometer (Sammons Preston Inc., Bolingbrook, Illinois, USA). As recommended by the American Society of Hand Therapists, participants were asked to sit in a chair without arm rest, with their shoulders adducted, their elbows flexed 90° and their forearms in neutral position [34]. Three measurements with a one-minute pause between them were performed by each individual and the higher value, recorded in kilogram-force (kgf), was used for the analysis. Individuals unable to perform the measurement with the non-dominant hand were asked to use the dominant hand.

Walking time was measured over a distance of 4.6 meters, in an unobstructed corridor. Individuals were instructed to walk at usual pace and walking time was recorded by a chronometer (School electronic stopwatch, Dive049, Topgim, Portugal), in seconds. Those unable to perform the test due to mobility or balance limitations were considered frail for this criterion (n=28).

Self-reported exhaustion was measured using two items from the Center for Epidemiologic Studies Depression Scale (CES-D) [35]. The following two statements were read: “I felt that everything I did was an effort” and “In the last week I could not get going.” The exhaustion criterion was considered present if a participant answered “a moderate amount of the time” or “most of the time” to the question: “How often in the last week did you feel this way?”.

Physical activity, assessed by the short form of the International Physical Activity Questionnaire [36], included information regarding the previous seven days, namely on how many days and how much time the participant spent: walking or hiking (at home or

at work, moving from place to place, for recreation or sport), sitting (at a desk, visiting friends, reading, studying or watching television), moderate activities (carrying light objects, hunting, carpentry, gardening, cycling at a normal pace or tennis in pairs) and vigorous activities, namely lifting heavy objects, agriculture, digging, aerobics, swimming, playing football and cycling at a fast pace was gathered.

Frailty status

Frailty was defined according to Fried *et al*. frailty phenotype [17]. Pre-frailty was classified as the presence of one or two, and frailty as the presence of three or more of the following five criteria: "shrinking": evaluated by self-reported unintentional weight loss (>4.5 kg lost unintentionally in prior year); "weakness": assessed by low HGS adjusted for sex and BMI; "poor endurance and energy": evaluated by self-reported exhaustion; "slowness": identified by walking time adjusted for sex and standing height and "low physical activity": by means of energy expended per week, adjusted for sex (men <383 kcal/week and women <270 kcal/week).

Laboratory analyses

Qualified nurses collected blood samples for these analyses, preferentially after a 12-hour fasting period. Vitamin D status was evaluated by dosing the plasmatic levels of 25-hydroxycholecalciferol through electrochemiluminescence immunoassay, using Roche Cobas Vitamin D total assay reagent (Roche Diagnostics GmbH, Mannheim, Germany). All samples were analyzed with the same equipment. Since 25(OH)D serum concentrations were very low in our sample, 25(OH)D concentrations were categorized into quartiles (Q). For characterization purposes individuals were still classified according to the Institute of Medicine (IOM) criteria as being at risk of deficiency at serum 25(OH)D concentrations <12 ng/mL, at risk for inadequacy at levels ranging from 12–<20 ng/mL and having sufficient levels when 25(OH)D concentrations are ≥20 ng/mL [37]. Data concerning 25(OH)D levels in Nutrition UP 65 study were previously described [8,38].

Obesity indices

BMI was calculated as (weight (kg)/ height^2 (m)), and subjects were classified as underweight for BMI below 20.0 kg/m^2, for individuals younger than 70 years of age, and

below 22.0 kg/m^2 for individuals with 70 years and older, as normal weight for BMI between 20.0 or 22.0-24.9 kg/m^2, as pre-obese for BMI between 25.0-29.9 kg/m^2 and as obese for BMI of 30.0 kg/m^2 or above [39,40]. Underweight individuals were included in the reference group ("normal weight") for the multinomial logistic regression analyses. WC was categorized according to the risk of metabolic complications as increased (men >94 cm; women >80 cm) and substantially increased (men >102 cm; women >88 cm) [41]. BRI was calculated based on WC (m) and height (m) [27]:

$$BRI = 364.2 - 3655.5 \times \sqrt{1 - \left(\frac{(WC)/(2\pi)^2}{(0.5 \times height)^2}\right)}$$

ABSI (m$^{11/6}$·kg$^{-2/3}$) was calculated according to the following formula, based on WC (m), BMI (kg/m^2) and height (m) [26]:

$$ABSI = \frac{WC}{BMI^{2/3} \times height^{1/2}}$$

Quartiles of BRI and ABSI were calculated.

Variables collection and categorization

Information regarding educational level, smoking status, alcohol consumption and vitamin D supplementation was self-reported. Educational level was determined by the number of completed school years and the following categories were used: without schooling, 1–4 years, 5-12 years and >12 years. All individuals reported information on smoking status and this information was included as a dichotomous variable: smoker or non-smoker. Alcohol consumption was evaluated as the number of alcoholic drinks daily and was included in the analyses as a categorical variable: none, moderate consumption (women ≤1 and men ≤2 alcoholic drinks daily), and excessive consumption (women >1 and men >2 alcoholic drinks daily). The Portuguese version of the Mini-Mental State Examination was used to ascertain cognitive decline, which was dichotomized into not impaired and impaired. Cut-off scores for cognitive impairment were the following: individuals with no education, ≤15 points; 1 to 11 years of years of school completed, ≤22 points; and >11 years of school completed, ≤27 points [42]. Season of blood collection was presented as a dichotomous variable: spring/summer or autumn/winter. Skin phenotype was defined according to the Fitzpatrick classification [43], and categorized as follows: red-haired with freckles or fair-haired people; dark-haired or Latin people; and

Arab, Asian or Black people. Vitamin D supplements use was categorized as: no use, use of vitamin D supplements, unknown composition or use.

Ethics

This research was conducted according to the guidelines established by the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of the Department of "Ciências Sociais e Saúde" (Social Sciences and Health) from the "Faculdade de Medicina da Universidade do Porto" (PCEDCSS – FMUP 15/2015) and by the Portuguese National Commission of Data Protection (9427/2015). All study participants signed an informed consent form.

Statistical analyses

Descriptive analyses were conducted to compare participants' characteristics across 25(OH)D quartiles. Results were presented as number of participants (percentage), for categorical variables. For continuous variables, means (standard deviations) were used, or medians (interquartile range) to report variables with skewed distribution. ANOVA or Kruskal-Wallis were used to compare continuous variables between the study groups. Multiple comparisons between frailty and obesity groups were performed using Dunn-Bonferroni tests. Differences in proportions, as well comparison between included and excluded individuals, in the sensitivity analysis, were tested using Chi-square test or Fisher's exact test.

A multinomial logistic regression was carried out to quantify the association between 25(OH)D quartiles (dependent variable) and independent variables. Odds ratios (OR) and their respective 95% confidence intervals (CI) were calculated, with adjustments for sex, age, educational level, smoking status, alcohol consumption, cognitive function, season of blood collection, vitamin D supplementation and skin phenotype. A stepwise approach with forward entry was carried out to explore the following interactions terms in each model: frailty status*BMI, frailty status*WC, frailty status*BRI and frailty status*ABSI.

Statistical significance was established at a p-value <0.05. All statistical analyses were conducted with IBM SPSS Statistics 23 (SPSS, Inc, an IBM Company, Chicago, IL).

Results

Descriptive data of the 1447 older adults (57.8% women) included in this study and statistical differences in sociodemographic lifestyle and health conditions according to 25(OH)D quartiles are shown in Table 1. Median age of the individuals was 74 years (range 65-100). Based on Fried's frailty definition, 21.4% were frail and 39.1% were obese according to BMI. Overall, the majority of the older adults were non-smokers, however slightly more than half (51.3%) reported consuming alcoholic drinks daily.

Table 1. Characteristics of the 1447 included older adults by 25(OH)D quartiles.

	25(OH)D, N (%)				
	Q1 (3.0-8.7 ng/mL) 360 (24.9)	**Q2 (8.8-14.3 ng/mL) 364 (25.2)**	**Q3 (14.4-22.9 ng/mL) 361 (24.9)**	**Q4 (23.0-178.1 ng/mL) 362 (25.0)**	***p*-value**
Sex					
Women	246 (68.3)	221 (60.7)	186 (51.5)	184 (50.8)	<0.001[a]
Men	114 (31.7)	143 (39.3)	175 (48.5)	178 (49.2)	
Age (years)					
65-75	127 (35.3)	214 (58.8)	238 (65.9)	247 (68.2)	<0.001[a]
>75	233 (64.7)	150 (41.2)	123 (34.1)	115 (31.8)	
Education level					
Without schooling	84 (23.3)	70 (19.2)	25 (6.9)	26 (7.2)	<0.001[a]
1-4 years	242 (67.2)	243 (66.8)	262 (72.6)	245 (67.7)	
5-12 years	24 (6.7)	39 (10.7)	56 (15.5)	64 (17.7)	
>12 years	10 (2.8)	12 (3.3)	18 (5.0)	27 (7.5)	
Smoking status					
Non-smoker	345 (95.8)	346 (95.1)	343 (95.0)	347 (95.9)	0.909[a]
Smoker	15 (4.2)	18 (4.9)	18 (5.0)	15 (4.1)	
Alcohol consumption					
None	222 (61.7)	194 (53.3)	160 (44.3)	129 (35.6)	<0.001[a]
Moderate (W: ≤1/day; M: ≤2/day)	117 (32.5)	136 (37.4)	156 (43.2)	188 (51.9)	
Excessive (W: >1/day; M: >2/day)	21 (5.8)	34 (9.3)	45 (12.5)	45 (12.4)	
Cognitive function (MMSE)					
Not impaired	324 (90.0)	345 (94.8)	334 (92.5)	352 (97.2)	0.001[a]
Impaired	36 (10.0)	19 (5.2)	27 (7.5)	10 (2.8)	
Frailty status					
Normal	30 (8.3)	84 (23.1)	111 (30.7)	127 (35.1)	<0.001[a]
Pre-frailty	195 (54.2)	198 (54.4)	205 (56.8)	187 (51.7)	
Frailty	135 (37.5)	82 (22.5)	45 (12.5)	48 (13.3)	
BMI categories					
Underweight	14 (3.9)	8 (2.2)	6 (1.7)	21 (5.8)	<0.001[a]
Normal weight	41 (11.4)	37 (10.2)	60 (16.6)	52 (14.4)	
Pre-obesity	142 (39.4)	157 (43.1)	167 (46.3)	176 (48.6)	
Obesity	163 (45.3)	162 (44.5)	128 (35.5)	113 (31.2)	
WC (cm), median (IQR)[†]	102.0 (17.1)	101.2 (14.4)	98.0 (14.5)	96.6 (16.3)	<0.001[b]
WC[†]					
W: ≤80 cm; M: ≤94 cm	27 (7.6)	34 (9.4)	51 (14.2)	67 (18.6)	<0.001[a]
W: 81-88 cm; M: 95-102 cm	49 (13.7)	61 (16.9)	89 (24.8)	103 (28.6)	
W: >88 cm; M: >102 cm	281 (78.7)	266 (73.7)	219 (61.0)	190 (52.8)	
BRI, median (IQR)[†]	7.1 (2.6)	6.4 (2.3)	5.8 (2.1)	5.6 (2.3)	<0.001[b]
ABSI ($m^{11/6}\cdot kg^{-2/3}$), mean (SD)[†]	0.086 (0.005)	0.084 (0.005)	0.083 (0.005)	0.083 (0.006)	<0.001[c]
25(OH)D (ng/mL), median (IQR)	5.6 (3.0)	11.5 (2.9)	17.9 (3.6)	29.2 (8.7)	<0.001[b]
Skin phenotype					
Red-haired with freckles or fair-haired people	61 (16.9)	85 (23.4)	91 (25.2)	65 (18.0)	0.014[a]
Dark-haired or Latin people	277 (76.9)	257 (70.6)	251 (69.5)	286 (79.0)	
Arab, Asian or Black people	22 (6.1)	22 (6.0)	19 (5.3)	11 (3.0)	
Season of blood collection					
Spring/Summer	91 (25.3)	167 (45.9)	208 (57.6)	236 (65.2)	<0.001[a]
Autumn/Winter	269 (74.7)	197 (54.1)	153 (42.4)	126 (34.8)	
Vitamin D supplementation					
No use	290 (80.6)	315 (86.5)	319 (88.4)	294 (81.2)	<0.001[a]
Use of vitamin D supplements	5 (1.4)	10 (2.7)	15 (4.2)	47 (13.0)	
Unknown use or composition	65 (18.1)	39 (10.7)	27 (7.5)	21 (5.8)	

W, Women; M, Men; MMSE, Mini-Mental State Examination; BMI, Body mass index; WC, Waist circumference; BRI, Body roundness index; ABSI, Body shape index; SD, Standard Deviation; IQR, Interquartile range. Column percentages may not add to 100% due to rounding.
[†]Missing data in 10 individuals (0.7%)
[a] Chi-square test.
[b] Kruskal-Wallis test.
[c] ANOVA test.

Regarding vitamin D serum levels, 69% of participants had 25(OH)D <20 ng/mL, and 39.7% had 25(OH)D <12 ng/mL. Additionally, only 5.3% reported the use of vitamin D supplements. Median 25(OH)D levels of Q1 were 5.6 ng/mL (interquartile range (IQR): 3.0 ng/mL), for Q2 were 11.5 ng/mL (IQR: 2.9 ng/mL), for Q3 were 17.9 ng/mL (IQR: 3.6 ng/mL) and, lastly, for Q4 were 29.2 (IQR: 8.7 ng/mL). When studying participants' characteristics according to 25(OH)D quartiles, significant differences were observed for all studied variables, except for smoking status. As expected, individuals that reported the use of vitamin D supplements were more likely to present higher 25(OH)D serum values and to fit in the fourth quartile (p<0.001). Moreover, a higher proportion of frail (p<0.001), obese (p<0.001) and cognitive impaired (p=0.001) older adults was observed in the first quartile of 25(OH)D levels. Median values of WC and BRI, and mean values of ABSI decreased across 25(OH)D quartiles (p<0.001).

Sensitivity analysis comparing excluded and included older adults in the present study, showed that those who were excluded reported a lower alcohol consumption (p=0.001), were more likely to be cognitively impaired (p=0.049) and to have a darker skin phenotype (p=0.002) (S1 Table).

Regarding coexistence of frailty and obesity (S2 Table), approximately 75% of older adults presenting both frailty and obesity were women and nearly 67% were aged over 75 years. More than 60% of the participants with at least one condition (either frailty or obesity or both) were women (p<0.001). Individuals presenting only obesity were more likely to be younger (65.0%) and 70.9% of the older adults presenting only frailty were in the oldest age category (p<0.001). Median 25(OH)D values decreased across obesity and frailty status and were 17.1 ng/mL for non-obese non-frail individuals, 13.7 ng/mL for obese non-frail individuals, 10.1 ng/mL for non-obese frail individuals and 9.2 ng/mL in individuals presenting both obesity and frailty (p<0.001) (S2 Table).

To evaluate the association between BMI, WC, BRI and ABSI, Spearman correlation coefficients were also calculated. BMI was positively and significantly correlated with WC (ρ=0.748), BRI (ρ=0.824) and negatively correlated with ABSI (ρ= -0.121). However, ABSI correlated positively and significantly with WC (ρ=0.476) and BRI (ρ=0.358) (S3 Table).

Comparisons of median 25(OH)D serum levels between obesity and frailty status groups, are displayed in Figure 1. Median 25(OH)D levels in all groups were below 20 ng/ml. In women, median 25(OH)D levels were significantly higher in non-obese non-frail group, comparing with obese non-frail group [15.7 (IQR: 16.5) vs 12.4 (IQR:

10.2)], *p*=0.007; non-obese frail group [15.7 (IQR: 16.5) vs 10.2 (IQR: 11.9)], *p*<0.001 and obese frail group [15.7 (IQR: 16.5) vs 9.0 (IQR: 11.0)], *p*<0.001. Also, obese non-frail women had significantly higher median 25(OH)D levels comparing with the obese frail group [12.4 (IQR: 10.2) vs 9.0 (IQR: 11.0)], *p*=0.006. Among men, median 25(OH)D levels were only significantly higher in non-obese non-frail group, comparing with non-obese frail [17.7 (IQR: 14.0) vs 9.5 (IQR: 9.2)] and obese frail group [17.7 (IQR: 14.0) vs 10.1 (IQR: 10.8)], *p*<0.001. However, the obese non-frail group also presented significantly higher median 25(OH)D levels than non-obese frail [18.4 (IQR: 14.9) vs 9.5 (IQR: 9.2)] and obese frail groups [18.4 (IQR: 14.9) vs 10.1 (IQR: 10.8)], *p*<0.001 and *p*=0.001, respectively.

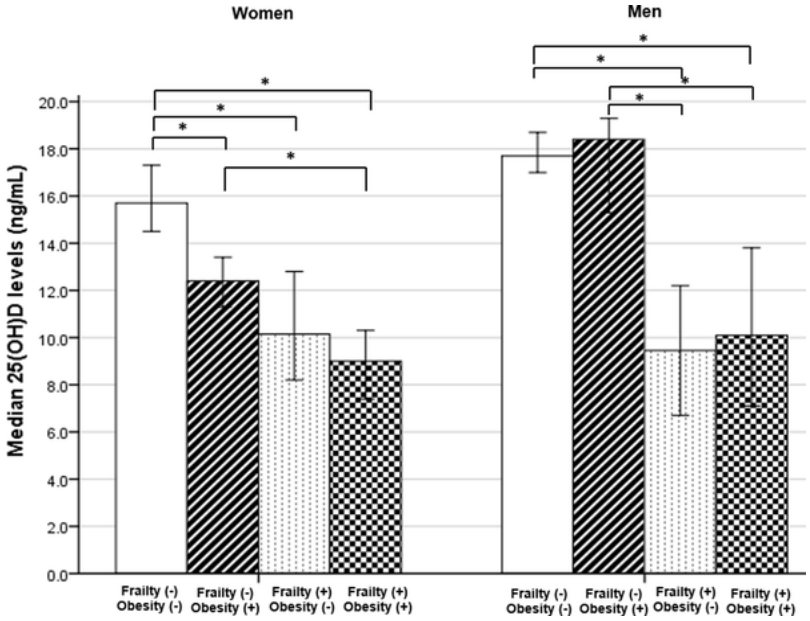

Figure 1. Differences in median (95% CI) 25(OH)D serum levels between Obesity(-) Frailty(-) (W: n=359; M: n=364), Obesity(+) Frailty(-) (W: n=263; M: n=151), Obesity(-) Frailty(+) (W: n=102; M: n=56) and Obesity(+) Frailty(+) (W: n=113; M: n=39) groups, in older women (W) and men (M), using Kruskal-Wallis with Dunn-Bonferroni tests for multiple comparisons. *p<0.05 for pairwise comparisons.

The association between obesity and frailty status and 25(OH)D quartiles was further investigated through multivariate multinomial regression (Table 2). Considering the fourth quartile of serum 25(OH)D as the reference category, pre-frail older adults were 2.65 (95% CI: 1.63-4.33) times more likely to be in the first quartile of serum 25(OH)D (3.0-8.7 ng/mL), and frail individuals were 3.77 (95% CI: 2.08-6.83) times more likely to present serum 25(OH)D levels in the first quartile (*P* for trend <0.001). For individuals in the two lowest quartiles of serum 25(OH)D levels (Q1: 3.0-8.7 ng/mL and Q2: 8.8-14.3 ng/mL), the adjusted odds ratios for obesity were 1.74 (95% CI: 1.06-2.86) for the first (*P* for trend =0.018) and 2.19 (95% CI: 1.36-3.52) for the second (*P* for trend

=0.001) quartiles. The association between pre-obesity and serum 25(OH)D levels did not reach statistical significance in any quartile.

Table 2. Multinomial logistic regression regarding frailty status and body mass index with 25(OH)D quartiles. Reference category was the fourth quartile of serum 25(OH)D (23.0-178.1 ng/mL)†.

	25(OH)D					
	Q1 (3.0-8.7 ng/mL)		Q2 (8.8-14.3 ng/mL)		Q3 (14.4-22.9 ng/mL)	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Frailty status						
Normal	1.00	1.00	1.00	1.00	1.00	1.00
Pre-frailty	**4.41 (2.83-6.89)***	**2.65 (1.63-4.33)***	**1.60 (1.14-2.25)**	1.18 (0.81-1.72)	1.25 (0.91-1.73)	1.12 (0.79-1.60)
Frailty	**11.91 (7.10-19.96)***	**3.77 (2.08-6.83)***	**2.58 (1.65-4.05)***	1.30 (0.77-2.19)	1.07 (0.66-1.73)	0.76 (0.45-1.31)
P for trend	<0.001	<0.001	<0.001	0.235	0.612	0.405
BMI categories						
Underweight/Normal weight	1.00	1.00	1.00	1.00	1.00	1.00
Pre-obesity	1.07 (0.71-1.62)	1.28 (0.80-2.07)	1.45 (0.94-2.22)	1.58 (0.99-2.48)	1.05 (0.71-1.56)	1.11 (0.74-1.68)
Obesity	**1.92 (1.25-2.93)**	**1.74 (1.06-2.86)**	**2.33 (1.49-3.62)***	**2.19 (1.36-3.52)**	1.25 (0.83-1.90)	1.28 (0.83-1.99)
P for trend	<0.001	0.018	<0.001	0.001	0.200	0.228
Sex						
Women	1.00	1.00	1.00	1.00	1.00	1.00
Men	**0.48 (0.35-0.65)***	0.83 (0.57-1.21)	**0.67 (0.50-0.90)**	0.93 (0.66-1.32)	0.97 (0.73-1.30)	1.08 (0.77-1.51)
Age (years)						
65-75	1.00	1.00	1.00	1.00	1.00	1.00
>75	**3.94 (2.89-5.37)***	**1.73 (1.19-2.51)**	**1.51 (1.11-2.04)**	0.98 (0.68-1.39)	1.11 (0.81-1.51)	0.97 (0.69-1.38)
Education level						
Without schooling	1.00	1.00	1.00	1.00	1.00	1.00
1-4 years	**0.31 (0.19-0.49)***	0.62 (0.37-1.05)	**0.37 (0.23-0.60)***	**0.49 (0.29-0.83)**	1.11 (0.63-1.98)	1.24 (0.68-2.26)
5-12 years	**0.12 (0.06-0.22)***	**0.28 (0.14-0.57)***	**0.23 (0.12-0.41)***	**0.33 (0.17-0.63)**	0.91 (0.47-1.75)	1.06 (0.53-2.11)
>12 years	**0.12 (0.05-0.27)***	0.43 (0.16-1.12)	**0.17 (0.07-0.37)***	**0.28 (0.12-0.68)**	0.69 (0.31-1.56)	0.86 (0.36-2.04)
Smoking status						
Non-smoker	1.00	1.00	1.00	1.00	1.00	1.00
Smoker	1.01 (0.48-2.09)	2.18 (0.93-5.07)	1.20 (0.60-2.43)	1.94 (0.91-4.12)	1.21 (0.60-2.45)	1.41 (0.67-2.94)
Alcohol consumption						
None	1.00	1.00	1.00	1.00	1.00	1.00
Moderate (W≤1/day; M≤2/day)	**0.36 (0.26-0.50)***	**0.61 (0.42-0.89)**	**0.48 (0.35-0.66)***	**0.59 (0.41-0.84)**	**0.67 (0.49-0.92)**	**0.69 (0.49-0.98)**
Excessive (W>1/day; M>2/day)	**0.27 (0.16-0.48)***	**0.52 (0.27-0.98)**	**0.50 (0.31-0.83)**	0.62 (0.36-1.07)	0.81 (0.50-1.30)	0.85 (0.51-1.42)
Cognitive function (MMSE)						
Not impaired	1.00	1.00	1.00	1.00	1.00	1.00
Impaired	**3.91 (1.91-8.01)***	**2.43 (1.09-5.38)**	1.94 (0.89-4.23)	1.66 (0.72-3.82)	**2.85 (1.36-5.97)**	**2.81 (1.29-6.13)**
Skin phenotype						
Red-haired with freckles or fair-haired people	1.00	1.00	1.00	1.00	1.00	1.00
Dark-haired or Latin people	1.03 (0.70-1.52)	1.24 (0.81-1.91)	**0.69 (0.48-0.99)**	0.76 (0.52-1.12)	**0.63 (0.44-0.90)**	**0.64 (0.44-0.93)**
Arab, Asian or Black people	2.13 (0.95-4.76)	1.88 (0.77-4.56)	1.53 (0.69-3.38)	1.43 (0.62-3.28)	1.23 (0.55-2.77)	1.17 (0.51-2.68)
Season of blood collection						
Spring/Summer	1.00	1.00	1.00	1.00	1.00	1.00
Autumn/Winter	**5.54 (4.02-7.64)***	**4.46 (3.08-6.46)***	**2.21 (1.64-2.98)***	**2.10 (1.50-2.95)***	**1.38 (1.02-1.86)**	**1.48 (1.06-2.07)**
Vitamin D supplementation						
No use	1.00	1.00	1.00	1.00	1.00	1.00
Use of vitamin D supplements	**0.11 (0.04-0.28)***	**0.08 (0.03-0.20)***	**0.20 (0.10-0.40)***	**0.16 (0.08-0.34)***	**0.29 (0.16-0.54)***	**0.26 (0.14-0.49)***
Unknown use or composition	**3.14 (1.87-5.27)***	1.75 (0.99-3.08)	1.73 (0.99-3.02)	1.18 (0.66-2.12)	1.19 (0.66-2.14)	1.07 (0.58-1.98)

BMI, Body mass index; W, Women; M, Men; OR, Odds ratio; CI, Confidence interval; MMSE, Mini-Mental State Examination.

†Adjusted for all covariates included in the table. Bold text indicates a statistically significant difference with a *p*-value less than 0.05.

**p*<0.001

Multinomial logistic regressions were conducted to evaluate the association of WC, BRI and ABSI with serum 25(OH)D using 25(OH)D quartiles as the dependent variable and the fourth quartile as the reference category (Table 3). Older adults in the highest category of WC presented the odds of 3.46 (95% CI: 1.95-6.15) and 2.61 (95% CI: 1.58-4.29) for being in the first and second serum 25(OH)D levels quartiles, respectively (*P* for trend <0.001). Although no significant associations were identified in the third 25(OH)D quartile, a significant trend was also observed (*P* for trend =0.041). The participants in first quartile of serum 25(OH)D levels showed an increasing adjusted odds ratio for BRI, from the second through the fourth quartile: 1.69 (95% CI: 1.02-2.79), 2.26 (95% CI: 1.36-3.75) and 4.35 (95% CI: 2.60-7.29), *P* for trend <0.001. Regarding ABSI and for the participants placed in the lowest 25(OH)D serum levels (first) quartile, the odds ratios were 4.03 (95% CI: 2.37-6.86) and 3.17 (95% CI: 1.86-5.38) for the third and fourth ABSI quartiles, respectively (*P* for trend <0.001).

In the second quartile of serum 25(OH)D levels, there was also a significant positive association with the third BRI quartile (OR: 2.14; 95% CI: 1.37-3.34) and fourth BRI quartile (OR: 2.51; 95% CI: 1.55-4.05), *P* for trend <0.001. Similarly, the third ABSI quartile was also positively associated with the second quartile of serum 25(OH)D levels (OR: 1.99; 95% CI: 1.23-3.21).

Additionally, when an interaction effect between frailty status and obesity indices was tested statistical differences were not found.

Table 3. Association between waist circumference, body roundness index and body shape index with 25(OH)D quartiles. Multinomial logistic regression models. Reference category was the fourth quartile of serum 25(OH)D (23.0-178.1 ng/mL)[†].

	25(OH)D					
	Q1 (3.0-8.7 ng/mL)		Q2 (8.8-14.3 ng/mL)		Q3 (14.4-22.9 ng/mL)	
	Crude OR (95% CI)	Adjusted[†] OR (95% CI)	Crude OR (95% CI)	Adjusted[†] OR (95% CI)	Crude OR (95% CI)	Adjusted[†] OR (95% CI)
Waist circumference (WC)[¶]						
W: ≤80cm; M: ≤94cm	1.00	1.00	1.00	1.00	1.00	1.00
W: 81-88 cm; M: 95-102 cm	1.18 (0.67-2.07)	1.31 (0.69-2.48)	1.17 (0.69-1.96)	1.27 (0.73-2.20)	1.14 (0.72-1.80)	1.23 (0.76-1.98)
W: >88 cm; M: >102 cm	**3.67 (2.26-5.95)***	**3.46 (1.95-6.15)***	**2.76 (1.75-4.34)***	**2.61 (1.58-4.29)***	**1.51 (1.00-2.29)**	1.56 (0.99-2.45)
P for trend	<0.001	<0.001	<0.001	<0.001	0.019	0.041
Body roundness index (BRI)[¶]						
Q1 (1.93-5.09)	1.00	1.00	1.00	1.00	1.00	1.00
Q2 (5.10-6.10)	**1.78 (1.14-2.78)**	**1.69 (1.02-2.79)**	**1.68 (1.12-2.52)**	1.51 (0.98-2.31)	1.27 (0.87-1.86)	1.15 (0.77-1.71)
Q3 (6.11-7.49)	**2.88 (1.85-4.50)***	**2.26 (1.36-3.75)**	**2.48 (1.64-3.75)***	**2.14 (1.37-3.34)**	**1.56 (1.05-2.32)**	1.45 (0.95-2.20)
Q4 (7.50-15.83)	**6.91 (4.41-10.80)***	**4.35 (2.60-7.29)***	**3.35 (2.16-5.20)***	**2.51 (1.55-4.05)***	1.42 (0.91-2.23)	1.31 (0.81-2.12)
P for trend	<0.001	<0.001	<0.001	<0.001	0.090	0.218
Body shape index (ABSI)[¶]						
Q1 (0.0643-0.0803)	1.00	1.00	1.00	1.00	1.00	1.00
Q2 (0.0804-0.0840)	1.55 (0.99-2.42)	1.59 (0.96-2.63)	1.31 (0.89-1.95)	1.33 (0.87-2.04)	0.93 (0.63-1.37)	0.91 (0.60-1.38)
Q3 (0.0841-0.0874)	**3.55 (2.27-5.56)***	**4.03 (2.37-6.86)***	**1.81 (1.19-2.76)**	**1.99 (1.23-3.21)**	1.46 (0.96-2.20)	1.40 (0.88-2.22)
Q4 (0.0875-0.1034)	**3.17 (2.06-4.88)***	**3.17 (1.86-5.38)***	1.30 (0.86-1.97)	1.29 (0.79-2.09)	0.95 (0.63-1.44)	0.87 (0.54-1.39)
P for trend	<0.001	<0.001	0.115	0.240	0.846	0.691

OR, Odds ratio, CI: Confidence interval, W, Women; M, Men.
[†]Adjusted for sex, age, educational level, alcohol consumption, smoking, skin phenotype, vitamin D supplementation, season of blood collection, cognitive function and frailty status. Waist circumference was further adjusted for height. Bold text indicates a statistically significant difference with a *p*-value less than 0.05.
[¶]Missing data in 10 individuals.
**p*<0.001

Discussion

In this cross-sectional study an inverse association between frailty and obesity with serum 25(OH)D concentrations, independently of sex, age, educational level, alcohol consumption, smoking, skin phenotype, vitamin D supplementation, season of blood collection and cognitive function, was found. These results were consistent with findings of several meta-analyses which evaluate the association between each of these conditions with vitamin D deficiency [18,20,21]. The interaction between frailty and obesity indices concerning serum 25(OH)D was further explored but no significant results were found, meaning that frailty and obesity are independently associated with lower serum 25(OH)D levels, and the effect of frailty (or obesity) on serum 25(OH)D levels is the same at all levels of obesity (or frailty).

When we compared vitamin D levels between frailty and obesity groups we found decreasing 25(OH)D concentrations across them. Thus, individuals that were not frail or obese presented higher unadjusted median 25(OH)D serum concentrations than the other study participants. Interestingly, when data were stratified by sex the pattern was very similar in women, however results were not as evident among men. These observations were supported after by the results of logistic regression, which revealed an association between these conditions and lower serum 25(OH)D levels.

All obesity indicators evaluated were inversely associated with 25(OH)D serum concentrations. Regarding BMI, an inverse association between 25(OH)D levels and obesity was found, but not for pre-obesity. Moreover, being at the fourth quartile of BRI was associated with a four-fold increased risk of presenting 25(OH)D levels in the first quartile, and it was more strongly associated than the other studied obesity indicators. It was also observed that the odds of being in the first quartile of 25(OH)D increased significantly across BRI quartiles.

Physiological changes that occur with aging predispose older adults to lower levels of serum 25(OH)D and frailty status. In addition, lower vitamin D concentrations may also have a negative impact on frailty status through multiple pathways. It has been previously demonstrated that vitamin D was linked with physical function, muscle strength and physical activity [25,44,45]. Accordingly, results from several clinical trials carried out in older adults showed that vitamin D supplementation had a beneficial effect in muscle strength and function [15]. Evidence suggests the presence of vitamin D receptors (VDR) in the muscle, which mediate multiple effects [46]. Furthermore, several

mechanisms have been suggested to explain the association between muscle function and vitamin D deficiency. In more depth, vitamin D may play an important role in muscle, mediated by several signaling pathways derived from genomic and non-genomic actions of VDR. These mechanisms include regulation of calcium homeostasis, cell proliferation and differentiation, fibers size and protection against insulin resistance, fatty degeneration of the muscle and arachidonic acid mobilization [47]. Nevertheless, this receptor was recently found to be undetectable in skeletal muscle, which brings this issue to the fore [48]. On the other hand, frailty may contribute to lower 25(OH)D levels, since frail older adults may spend fewer hours engaged in outdoor activities and, consequently, have a reduced sunlight exposure.

Present study results are also consistent with previous data reporting an inverse relationship between 25(OH)D levels and increased adiposity [20-22,28,29]. Besides vitamin D deficiency being frequent in older adults, it is also common in obese people. A possible explanation is that obese individuals usually have less skin exposed compared with normal weight individuals [49]. Nevertheless, we were unable to evaluate sunlight exposure in the present research. A study which intended to explore the causality and direction of this association using genetic markers, revealed that a higher BMI leads to lower 25(OH)D concentrations [50]. In addition, improvement in circulating levels of 25(OH)D was observed in pre-obese and obese after a weight loss intervention [51,51]. Since adipose tissue acts as a reservoir for vitamin D, it has been hypothesized that inadequate levels of vitamin D in obese individuals may be predisposed by the sequestration of vitamin D by fat tissue [53]. However, it has been recently suggested that this association may be related to a simple volumetric dilution due to higher volume of distribution of 25(OH)D in the adipose tissue [54]. Therefore, it is expected that individuals with higher levels of adiposity may be predisposed to inadequate serum 25(OH)D concentrations. Supporting the volumetric dilution hypothesis, a higher dose was required to produce the desired increment in serum 25(OH)D concentrations among obese individuals [55]. This supports the Endocrine Society guidelines, which state that the therapy should be adjusted in the presence of obesity [1]. Also, evidence suggests that adipocytes express VDR [56], 25-hydroxylase [57] and 1α-hydroxylase enzymes [57,58] which are involved in vitamin D metabolism. Interestingly these enzymes seem to have a decreased expression in obesity [57].

BMI and WC are traditionally chosen as anthropometric indicators of general and abdominal adiposity, respectively. Nevertheless, in the present study, the other obesity

indices evaluated (BRI and ABSI), were positively associated with lower vitamin D levels, showing that these may also be used as alternative obesity indicators to identify older adults at risk of low 25(OH)D levels. Despite the lack of positive correlation between ABSI and BMI, our study also demonstrated the link between these indices and lower vitamin D levels, which reinforces their utility.

The present study has some limitations. Firstly, this was a cross-sectional study, therefore the possibility of reverse causation should not be excluded. Secondly, although we have adjusted for multiple covariates, the possible occurrence of residual confounding cannot be ruled out. Thirdly, serum 25(OH)D concentrations were measured using electrochemiluminescence immunoassay, when liquid chromatography-tandem mass spectrometry is considered the golden standard, which can introduce variability in the results [59]. And, lastly, participants' sun exposure levels were not assessed.

In contrast, some strengths can also be pointed out. To our knowledge, this is the first study to explore the association of BRI and ABSI with serum 25(OH)D levels and to elucidate the impact of both obesity and frailty status on 25(OH)D serum levels. Moreover, for all the studied participants, vitamin D was dosed with the same method, the same equipment and in the same laboratory. The very low serum 25(OH)D levels in our sample, with only 30% of the sample presenting adequate 25(OH)D serum concentrations, allowed to study this association.

In summary, present results show that frailty and all obesity indices included, such as BMI, WC, BRI and ABSI, are inversely associated with serum 25(OH)D concentrations. Furthermore, these associations were independent, as no interaction effect between frailty and obesity concerning 25(OH)D levels was found. As discussed above, several studies reported conflicting results, however present results reinforce the positive relationship between vitamin D deficiency and both frailty and obesity. Plus, they emphasize the need to target obese and frail older people and monitoring their serum vitamin D levels with special care. Nevertheless, longitudinal studies are necessary to fully elucidate these associations.

Supplemental material

Supplemental material for this article can be found online:

S1 Table. Comparison of the included and excluded individuals[†].

https://doi.org/10.1371/journal.pone.0198650.s001

S2 Table. Characteristics of the 1447 study participants by obesity and frailty status.

https://doi.org/10.1371/journal.pone.0198650.s002

S3 Table. Correlation between body mass index, waist circumference, body roundness index and body shape index.

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3.2.

Frailty status is related to general and abdominal obesity in older adults.

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Abstract

The association between frailty and obesity may differ according to the heterogeneity of body mass index (BMI) and waist circumference (WC) phenotypes in older adults. We hypothesized that the use of simple indicators of general and abdominal obesity combined, may more accurately represent obesity and allow to further elucidate on how frailty status and its criteria are related to obesity. A sample of 1444 older adults, aged ≥65 years (Nutrition UP 65 study) was included in a cross-sectional analysis. General and abdominal obesity were defined according to World Health Organization BMI and WC cut-offs, and frailty by Fried et al. phenotype. A cluster analysis defined groups according to BMI and WC levels. Overweight (BMI between 25.0 and 29.9 kg/m^2; 44.6%), general obesity (BMI ≥30.0 kg/m^2; 39.0%), and abdominal obesity (WC >102 cm for men and >88 cm for women) were highly frequent (66.5%). Prefrailty (odds ratio [OR]: 2.33; 95% confidence interval [CI]: 1.52-3.57) and frailty (OR: 2.87; 95% CI: 1.58-5.22) were directly associated with the "general and abdominal obesity" cluster. Regarding frailty criteria, low handgrip strength (OR: 2.29; 95% CI: 1.55-3.38) and weight loss (OR: 0.27; 95% CI: 0.14-0.52) were also associated with this cluster. In this sample of older adults presenting a high frequency of overweight and obesity, prefrailty and frailty are linked to higher levels of adiposity, but only when both general and abdominal obesity are present. Present results emphasize the importance of the evaluation of both BMI and WC in the geriatric clinical practice and suggest that older adults presenting both general and abdominal obesity should be routinely screened for frailty.

Keywords: body mass index, obesity, frailty, waist circumference.

Introduction

Obesity is considered one of the world's most problematic public health issues [1]. While body mass index (BMI) is the most widely used tool to estimate adiposity levels, the optimal level of adiposity in older adults is still a matter of discussion. Since aging is associated with considerable changes in body composition and fat distribution [2,3], waist circumference (WC), as an indicator of regional distribution of fat, has had an important role in the determination of health risks resulting from excess adiposity in older adults [3].

Research has been focused on the association of surrogate adiposity indicators with different outcomes. A higher risk of mortality in older adults with BMI <23 kg/m^2 and >33 kg/m^2 was observed in a meta-analysis [4]. Interestingly, increased mortality risk for high WC values was found across all BMI categories in other meta-analysis [5]. Furthermore, it was observed that older Americans presenting a BMI <18.5 kg/m^2 or >30 kg/m^2 at baseline were significantly more likely to experience disability during the follow-up period [6].

Frailty is a state of increased vulnerability to several adverse health outcomes with major implications for clinical practice and public health [7-9], but studies on the association between frailty and obesity have produced controversial results. A systematic review of longitudinal studies revealed a direct association between obesity and the incidence of frailty [10]. However, in frail community-dwelling older women, another study showed that those who were overweight or obese had reduced risk of clinical adverse events [11]. In fact, a U-shape relationship between frailty and BMI was also reported, with the lowest prevalence of frailty observed in individuals with a BMI between 25 and 29.9 kg/m^2 [12,13].

Obesity may exacerbate the age-related decline in health and physical function, resulting in a deterioration of overall health and quality of life [14]. Interestingly, the presence of obesity in frail older adults significantly contributed to a higher mortality rate [15], with both high BMI and WC being suggested as risk factors for frailty [16]. In a study that included Chinese older adults, it was found that WC was a better predictor of frailty than BMI [17].

The link between frailty and excess adiposity levels in older adults has been described in the literature, however, it merits further investigation. Despite BMI often being considered unsuitable for older adults, the use of sophisticated technologies that accurately measure body fat mass is not readily available in most clinical settings [2].

Therefore, it is important to explore the link between frailty and anthropometric measures, such as BMI and WC, which are easily assessed in clinical practice. Understanding this issue is relevant for developing strategies to target individuals with different levels of adiposity regarding their frailty status and to improve overall health and quality of life at an older age.

The described association between frailty and obesity may differ according to the heterogeneity of BMI and WC phenotypes. We hypothesized that the use of simple anthropometric measures of general and abdominal obesity combined, may more accurately represent obesity in older adults and allow to further elucidate on how frailty status and its criteria are related to obesity. Therefore, this study aims to explore the association between frailty status and indicators of body adiposity, such as BMI and WC. Moreover, the link between each frailty criterion, and these indicators will also be studied.

Methods and materials

The present analysis includes data from the Nutrition UP 65 Project, which is a cross-sectional study conducted in Portugal. Data from the most recent national census in 2011 showed that the number of Portuguese residents was 10,562,178 and a total of 2,010,064 older Portuguese adults were identified, corresponding to 19% of the Portuguese population [18]. Thus, the recruited study sample (n=1500) corresponds to 0.075% of the Portuguese older population. Further details regarding the study protocol were previously described [19]. A sample of Portuguese older adults with 65 years or older, representative in terms of age, sex, education, and regional area was selected. A cluster approach was used and for each regional area, 3 or more town councils with >250 inhabitants were randomly selected and potential community-dwelling participants were contacted via home approach, telephone, or via institutions such as town councils and parish centers. Individuals were excluded if they presented any condition that precluded the collection of venous blood samples or urine (e.g., dementia or urinary incontinence). From the initial sample, 56 individuals could not be assessed regarding BMI, WC, and frailty status, due to missing data and were, therefore, excluded from the present analysis (Figure 1). The final sample comprised 1444 older adults.

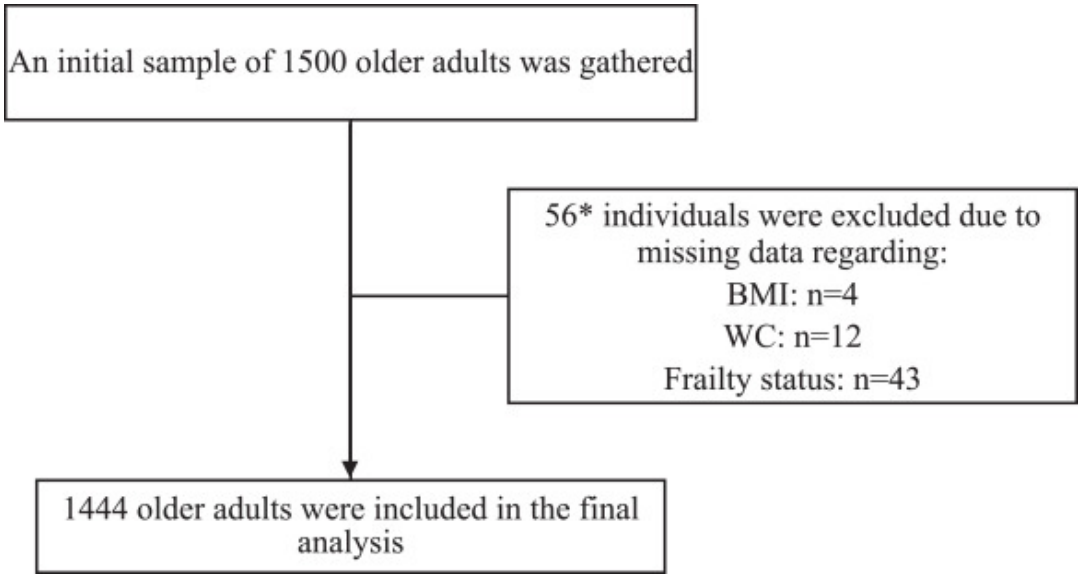

Figure 1. Flow diagram of the study selection process. *Due to missing data, 56 older adults were excluded, and a total of 1444 individuals were included in the final analysis.

Data collection

Data were gathered between December 2015 and June 2016. Eight trained registered nutritionists applied a structured questionnaire by interview and collected anthropometric measurements using standard procedures [20].

As part of the anthropometric evaluation, standing height was measured with a calibrated stadiometer (SECA 213, SECA GmbH, Hamburg, Germany) with 0.1 cm resolution, and body weight (in kilograms) was measured with a calibrated portable electronic scale (SECA 803, SECA GmbH, Hamburg, Germany) with 0.1 kg resolution, with the participants wearing light clothes. When it was not possible to measure standing height or weight, subject height was obtained indirectly from nondominant hand length [21], measured with a calibrated caliper (Fervi Equipment) with 0.1 cm resolution and body weight was estimated from mid-upper arm and calf circumferences [22]. Mid-upper arm, waist and calf circumferences were measured with a metal tape (Lufkin W606 PM, Lufkin, Sparks, MD, USA), with 0.1 cm resolution.

Handgrip strength (HGS) was measured in the nondominant hand with a calibrated Jamar Plus Digital Hand Dynamometer (Sammons Preston Inc., Bolingbrook, IL, USA). Participants were asked to sit in a chair without arm rest, with their shoulders adducted, their elbows flexed 90° and their forearms in neutral position, as recommended by the American Society of Hand Therapists [23]. Three measurements with a 1 minute pause between them were performed by each individual and the higher value, recorded in

kilogram force (kgf), was used for the analysis. Those unable to perform the measurement with the nondominant hand were asked to use the dominant hand.

Walking time was measured over a distance of 4.6 m, in an unobstructed corridor. Individuals were instructed to walk at usual pace and walking time was recorded by a chronometer (school electronic stopwatch, Dive049, Topgim, Portugal), in seconds. Individuals unable to perform the test due to mobility or balance limitations were considered frail for this criterion (n=28).

Self-reported exhaustion was measured using two items from the Center for Epidemiologic Studies Depression Scale [24]. The following two statements were read: "I felt that everything I did was an effort." and "In the last week I could not get going." The exhaustion criterion was considered present if a participant answered "a moderate amount of the time" or "most of the time" to the question: "How often in the last week did you feel this way?".

Physical activity, assessed by the short form of the International Physical Activity Questionnaire, included information regarding the previous seven days, namely on how many days and how much time the participant spent: walking or hiking, sitting, moderate activities, and vigorous activities [25].

BMI was calculated as weight (kg) divided by height (m) squared, and subjects were classified according to the World Health Organization (WHO) classification as underweight for BMI <18.5 kg/m^2, as normal weight for BMI between 18.5 and 24.9 kg/m^2, as overweight for BMI between 25.0 and 29.9 kg/m^2 and as obese for BMI ≥30.0 kg/m^2 [26]. Underweight individuals were included in the reference group ("normal weight") due to its small number (n=3). WC was categorized into the following categories: low WC for values ≤94 cm for men and ≤80 cm for women; high WC for values between 95 and 102 cm for men and 81 to 88 cm for women; and abdominal obesity for values >102 cm for men and >88 cm for women [27].

Frailty status

Frailty was defined according to Fried et al. frailty phenotype [8]. The following 5 criteria were evaluated: "shrinking"—evaluated by self-reported unintentional weight loss (>4.5 kg lost unintentionally in the prior year); "weakness"—assessed by low HGS adjusted for sex and BMI; "poor endurance and energy"—evaluated by self-reported exhaustion; "slowness"—identified by walking time adjusted for sex and standing height; and "low physical activity"—evaluated by means of energy expended per week, adjusted

for sex (men <383 kcal/week and women <270 kcal/week). Frailty was classified as the presence of 3 or more, and prefrailty as the presence of 1 or 2 of these criteria.

Covariates

Information regarding educational level, marital status, smoking status, and alcohol consumption was self-reported. The Portuguese version of the Mini-Mental State Examination and Mini-Nutritional Assessment – Short Form (MNA-SF) were used to ascertain cognitive impairment and undernutrition status, respectively. Cut-off scores for cognitive impairment were the following: individuals with no education, ≤15 points; 1 to 11 years of school completed, ≤22 points; and >11 years of school completed, ≤27 points [28]. Concerning undernutrition status, a participant scoring ≤7 out of 14 points was classified as undernourished, one that scores between 8 and 11 is at risk of undernutrition, and one scoring between 12 and 14 points was considered not undernourished [29].

Ethics

This research was conducted according to the guidelines established by the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of the Department of "Ciências Sociais e Saúde" (Social Sciences and Health) from the "Faculdade de Medicina da Universidade do Porto" (PCEDCSS – FMUP 15/2015) and by the Portuguese National Commission of Data Protection (9427/2015). All study participants signed an informed consent form.

Statistical analyses

Descriptive analyses were conducted to compare socio-demographic, lifestyle, and clinical characteristics of study participants. For continuous variables, the Kolmogorov-Smirnov test was used to test the normality of the distribution, and results were expressed as medians and interquartile range for variables with non-normal distributions. Mann-Whitney and Kruskal-Wallis tests were performed to test differences between 2 groups or more than 2 groups, respectively, for these variables. Regarding categorical variables, results were presented as frequencies. Qui-square test and Fisher's exact test were used to test differences in proportions among study variables. Clusters of obesity phenotypes were identified among the 1444 individuals included, using a 2-step cluster approach, using a log-likelihood distance measure to combine BMI and WC categories [30]. To select the best cluster solution, the Bayesian information criterion was

used, with smaller values indicating better models. The quality of fit of the resulting clusters was evaluated using the silhouette measure of cohesion and separation.

To handle missing data for the variables marital status (n=1), self-perception of health status (n=4), alcohol consumption (n=2), walking time (n=18), and weight loss (n=37), multiple imputation was performed using a Markov Chain Monte Carlo approach, with 5 imputation data sets and 10 iterations. Subsequently, a multinomial logistic regression was performed to quantify the association between frailty and frailty criteria, and obesity phenotypes. Odds ratios (OR) and their respective 95% confidence intervals (CI) were calculated, with adjustments for sex, age, educational level, marital status, self-perception of health status, smoking status, alcohol consumption, cognitive function, and undernutrition status. When testing for a single frailty criterion, the other remaining frailty criteria were also included in the adjusted model.

Statistical significance was established at a p value <0.05. All statistical analyses were conducted with IBM SPSS Statistics 23 (SPSS, Inc, an IBM Company, Chicago, IL, USA).

Results

Characteristics of the study sample

A total of 1444 older adults were included in this study. The sample was composed of 58% women and the mean age of the participants was 74.9 (±7.0) years. Comparison of main characteristics of included and excluded individuals revealed that a higher proportion of excluded individuals reported no alcohol consumption (p=0.002), had a greater decline in cognitive function (p=0.018), and a lower median MNA-SF score (p=0.001; Supplemental Table S1).

General and abdominal adiposity

Using the WHO definition for BMI, the frequency of obesity was 39.0% (n = 563), and 44.6% of the older adults were overweight (n = 644). Comparison between sexes shows that women presented a higher frequency of obesity (44.8% vs 31.0%) and lower frequency of overweight (40.9% vs 49.8%; p<0.001) (data not shown). Moreover, taking into consideration WC categories, 66.5% had abdominal obesity (WC >102 cm for men and >88 cm for women), and 21.1% had high WC values (between 81 and 88 cm for women and 95 to 102 cm for men). Also, a larger proportion of women was placed in the

highest WC category (78.3%), while 50.2% of men were placed in the same category (p<0.001).

Clusters characterization

Cluster analysis resulted in 4 phenotypes. The analysis produced a solution with 4 clusters with a good average silhouette measure of 0.8. The main phenotype included older adults allocated in the highest BMI and WC categories, and was named: (1) "general and abdominal obesity" (n=547, 37.9%); (2) "overweight with abdominal obesity" (n=383, 26.5%) which comprised only individuals with BMI between 25.0 and 29.9 kg/m^2 and WC >88 cm for women and >102 cm for men; (3) "overweight with high WC" (n=304; 21.1%) which included older adults with WC values between 81 and 88 cm for women and 95 to 102 cm for men, and 65.8% of the individuals had BMI between 25.0 and 29.9 kg/m^2; and the remaining phenotype; (4) "normal weight with low WC" (n=210, 14.5%) that included older adults in which 71.0% had BMI <25.0 kg/m^2 and 85.7% had WC ≤80 cm for women and ≤94 cm for men. Interestingly, none of the normal weight individuals had concomitantly a high WC, but a small percentage of older adults was normal weight with a very high WC (14.3%; Figure 2).

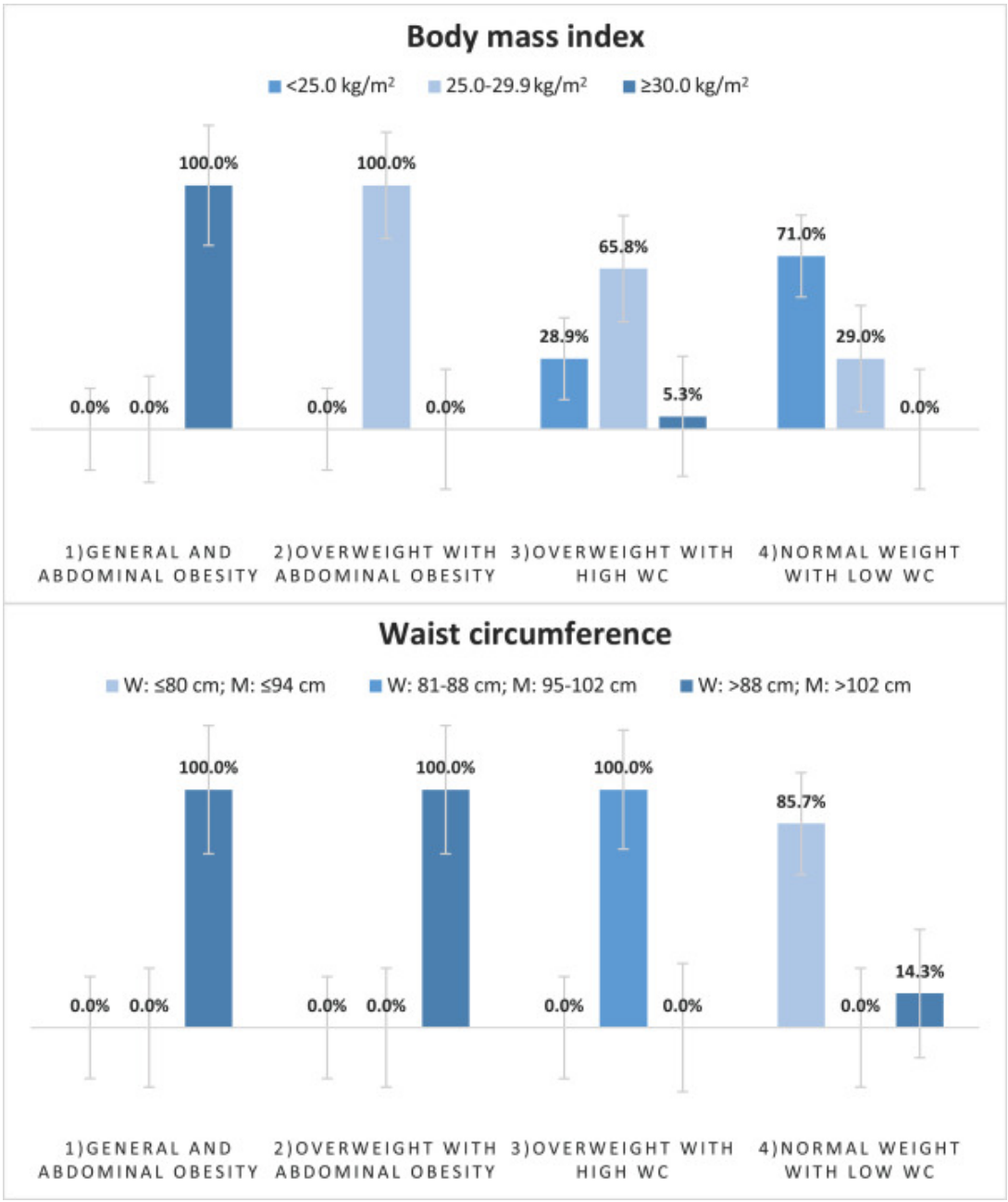

Figure 2. Body mass index and waist circumference percentages and respective error bars, according to the study clusters. WC, waist circumference.

Socio-demographic, lifestyle, and clinical characteristics of the participants, according to the 4 study clusters are presented in Table 1. Comparison between study clusters revealed differences for all the studied variables, except for age (p=0.244), regional area (p=0.521), residence (p=0.172), alcohol consumption (p=0.096), and cognitive function (p=0.520).

Table 1. Socio-demographic, lifestyle, and clinical characteristics of the participants, according to the study clusters [a].

	Clusters, n (%)				
	General and abdominal obesity 547 (37.9)	**Overweight with abdominal obesity 383 (26.5)**	**Overweight with high WC 304 (21.1)**	**Normal weight with low WC 210 (14.5)**	***p*-value**
Sex					
Women	372 (68.0)	258 (67.4)	126 (41.4)	81 (38.6)	<0.001[b]
Men	175 (32.0)	125 (32.6)	178 (58.6)	129 (61.4)	
Age (years), median (IQR)	74.0 (11.0)	74.0 (11.0)	73.0 (10.0)	73.0 (10.3)	0.244[c]
Regional area					
North/Centre/Lisbon	451 (82.4)	318 (83.0)	261 (85.9)	179 (85.2)	0.521[b]
Alentejo/Algarve	74 (13.5)	52 (13.6)	30 (9.9)	27 (12.9)	
Madeira/Azores	22 (4.0)	13 (3.4)	13 (4.3)	4 (1.9)	
Residence					
Home	523 (95.6)	358 (93.5)	292 (96.1)	204 (97.1)	0.172[b]
Care home	24 (4.4)	25 (6.5)	12 (3.9)	6 (2.9)	
Education level					
Without schooling	89 (16.3)	57 (14.9)	32 (10.5)	21 (10.0)	<0.001[b]
1-4 years	393 (71.8)	261 (68.1)	205 (67.4)	135 (64.3)	
5-12 years	49 (9.0)	51 (13.3)	46 (15.1)	38 (18.1)	
>12 years	16 (2.9)	14 (3.7)	21 (6.9)	16 (7.6)	
Marital status					
Single/Divorced/Widower	321 (58.7)	214 (56.0)	126 (41.4)	103 (49.0)	<0.001[b]
Married/Common-law marriage	226 (41.3)	168 (44.0)	178 (58.6)	107 (51.0)	
Self-perception of health status					
Very good/Good	147 (26.9)	108 (28.3)	112 (37.0)	95 (45.2)	<0.001[b]
Fair	278 (50.9)	199 (52.2)	152 (50.2)	81 (38.6)	
Poor/Very poor	121 (22.2)	74 (19.4)	39 (12.9)	34 (16.2)	
Smoking status					
Nonsmoker	536 (98.0)	371 (96.9)	287 (94.4)	184 (87.6)	<0.001[b]
Smoker	11 (2.0)	12 (3.1)	17 (5.6)	26 (12.4)	
Alcohol consumption					
None	277 (50.6)	200 (52.5)	126 (41.4)	97 (46.2)	0.096[b]
Moderate (W: ≤1 drink/day; M: ≤2 drinks/day)	215 (39.3)	145 (38.1)	141 (46.4)	94 (44.8)	
Excessive (W: >1 drink/day; M: >2 drinks /day)	55 (10.1)	36 (9.4)	37 (12.2)	19 (9.0)	
Cognitive function					
Not impaired	516 (94.3)	360 (94.0)	285 (93.8)	192 (91.4)	0.520[b]
Impaired	31 (5.7)	23 (6.0)	19 (6.3)	18 (8.6)	
MNA-SF score, median (IQR)	14 (2)	14 (2)	14 (1)	13 (2)	<0.001[c]
BMI, median (IQR)	33.3 (4.2)	28.3 (2.1)	26.5 (3.5)	24.1 (2.7)	<0.001[c]
WC, median (IQR)	109.0 (11.8)	98.2 (11.3)	95.5 (13.6)	88.5 (13.4)	<0.001[c]

BMI, Body mass index; IQR, Interquartile range; M, Men; MNA-SF, Mini-Nutritional Assessment – Short Form; W, Women; WC, Waist circumference.

[a] Data are presented as n (%) or medians (IQR). Column percentages may not add to 100% due to rounding. Total sample: n=1444. Missing data for: Marital status n=1 (0.1%); Self-perception of health status n=4 (0.3%); Alcohol consumption n=2 (0.1%).

[b] Qui-square test.

[c] Kruskal-Wallis test.

Frailty status and general and abdominal adiposity

Overall, frailty status and the presence of the 5 frailty criteria differed across clusters (p<0.05). A lower frequency of frailty was observed among individuals included in the cluster "overweight with high WC", and similar frailty frequencies were observed for the "normal weight with low WC" and "overweight with abdominal obesity" clusters. However, prefrailty rates were lower for the "normal weight with low WC" cluster (p<0.001) than for the other studied clusters (Table 2). It is worth noting that in the "normal weight with low WC" cluster, a higher frequency of weight loss >4.5 kg was also found (p=0.002; Table 2).

Table 2. Frailty status and frailty criteria by obesity clusters [a].

	Clusters, n (%)				
	General and abdominal obesity 547 (37.9)	**Overweight with abdominal obesity 383 (26.5)**	**Overweight with high WC 304 (21.1)**	**Normal weight with low WC 210 (14.5)**	***p*-value**
Frailty					
Not frail	88 (16.1)	90 (23.5)	105 (34.5)	70 (33.3)	<0.001[b]
Prefrailty	313 (57.2)	220 (57.4)	157 (51.6)	101 (48.1)	
Frailty	146 (26.7)	73 (19.1)	42 (13.8)	39 (18.6)	
Frailty criteria					
Exhaustion					
No	309 (56.5)	239 (62.4)	225 (74.0)	146 (69.5)	<0.001[b]
Yes	238 (43.5)	144 (37.6)	79 (26.0)	64 (30.5)	
Handgrip strength					
Not low	163 (29.8)	180 (47.0)	156 (51.3)	107 (51.0)	<0.001[b]
Low	384 (70.2)	203 (53.0)	148 (48.7)	103 (49.0)	
Physical activity					
Not low	437 (79.9)	317 (82.8)	264 (86.8)	183 (87.1)	0.023[b]
Low	110 (20.1)	66 (17.2)	40 (13.2)	27 (12.9)	
Walking time					
Not slow	356 (65.6)	261 (69.4)	235 (78.3)	163 (78.7)	<0.001[b]
Slow	187 (34.4)	115 (30.6)	65 (21.7)	44 (21.3)	
Weight loss					
≤4.5 kg	505 (94.7)	345 (92.0)	269 (90.9)	175 (86.2)	0.002[b]
>4.5 kg	28 (5.3)	30 (8.0)	27 (9.1)	28 (13.8)	

WC, Waist circumference.

[a] Data are presented as n (%). Column percentages may not add to 100% due to rounding. Total sample: n=1444. Missing data for: walking time: n=18 (1.3%); weight loss: n=37 (2.6%).

[b] Qui-square test.

The multinomial logistic regression model revealed associations between frailty status or frailty criteria and obesity phenotypes, considering the cluster "normal weight with low WC" as the reference category (Table 3). Overall, to be placed in the "overweight with high WC" cluster was neither significantly associated with prefrailty or frailty, nor with each one of the 5 frailty criteria. Considering the phenotype of

"overweight with abdominal obesity", a statistically significant association was only found for weight loss above 4.5 kg (OR: 0.51; CI: 0.27-0.97).

Table 3. Results of the multinomial logistic regression, regarding frailty status and frailty criteria and obesity clusters [a].

	Clusters					
	General and abdominal obesity		**Overweight with abdominal obesity**		**Overweight with high WC**	
	Crude OR (95% CI)	**Adjusted OR (95% CI)**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**
Frailty status						
Normal	1.00	1.00	1.00	1.00	1.00	1.00
Prefrailty	**2.47 (1.68-3.63)***	**2.33 (1.52-3.57)***	**1.69 (1.15-2.51)**	1.46 (0.99-2.15)	1.04 (0.70-1.53)	1.03 (0.67-1.58)
Frailty	**2.98 (1.86-4.78)***	**2.87 (1.58-5.22)***	1.46 (0.88-2.40)	1.18 (0.63-2.20)	0.72 (0.42-1.22)	0.79 (0.41-1.52)
Frailty criteria						
Exhaustion						
No	1.00	1.00	1.00	1.00	1.00	1.00
Yes	**1.76 (1.25-2.47)***	1.34 (0.91-1.99)	1.37 (0.96-1.97)	1.07 (0.71-1.61)	0.80 (0.54-1.18)	0.78 (0.51-1.20)
Handgrip strength						
Not low	1.00	1.00	1.00	1.00	1.00	1.00
Low	**2.45 (1.77-3.39)***	**2.29 (1.55-3.38)***	1.17 (0.84-1.64)	0.94 (0.63-1.41)	0.99 (0.69-1.40)	0.96 (0.64-1.45)
Physical activity						
Not low	1.00	1.00	1.00	1.00	1.00	1.00
Low	**1.71 (1.08-2.69)**	1.42 (0.84-2.38)	1.41 (0.87-2.29)	1.37 (0.80-2.36)	1.03 (0.61-1.73)	1.22 (0.69-2.16)
Walking time[b]						
Not slow	1.00	1.00	1.00	1.00	1.00	1.00
Slow	**1.95 (1.34-2.84)***	1.32 (0.82-2.10)	**1.63 (1.10-2.43)**	1.33 (0.81-2.16)	1.03 (0.67-1.58)	1.09 (0.65-1.82)
Weight loss[c]						
≤4.5 kg	1.00	1.00	1.00	1.00	1.00	1.00
>4.5 kg	**0.35 (0.20-0.60)***	**0.27 (0.14-0.52)***	**0.54 (0.32-0.94)**	**0.51 (0.27-0.97)**	0.63 (0.36-1.10)	0.83 (0.42-1.60)

CI, Confidence interval; WC, Waist circumference.

[a] The significance of differences between groups evaluated using multinomial logistic regression. Model adjusted for sex, age, educational level, marital status, self-perception of health status, smoking status, alcohol consumption, cognitive function and undernutrition status. When testing for frailty criteria, the other frailty measures were also included in the adjusted model. Bold type indicates statistical significance (P<.05). Total sample: n=1444.

[b] n=1426.

[c] n=1407.

*p≤.001.

Prefrailty was linked with the "general and abdominal obesity" cluster (OR: 2.33; 95% CI: 1.52-3.57). Individuals with frailty had 2.87 times higher odds (95% CI: 1.58-5.22) of fitting in the same cluster. Unlike the other frailty measures, individuals with low HGS were 2.29 times (95% CI: 1.55-3.38) more likely to fit in the "general and abdominal obesity" cluster, and weight loss above 4.5 kg was inversely associated with this cluster (OR: 0.27; CI: 0.14-0.52). Plus, a stronger inverse association was also observed between weight loss criterion and the phenotype with higher BMI (≥30 kg/m^2 vs between 25.0 and 29.9 kg/m^2), when compared to the "normal weight with low WC" category (Table 3).

Discussion

This research carried out among older adults with a high frequency of overweight and obesity revealed, as we hypothesized, that both prefrailty and frailty are strongly associated with the "general and abdominal obesity" phenotype. Similarly, having low HGS was also associated with increased odds of being placed in this cluster. However, an inverse association was found between "weight loss" frailty criterion and obesity, independently of presenting high or very high WC values.

Overall, the frequency of overweight and obese individuals was high in this sample of older adults, 44.6% and 39.0%, respectively. Women had higher rates of general and abdominal obesity, while overweight was more frequent among men. Comparing present results with data from the recent National Food, Nutrition, and Physical Activity Survey, a slightly higher frequency of overweight individuals (44.6% vs 41.8%) and a comparable frequency of obesity (39.0% vs 39.2%) are noticeable [31]. Results may differ because in the present sample, a larger age range (65-100 years) was selected, and 4.6% of the participants were institutionalized. However, when results of the present sample were confined to individuals from the community setting, aged <85 years, higher frequencies of overweight (44.7%) and obesity (39.7%) were observed.

Considering WC results, 66.5% of included older adults were classified with abdominal obesity vs the 62.4% observed previously [31]. Interestingly, we found similar data (66.2%) when the present sample was restricted to younger (<85 years) and noninstitutionalized individuals. In the 2015 National Health Examination Survey, it was estimated that 39.5% of Portuguese older adults aged between 65 and 74 years were overweight, 41.8% were obese and 88.1% had abdominal obesity [32]. While the number of obese individuals between 65 and 74 years is lower in the present study (38.3%), the proportion of overweight is considerably higher (46.2%).

One key finding of the present study is that frail older adults have higher odds of presenting higher WC and being classified as obese using WHO BMI classification. These results are consistent with previous data in which a higher incidence of frailty was observed in older adults with general and abdominal obesity [16]. However, we go into further detail by considering intermediate WC categories to elucidate the association of frailty with different levels of abdominal adiposity. The present results are also consistent with the "obesity paradox" theory, as a positive association with frailty was only found for the phenotype that included older adults allocated in the highest BMI and WC

categories, but not for the other phenotypes. It supports the hypothesis that only excessive body fat may exert detrimental effects on older adults' health and physical function, which may not occur in overweight individuals. Moreover, it also highlights the importance of the evaluation of both BMI and WC in older adults. Despite most studies supporting the "obesity paradox" being cross-sectional and that the largest limitation of BMI is its inability to distinguish between fat mass and fat free mass [33], the combination with WC may help identify individuals with higher levels of abdominal obesity. Furthermore, although the use of BMI in older adults is often questioned, and WC is indicated as a better indicator of adiposity in older adults, the latter may be insufficient, since in the present analysis, the link between frailty and abdominal obesity was only observed in the presence of general obesity, but not for overweight older adults.

This association between frailty status and obesity phenotypes can be explained by the fact that frailty is characterized by an increased inflammatory state [34], which is known to be present in individuals with higher BMI and WC [35]. Additionally, it has been described that the density of skeletal muscle decreases with age and is lower in individuals which present higher BMI and total body fatness, revealing that variations in muscle density in the older adults and in obesity are likely due to changes in muscle lipid content [36]. This could potentially explain some of the functional and metabolic defects observed in frail older adults.

Similarly, the association of weakness (identified through low HGS) with obesity allows comparable observations. These results are in line with longitudinal data, which states that low HGS is associated with obesity later in life [16,37]. Therefore, maintaining a healthy body weight throughout the lifespan may be important to maintain adequate muscle strength at an older age. Interestingly, it was also previously reported that a higher BMI was associated with greater HGS, while high WC may exert the opposite effect [38]. This could be explained because a high BMI does not always represent high adiposity levels, and abdominal obesity is more strongly associated with several inflammatory markers that may be involved in the genesis of frailty. Here, a significant association between low HGS and excess adiposity levels was observed only when both BMI and WC presented the highest values.

In addition, in line with previous research [12,39], a higher degree of general and abdominal obesity was inversely associated with the frailty criterion "weight loss". However, it is also worth noting that the impact of weight loss may be different among individuals with excess adiposity, and sometimes weight variations may go unnoticed in

these cases. In fact, evidence has shown that weight reduction and/or exercise interventions can improve physical function and biomarkers of physical dysfunction among overweight/obese older adults [14], which supports the results found in the present study and the theory that obesity contributes to physical frailty. Taking into account previous research [16], we expected to find a positive association between the "exhaustion" criterion and obesity; however, present data do not support these findings.

Because the prevalence of overweight and obesity has been increasing among the younger population [40], a growing number of people will suffer from obesity later in life. The results of this study suggest that general and abdominal obesity in older adults may induce a potentially endangering state of imbalance between fat and muscle mass or strength.

Despite current evidence supporting weight loss and/or physical activity interventions in overweight and obese older adults as strategies to improve physical function, weight loss in older adults must be carefully considered due to its potential detrimental effects in lean body mass [14]. In such cases, increasing physical activity levels alone may improve physical function, and therefore still exert some benefits on frailty status [14,41,42]. Moreover, obesity and frailty are preventable. In order to avoid its deleterious effects in older adults, strategies to manage these conditions should start at an earlier age and focus on maintaining healthy body weight and functionality [43,44].

Some limitations should also be noted. First, the cross-sectional study design does not allow us to conclude if frailty is causally related to the general and abdominal obesity phenotype in older adults. Second, the use of anthropometric measures in older adults to identify overweight and obesity through BMI is still a controversial matter, due to the changes in body composition that occur with aging. Plus, the use of WHO BMI cut-off points in older adults is often questioned. Notwithstanding, the other cut-offs suggested in the literature for this age group are based on limited scientific evidence. Despite these limitations, some strengths can be recognized. The high proportion of prefrail and frail individuals in this sample permitted us to study these associations. Furthermore, the use of a cluster approach to combine BMI and WC into a single measure of obesity phenotypes allowed to explore the link between frailty status or its criteria and the anthropometric indicators of body adiposity. Additionally, the present study identifies patterns of adiposity, considering intermediate WC categories, which is a major strength of this study as it allows to further elucidate the association of frailty with different levels of abdominal adiposity.

This study highlights a high frequency of overweight and obesity in Portuguese older adults. Our data provide important insights showing that frailty and weakness identified by low HGS are associated with higher odds of presenting both general and abdominal obesity in older adults. Present results emphasize the importance of the evaluation of both BMI and WC in older adults and suggest that older adults presenting both general and abdominal obesity should be routinely screened for frailty in clinical practice. Moreover, strategies to maintain a healthy body weight throughout the lifespan, and physical activity interventions may be considered to preserve muscle strength and prevent or delay the onset of frailty at an older age.

Supplemental material

Supplemental material for this article can be found online:

https://ars.els-cdn.com/content/image/1-s2.0-S0271531720305650-mmc1.docx

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3.3.

Sarcopenia, physical frailty, undernutrition and obesity cooccurrence among Portuguese community-dwelling older adults: results from Nutrition UP 65 cross-sectional study.

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Abstract

Objectives: To investigate the coexistence of sarcopenia, frailty, undernutrition and obesity and to identify the factors associated with the cooccurrence of these conditions in an older population.

Design: Cross-sectional.

Setting: Portugal.

Participants: 1454 older adults with 65 years or older, from Nutrition UP 65 study.

Primary and secondary outcome measures: Sarcopenia was identified using the European Working Group on Sarcopenia in Older People 2 guidelines and physical frailty using Fried phenotype. Mini-Nutritional Assessment – Short Form was used to ascertain undernutrition, and obesity was evaluated by body mass index.

Results: 57.3% presented at least one condition, 38.0% were identified with one and 19.3% were identified with two or more conditions. When all preconditions were considered, 95.7% of the older adults presented at least one of these preconditions or conditions. Multinomial logistic regression multivariate analysis revealed that being male (OR: 0.61; 95% CI: 0.43-0.88), being married or in a common-law marriage (OR: 0.58; 95% CI: 0.40-0.84) and having a higher educational level (OR: 0.23; 95% CI: 0.07-0.73) were inversely associated with having two or more conditions, while age >75 years (OR: 1.60; 95% CI: 1.14-2.24), a poor self-perception of health status (OR 5.61; 95% CI 3.50-9.01), ≥5 medications (OR: 3.11; 95% CI: 1.77-5.46) and cognitive impairment (OR: 1.84; 95% CI 1.37-2.48) were directly associated.

Conclusions: Almost three out of five older adults presented at least one of the conditions related to nutritional status, and about one in five had two or more of these occurrences. However, the low coexistence observed between all of these reinforces the need to assess them all individually during the geriatric assessment.

Keywords: coexistent conditions, frailty, obesity, sarcopenia, undernutrition.

Introduction

Sarcopenia, frailty, undernutrition and obesity are frequently identified in older populations. Although research on health in older adults generally focuses on the presence of multiple chronic diseases, commonly termed 'multimorbidity' [1], there are other relevant health conditions such as geriatric syndromes that are multifactorial conditions highly prevalent in older adults and that do not fall into discrete disease categories [2].

Both sarcopenia and physical frailty include measures of muscle strength and performance to diagnose muscle dysfunction and are both associated with similar poor health outcomes [3,4]. Despite the similarities, sarcopenia was not found to be a useful biomarker of frailty, but its absence is a good indicator for the absence of frailty [5]. In a large sample of community-dwelling older adults, sarcopenia prevalence in frail individuals ranged from 40% to 72%, depending on the definition used [5]. Moreover, sarcopenia and frailty were agreed to be separate conditions often associated with malnutrition [6]. In fact, in a study with overweight and obese cancer patients, sarcopenia was prevalent across different levels of nutrition risk [7]. In addition, the double burden of malnutrition was characterised by World Health Organization (WHO) as the coexistence of undernutrition along with overweight and obesity, namely, within individuals, but it needs to be further explored.

Despite being distinct, these conditions share many common pathophysiological pathways [3,4,8] and are associated with poor health outcomes [9-11]. Even though they have been extensively studied in older adults, the majority of the previous studies focused in each individual condition. Therefore, the study of their cooccurrence and their associated factors may help identify which individuals have an increased risk of cumulative health consequences and ascertain about older adults' health status. Additionally, it may provide useful information to support the development of suitable healthcare responses. Hence, the main goals of the present study are to investigate the coexistence of sarcopenia, physical frailty, undernutrition and obesity, and to evaluate the factors associated with the cooccurrence of these conditions in a large sample of the Portuguese older population.

Materials and methods

Design and participants

The study sample included individuals enrolled in the Nutrition UP 65 study, a cross-sectional observational study conducted in Portugal. As described in detail

previously [12], a cluster sample of 1500 individuals with 65 years or older, representative of the Portuguese older population in terms of age, sex, education and regional area was selected. Individuals presenting any condition that precluded the collection of venous blood samples or urine (eg, dementia or urinary incontinence) were not included. Data were gathered between December 2015 and June 2016. A structured questionnaire was applied by interview, conducted by eight trained registered nutritionists and anthropometric data were also collected. From the initial sample, 46 individuals could not be evaluated regarding frailty status (n=43) and body mass index (BMI; n=4) due to missing data and were therefore excluded from the present analysis.

Measurements

Anthropometric measurements were collected following standard procedures [13]. A calibrated stadiometer (SECA 213, SECA GmbH, Hamburg, Germany) with 0.1 cm resolution was used to measure standing height. Body weight (in kg) was measured with a calibrated portable electronic scale (SECA 803, SECA GmbH, Hamburg, Germany) with 0.1 kg resolution, with the participants wearing light clothes. When it was not possible to measure standing height or weigh a patient, height was obtained indirectly from non-dominant hand length [14], measured with a calibrated calliper (Fervi Equipment) with 0.1 cm resolution and body weight was estimated from mid-upper arm and calf circumferences [15]. Mid-upper arm and calf circumferences were measured with a metal tape measure (Lufkin W606 PM, Lufkin, Sparks, Maryland, USA) with 0.1 cm resolution.

Handgrip strength (HGS) was measured in the non-dominant hand with a calibrated Jamar Plus Digital Hand Dynamometer (Sammons Preston, Bolingbrook, Illinois, USA). As recommended by the American Society of Hand Therapists, participants were asked to sit in a chair without arm rest, with their shoulders adducted, their elbows flexed 90° and their forearms in neutral position [16]. Three measurements with a 1 minute pause between them were performed by each individual and the higher value, recorded in kilogram-force (kgf), was used for the analysis. Individuals unable to perform the measurement with the non-dominant hand were asked to use the dominant hand.

Walking time was measured over a distance of 4.6 m in an unobstructed corridor. Individuals were instructed to walk at usual pace and walking time was recorded by a chronometer (School Electronic Stopwatch, Dive049, Topgim, Portugal), in seconds.

Those unable to perform the test due to mobility or balance limitations were considered frail for this criterion (n=28).

Information regarding educational level, household income, smoking status, alcohol consumption and prescription medication use was self-reported. Cognitive impairment was ascertained using the Portuguese version of the Mini-Mental State Examination. Individuals were classified as cognitive impaired using the following criteria: individuals with no education, ≤15 points; 1–11 years of school completed, ≤22 points and >11 years of school completed, ≤27 points [17].

Sarcopenia status

Sarcopenia was identified using the European Working Group on Sarcopenia in Older People (EWGSOP) 2 guidelines, as the presence of low muscle strength measured by HGS, plus low muscle quantity and quality [4]. Low muscle strength was classified as grip strength <16 kgf in women and <27 kgf in men [18], and low muscle quantity and quality was classified as calf circumference <31 cm [19]. Presarcopenia was identified by the presence of low muscle strength.

Frailty status

Physical frailty was defined according to the Fried *et al* frailty phenotype [3]. Frailty was classified as the presence of three or more of the following five criteria: 'shrinking': evaluated by self-reported unintentional weight loss (>4.5 kg lost unintentionally in prior year); 'weakness': assessed by low HGS adjusted for gender and BMI; 'poor endurance and energy': evaluated by self-reported exhaustion using two items from the Center for Epidemiologic Studies Depression Scale [20]; 'slowness': identified by walking time, adjusted for gender and standing height; and 'low physical activity': assessed by the short form of the International Physical Activity Questionnaire [21], by means of kilocalories expended per week, adjusted for gender (men <383 kcal/week and women <270 kcal/week). Individuals with one or two of these criteria were classified as prefrail.

Undernutrition status

The Portuguese version of the Mini-Nutritional Assessment – Short Form was applied. A participant scoring ≤7 out of 14 points was classified as undernourished, one that scores between 8 and 11 is at risk of undernutrition and one scoring between 12 and

14 points was considered well nourished [22]. Due to the small number of undernourished individuals (n=18), undernutrition and undernutrition risk were studied as a single category.

Body mass index (BMI)

BMI was calculated as weight (kg)/height^2 (m) and subjects were classified as overweight for BMI between 25.0 and 29.9 kg/m^2 and obese for BMI of 30.0 kg/m^2 or above [11].

Statistical analysis

Characteristics of the study sample were described as frequencies and percentages, computed separately according to the number of conditions, and χ^2 or Fisher's exact test was applied to test differences between study groups.

Multiple imputations were carried out to handle missing data for the following variables: marital status (n=1), self-perception of health status (n=4) and alcohol consumption (n=2). The Markov Chain Monte Carlo approach was used, with 5 imputation data sets and 10 iterations. Then, a multinomial logistic regression was conducted to quantify the association between the number of diseases or conditions (dependent variable) and independent variables. Sex, age, residential status, regional area, marital status, educational level, household income, self-perception of health status, smoking status, alcohol consumption, medication use and cognitive function were variables included in the model. Odds ratios (OR) and their respective 95% Confidence Intervals (CI) were calculated.

All statistical analyses were performed with IBM SPSS Statistics V.25 (SPSS, an IBM Company), and the statistical significance level was set at a p value <0.05.

Results

In the 1454 older adults included in this study, 42.6% (n=620) presented none of the conditions evaluated, 38.0% (n=553) were identified with one of the conditions, 225 older adults (15.5%) were identified with two conditions, 55 individuals had three of the conditions evaluated (3.8%) and only 1 older adult was identified with all (0.1%). The median age of the individuals was 74 years (65–100). Comparison between included and excluded individuals revealed a higher proportion of excluded individuals from the

Alentejo/Algarve and Madeira/Azores (p=0.001), who do not know or did not declare their income (p=0.030), who were non-drinkers (p=0.005) and who were more likely to be cognitively impaired (p=0.017) (Online Supplementary Table 1). Older adults identified with multiple conditions (≥2) were more likely to be women, more than 75 years and being single, divorced or widower (p<0.001) (Table 1). Presarcopenia and sarcopenia were diagnosed in 457 (31.4%) and 65 (4.5%) older adults, respectively, while prefrailty was identified in 791 (54.4%) and frailty in 310 (21.3%) individuals. Also 646 (44.4%) were classified as overweight and 568 (39.1%) were obese. Undernutrition was present in 18 (1.2%) older adults and 211 (14.5%) were at risk of undernutrition.

Table 1. Characteristics of the participants according to the number of conditions evaluated in this study[†].

	Number of conditions N (%)			
	0 620 (42.6)	**1 553 (38.0)**	**≥2 281 (19.3)**	***p*-value**
Sex				
Women	297 (47.9)	338 (61.1)	206 (73.3)	<0.001*
Men	323 (52.1)	215 (38.9)	75 (26.7)	
Age				
65-75 years	403 (65.0)	316 (57.1)	111 (39.5)	<0.001*
>75 years	217 (35.0)	237 (42.9)	170 (60.5)	
Regional area				
North/Centre/Lisbon	527 (85.0)	443 (80.1)	246 (87.5)	0.049*
Alentejo/Algarve	71 (11.5)	86 (15.6)	29 (10.3)	
Madeira/Azores	22 (3.5)	24 (4.3)	6 (2.1)	
Residence				
Home	598 (96.5)	532 (96.2)	254 (90.4)	<0.001*
Institutionalized	22 (3.5)	21 (3.8)	27 (9.6)	
Marital status				
Single/Divorced/Widower	267 (43.1)	302 (54.6)	202 (71.9)	<0.001*
Married/Common-law marriage	352 (56.9)	251 (45.4)	79 (28.1)	
Education level				
Without education	57 (9.2)	85 (15.4)	63 (22.4)	<0.001*
1-4 years	417 (67.3)	384 (69.4)	197 (70.1)	
5-12 years	100 (16.1)	67 (12.1)	17 (6.0)	
Higher education	46 (7.4)	17 (3.1)	4 (1.4)	
Household income				
<500€	309 (49.8)	280 (50.6)	150 (53.4)	<0.001*
500-999€	101 (16.3)	57 (10.3)	16 (5.7)	
≥1000€	133 (21.5)	124 (22.4)	41 (14.6)	
Does not know or does not declare	77 (12.4)	92 (16.6)	74 (26.3)	
Self-perception of health status				
Very good/Good	248 (40.1)	170 (30.9)	44 (15.7)	<0.001*
Fair	305 (49.3)	283 (51.5)	127 (45.2)	
Poor/ Very poor	66 (10.7)	97 (17.6)	110 (39.1)	
Smoking status				
Non-smoker	585 (94.4)	532 (96.2)	271 (96.4)	0.215*
Smoker	35 (5.6)	21 (3.8)	10 (3.6)	
Alcohol consumption				
None	250 (40.5)	282 (51.0)	176 (62.6)	<0.001*
Moderate (W: ≤1/day; M: ≤2/day)	295 (47.7)	215 (38.9)	87 (31.0)	
Excessive (W: >1/day; M: >2/day)	73 (11.8)	56 (10.1)	18 (6.4)	
Medication use				
0	117 (18.9)	64 (11.6)	25 (8.9)	<0.001*
1-4	363 (58.5)	321 (58.0)	126 (44.8)	
≥5	107 (17.3)	122 (22.1)	92 (32.7)	
Unknown	33 (5.3)	46 (8.3)	38 (13.5)	
Cognitive function (MMSE)				
Not impaired	589 (95.0)	527 (95.3)	246 (87.5)	<0.001*
Impaired	31 (5.0)	26 (4.7)	35 (12.5)	

M, Men; MMSE, Mini-Mental State Examination; W, Women.

[†]Percentages may not add to 100% due to rounding. Data before multiple imputations. Information was not obtained: marital status n=1 (0.1%); self-perception of health status n=4 (0.3%); alcohol consumption n=2 (0.1%).

*χ^2 test.

When presarcopenia, prefrailty and overweight status were also accounted for the analysis, together with sarcopenia, frailty, obesity and undernutrition status, it was observed that only 4.3% of the older adults (n=63) presented none of the preconditions or conditions evaluated, and 22.6% were identified with one, 36% with two and 32.1% with three of the preconditions or conditions. All four preconditions or conditions were identified in 5% of the sample (n=72) (Online Supplementary Table 2).

Figure 1 shows the distribution of each condition across the study groups. Obesity was the most frequent condition among the group with only one condition (66.5%), followed by frailty (14.6%) and undernutrition or undernutrition risk (13.6%). For the group with two or more conditions, frailty was the most frequent (81.5%), followed by obesity (71.2%) and undernutrition or undernutrition risk in third (54.8%). Sarcopenia was the less frequent condition among both groups, and it was identified in 5.2% of the individuals with one condition and 12.8% of the older adults with two or more conditions.

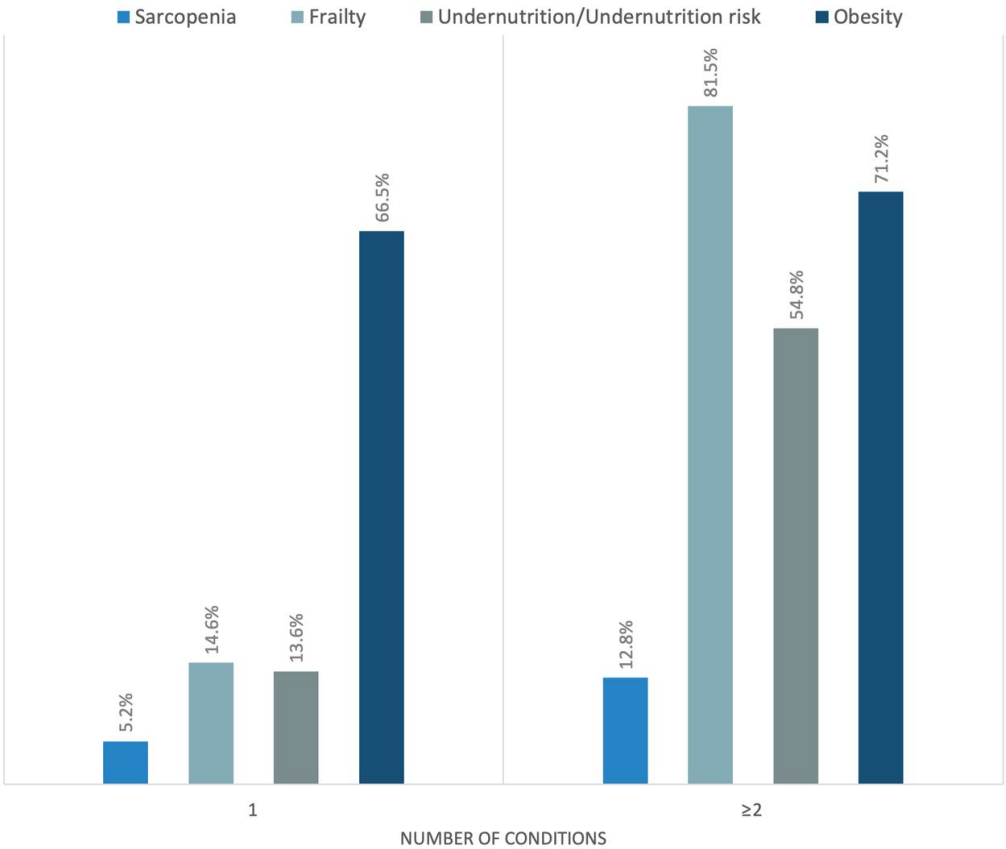

Figure 1. Frequency of sarcopenia, frailty, undernutrition or undernutrition risk and obesity according to the number of conditions.

Pairwise coexistence between the conditions evaluated is presented in Table 2. The highest coexistence was observed between frailty and obesity (10.5%). Furthermore, it was also observed that undernutrition or undernutrition risk coexisted with frailty in 7.0% and obesity in 5.9% of the sample. Sarcopenic obesity was identified in only two individuals (0.1%).

Table 2. Cooccurrence of sarcopenia, frailty, undernutrition or undernutrition risk and obesity.

	N (%)		
	Sarcopenia	**Physical frailty**	**Undernutrition/ Undernutrition risk**
Sarcopenia			
Physical frailty	32 (2.2)		
Undernutrition/Undernutrition risk	22 (1.5)	102 (7.0)	
Obesity	2 (0.1)	152 (10.5)	86 (5.9)

Results of coexistences when all preconditions were included revealed a higher coexistence for prefrailty/frailty with BMI over 25 kg/m^2 (64.2%), followed by prefrailty/frailty with presarcopenia/sarcopenia (35.9%) and presarcopenia/sarcopenia with BMI over 25 kg/m^2 (29.2%). Coexistence of undernutrition or undernutrition risk with prefrailty/frailty and pre-sarcopenia/sarcopenia was 14.4% and 6.9%, respectively. The double burden of malnutrition, characterised by the presence of undernutrition or undernutrition risk and overweight or obesity concurrently, was identified among 11.5% older adults (Online Supplementary Table 3).

The results of the multinomial logistic regression analyses after multiple imputations are shown in Table 3. When the category 'none of the conditions' was used as reference variable, it was found that presenting one condition was directly associated with living in Alentejo/Algarve (OR: 1.46; 95% CI: 1.02-2.07), poor or very poor self-perception of health status (OR: 1.64; 95% CI: 1.11-2.41), taking 1–4 medications (OR: 1.52; 95% CI: 1.08-2.14) and ≥5 medications (OR: 1.81; 95% CI: 1.21-2.70) and inversely associated with male gender (OR: 0.74; 95% CI: 0.57-0.96) and higher education (OR: 0.39; 95% CI: 0.20-0.78).

Table 3. Results from the multinomial logistic regression analysis, regarding the number of conditions. Reference category: none condition identified.

	Number of conditions			
	1		≥2	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Sex				
Women	1.00		1.00	
Men	**0.74 (0.57-0.96)**	**0.024**	**0.61 (0.43-0.88)**	**0.009**
Age				
65-75 years	1.00		1.00	
>75 years	1.10 (0.84-1.43)	0.483	**1.60 (1.14-2.24)**	**0.007**
Regional area				
North/Centre/Lisbon	1.00		1.00	
Alentejo/Algarve	**1.46 (1.02-2.07)**	**0.039**	0.88 (0.55-1.42)	0.629
Madeira/Azores	1.21 (0.88-1.65)	0.555	0.50 (0.30-0.84)	0.179
Residence				
Home	1.00		1.00	
Institutionalised	0.94 (0.49-1.77)	0.838	1.47 (0.76-2.84)	0.261
Marital status				
Single/Divorced/Widower	1.00		1.00	
Married/Common-law marriage	0.77 (0.58-1.00)	0.050	**0.58 (0.40-0.84)**	**0.003**
Education level				
Without education	1.00		1.00	
1-4 years	0.77 (0.52-1.12)	0.173	0.74 (0.47-1.15)	0.176
5-12 years	0.65 (0.40-1.06)	0.082	**0.36 (0.18-0.72)**	**0.004**
Higher education	**0.39 (0.20-0.78)**	**0.008**	**0.23 (0.07-0.73)**	**0.014**
Household income				
<500€	1.00		1.00	
500-999€	0.97 (0.65-1.45)	0.865	**0.50 (0.30-0.83)**	**0.008**
≥1000€	0.80 (0.49-1.30)	0.361	0.56 (0.28-1.13)	0.103
Does not know or does not declare	0.91 (0.63-1.31)	0.619	0.72 (0.47-1.10)	0.124
Self-perception of health status				
Very good/Good	1.00		1.00	
Fair	1.18 (0.90-1.53)	0.227	**1.94 (1.29-2.90)**	**0.001**
Poor/Very poor	**1.64 (1.11-2.41)**	**0.012**	**5.61 (3.50-9.01)**	**<0.001**
Smoking status				
Non-smoker	1.00		1.00	
Smoker	0.87 (0.65-1.17)	0.635	1.06 (0.69-1.60)	0.899
Alcohol consumption				
None	1.00		1.00	
Moderate (W: ≤1/day; M: ≤2/day)	0.85 (0.65-1.11)	0.233	0.77 (0.54-1.10)	0.147
Excessive (W: >1/day; M: >2/day)	0.91 (0.60-1.39)	0.674	0.68 (0.36-1.26)	0.219
Medication use				
0	1.00		1.00	
1-4	**1.52 (1.08-2.14)**	**0.020**	**1.71 (1.31-2.25)**	**0.047**
≥5	**1.81 (1.21-2.70)**	**0.005**	**3.11 (1.77-5.46)**	**<0.001**
Unknown	1.66 (0.95-2.91)	0.079	**2.56 (1.80-3.66)**	**0.008**
Cognitive function (MMSE)				
Not impaired	1.00		1.00	
Impaired	0.83 (0.47-1.47)	0.521	**1.84 (1.37-2.48)**	**0.040**

M, Men; MMSE, Mini-Mental State Examination; W, Women.
Bold text indicates a statistically significant difference with a *p*-value less than 0.05.

Furthermore, having two or more conditions was inversely associated with male gender (OR: 0.61; 95% CI: 0.43-0.88), being married or in a common-law marriage (OR: 0.58; 95% CI: 0.40-0.84), a higher educational level (OR: 0.36; 95% CI: 0.18-0.72 for 5–12 years of education; OR: 0.23; 95% CI: 0.07-0.73 for higher education), an household income between 500 and 999€ (OR: 0.50; 95% CI: 0.30-0.83) and directly associated with age >75 years (OR: 1.60; 95% CI: 1.14-2.24), a fair (OR: 1.94; 95% CI: 1.29-2.90) and poor or very poor self-perception of health status (OR: 5.61; 95% CI: 3.50-9.01), medication use: 1–4 medications (OR: 1.71; 95% CI 1.31-2.25), ≥5 medications (OR: 3.11; 95% CI: 1.77-5.46) and unknown medication (OR: 2.56; 95% CI: 1.80-3.66) and cognitive impairment (OR: 1.84; 95% CI: 1.37-2.48) (Table 3).

Discussion

Within this large sample of older adults, almost three out of five presented at least one of the studied conditions, namely, sarcopenia, physical frailty, obesity and undernutrition/undernutrition risk, and about one-fifth had two or more of these conditions. However, when the preconditions state was integrated in this analysis, only a small proportion (4.3%) of the older adults presented none of the preconditions or conditions evaluated. Considering the distribution of these conditions among study groups, it was found that obesity was unquestionably the main contributor to the group with one condition, nevertheless, a large frequency of frailty was observed in older adults with two or more conditions. Also, the highest coexistence was observed between frailty and obesity (10.5%), but these were also the most frequent conditions in our sample.

The prevalence of these conditions individually was previously discussed in depth [23-26]. Briefly, obesity and frailty are very frequent among Portuguese older adults [23-26], and lower frequencies of undernutrition and sarcopenia were observed in these individuals [24,25]. Nevertheless, the majority of the older adults had low muscle strength, the primary parameter of sarcopenia [25]. An important finding of this study is that the double burden of malnutrition within individuals was found in more than one-tenth of the sample. Interestingly, when only obesity and undernutrition or undernutrition risk were accounted, coexistence was still observed in 5.9% older adults, even though BMI is part of undernutrition assessment. This indicates that despite the higher adiposity levels observed in some individuals, some may still be at risk of experiencing several health consequences of a state of undernutrition.

Frailty and obesity were simultaneously identified in a large proportion of the participants with two or more conditions. The influence of these conditions on older adults' health has been brought up and discussed by several authors. When the impact of frailty and BMI on mortality was evaluated, it was found that frail older adults who were obese had a significantly higher mortality risk [27]. Also, it was observed that in older people who were normal weight or underweight, higher levels of frailty were associated with poorer survival [27]. Additionally, weight loss and exercise interventions had been pointed as beneficial among overweight or obese older adults, namely in the improvement of physical function and biomarkers of physical dysfunction [28,29]. Regardless of the evidence presented, weight loss in older adults must be taken with caution, because it can also result in losses of lean body mass and bone mineral density [29]. At the other end of the spectrum, physical frailty and undernutrition/undernutrition risk coexistence were lower to the one observed for frailty and obesity. Results of a meta-analysis conducted by Verlaan *et al.* revealed that older adults were likely to be physically frail, but only a small percentage of the physically frail older people in the community was identified as undernourished [30]. In the present study, 44.5% of the undernourished or at undernutrition risk individuals were frail, and 32.9% of the individuals who were frail were also undernourished or at undernutrition risk. However, in agreement with the previous results [30], when undernourished individuals were considered separately from those who were at nutritional risk, it was observed that 72.2% of the undernourished individuals were frail, while only 4.2% of frail older adults were undernourished. Nevertheless, it is still important to acknowledge the small number of undernourished older adults identified in this study (n=18).

Sarcopenia and physical frailty are not identical, but they share similar criteria and a close relationship between the two is often pointed out in the literature. Actually, overlap between sarcopenia and frailty is discussed in both EWGSOP consensus, suggesting that most frail people exhibit sarcopenia, and some older people with sarcopenia are also frail [4,8]. Our data showed a low coexistence between them (2.2%), which is in line with previous results that observed a low coexistence of sarcopenia and frailty even when various definitions were used [31]. This supports the fact that sarcopenia and frailty are still two distinct conditions. Indeed, in the recent EWGSOP consensus sarcopenia is described as a contributor to the development of physical frailty, while frailty syndrome represents a much broader concept [4]. However, it is worth mentioning that the methodologic differences often observed between the studies raise the difficulty

to draw conclusions. It was also interesting to find that when presarcopenia and prefrailty were also considered, they cooccurred in only 35.9% individuals, even though they share similar diagnostic measures. In fact, the difference in HGS cutoff points for sarcopenia and frailty diagnosis [3,4] is a major contributor to this low coexistence, as only 35.8% older adults had simultaneously the low HGS criterion for both conditions (data not shown). Sarcopenia and undernutrition coexistence was previously discussed [25].

Although, according to our knowledge, the study of coexistence of all these conditions is lacking. A recent cross-sectional study in 100 patients revealed a higher overlap between three of these conditions (sarcopenia, frailty and undernutrition), however this study was developed in hospital setting, and higher frequencies of each condition were observed among these older adults [32].

When factors associated with presenting several of these conditions were examined through multinomial regression analyses, being male, married or in common-law marriage and having attended 5 or more years to school were inversely associated with two or more of the studied conditions evaluated here. In the present study, all the studied conditions sarcopenia, frailty, undernutrition/undernutrition risk and obesity were more frequent among women.

As expected, age was positively associated with presenting more than one condition, since the aetiology of most of these conditions is closely related with the ageing process [3,4,8]. Moreover, a fair, and especially a poor or very poor self-perception of health status were positively linked with presenting multiple conditions. The decline in physical function commonly observed in older people suffering from these conditions may partially explain this, as it may influence individuals' perception of their health.

Medication usage was also associated with presenting one and two or more of the conditions evaluated. Furthermore, higher odds were observed for those with a higher medication use (≥5) and for the group with more than one condition. This reveals a state of vulnerability, as individuals with higher medication use were also more likely to refer two or more chronic diseases and, consequently, have poorer health status. This is in accordance with previous literature, which reported that those on more medication were more likely to be older and have worse health status [33]. Regarding cognitive impairment, a significant association was observed only with the group with two or more conditions identified. Although these conditions were not individually associated with a deterioration in cognitive status (data not shown), the cumulative effect of their cooccurrence, may have had an impact on this association.

In addition, the higher cooccurrence observed when the intermediate states of these conditions were considered is in line with current evidence that indicates that some of these conditions may contribute to the development of the other conditions or diseases. This emphasises the need to evaluate all of them separately, at early stages, during the geriatric assessment. Hence, besides the use of screening tools for undernutrition and obesity, it would be relevant to also routinely screen for frailty and sarcopenia.

Some study limitations can be enumerated. First, it should be noted that the cross-sectional nature of this study does not allow us to infer about causal relationships. Second, comparison between included and excluded individuals revealed statistically significant differences for some variables, hence generalisation of the present results should be made with caution. Furthermore, muscle mass assessment for sarcopenia diagnosis was carried out using anthropometric measures, which is not the reference method to estimate muscle quality and quantity. In addition, the appropriateness of the use of BMI to estimate excessive adiposity in older adults has been questioned in the literature [34]. Also, it would be of special interest to evaluate the outcomes of the cooccurrence of these conditions, namely, the extent of health consequences resulting from their cumulative effects. However, to our knowledge, this is the first study to analyse the coexistence of sarcopenia, frailty, undernutrition and obesity in older adults and to identify the factors associated with them.

The study of sarcopenia, physical frailty, undernutrition and obesity in the same sample of older adults is a novelty, and the low coexistence observed between the conditions evaluated, reinforces the need to assess them all individually during geriatric assessment. It also raises the question of how the presence of one of these conditions may mask or aggravate the state of others. Therefore, it would be important to carefully address their cumulative effects in older adults' health status and quality of life, in a near future.

Supplemental material

Supplemental material for this article can be found online:

Online Supplementary Table 1

https://bmjopen.bmj.com/content/bmjopen/10/6/e033661/DC1/embed/inline-supplementary-material-1.pdf?download=true

Online Supplementary Table 2

https://bmjopen.bmj.com/content/bmjopen/10/6/e033661/DC2/embed/inline-supplementary-material-2.pdf?download=true

Online Supplementary Table 3

https://bmjopen.bmj.com/content/bmjopen/10/6/e033661/DC3/embed/inline-supplementary-material-3.pdf?download=true

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Chapter 4

Muscle strength and muscle mass measurements to identify sarcopenia and frailty

4.1.

Sousa-Santos AR, Amaral TF. **Differences in handgrip strength protocols to identify sarcopenia and frailty - a systematic review.** BMC Geriatr. 2017 Oct 16;17(1):238. doi: 10.1186/s12877-017-0625-y.

4.2.

Sousa-Santos AR, Barros D, Montanha, TL, Carvalho J, Amaral, TF. **Which is the best alternative to estimate muscle mass for sarcopenia diagnosis when DXA is unavailable?** Arch Gerontol Geriatr. 2021 Nov 1;97:104517. doi: 10.1016/j.archger.2021.104517.

4.1.

Differences in handgrip strength protocols to identify sarcopenia and frailty – a systematic review.

Sousa-Santos AR, Amaral TF.
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doi: 10.1186/s12877-017-0625-y.

Abstract

Background: Hand grip strength (HGS) is used for the diagnosis of sarcopenia and frailty. Several factors have been shown to influence HGS values during measurement. Therefore, variations in the protocols used to assess HGS, as part of the diagnosis of sarcopenia and frailty, may lead to the identification of different individuals with low HGS, introducing bias. The aim of this systematic review is to gather all the relevant studies that measured HGS to diagnose sarcopenia and frailty and to identify the differences between the protocols used.

Methods: A systematic review was carried out following the recommendations of The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. PubMed and Web of Science were systematically searched, until August 16, 2016. The evidence regarding HGS measurement protocols used to diagnose sarcopenia and frailty was summarised and the most recent protocols regarding the procedure were compared.

Results: From the described search 4393 articles were identified. Seventy-two studies were included in this systematic review, in which 37 referred to sarcopenia articles, 33 to frailty and two evaluated both conditions. Most studies presented limited information regarding the protocols used.

Conclusions: The majority of the studies included did not describe a complete procedure of HGS measurement. The high heterogeneity between the protocols used, in sarcopenia and frailty studies, create an enormous difficulty in drawing comparative conclusions among them.

Keywords: Sarcopenia, frailty, handgrip strength, older adults.

Background

Ageing is accompanied by numerous underlying physiological changes and increasing risk of certain health conditions, such as chronic diseases. These changes that constitute and influence ageing are complex [1]. Sarcopenia and frailty are two geriatric syndromes that are frequently confounded [2].

Sarcopenia was initially proposed by Irwin Rosenberg, in 1989, to define the age-related decrease of muscle mass. It derives from the Greek words 'sarx', that means flesh, and 'penia', that means loss [3]. In 2009, the International Working Group on Sarcopenia (IWGS) provided a consensus definition describing sarcopenia as the age-associated loss of skeletal muscle mass and function. It was proposed that older patients who presented decline in physical function, strength or overall health should be considered for sarcopenia diagnosis [4]. In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) released a clinic definition and consensus diagnostic criteria for age-related sarcopenia. They presented sarcopenia as a syndrome characterised by progressive and generalised loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life, and death. The diagnosis should consider the presence of low muscle mass and low muscle function (strength or performance) to define conceptual stages as 'presarcopenia', 'sarcopenia' and 'severe sarcopenia' [2].

Frailty is a clinically recognisable state of increased vulnerability resulting from age-associated decline in reserve and function across multiple physiologic systems [5], which is associated with adverse outcomes, such as falls, functional decline, hospitalisations and mortality [6-9]. Even though, there is no single generally accepted clinical definition of frailty, in the Cardiovascular Health Study (CHS) it was defined as a clinical syndrome in which three or more of the following characteristics were present: unintended weight loss, exhaustion, weakness, slow gait speed and low physical activity [10]. Fried's frailty scale has been the most extensively tested for its validity and is the most widely used instrument in frailty research [11].

Hand grip strength (HGS) is used to diagnose both sarcopenia and frailty [2,4,10]. It can be quantified by measuring the amount of static force that the hand can squeeze around a dynamometer [12] and it is an indicator of overall muscle strength [13]. Age and gender are described as the strongest factors influencing HGS in healthy subjects, HGS declines with increasing age [14] and presents lower values for women [15,16]. It has good

intra- and inter-tester reliability and can be recommended the use in clinical practice [17,18]. HGS can independently identify changes in nutritional status [19]; it responds earlier than anthropometrical measurements to nutritional deprivation and has shown to be significantly associated with sarcopenia [2] and frailty [10].

While HGS is considered a reliable measure to assess muscle strength, several factors have been shown to influence HGS values during measurement. It was reported that a different posture [20], different positions of the elbow [20] and wrist [21], the hand used to test [22] and the setting of the dynamometer [23] may affect the values of strength. It is even reinforced that certain positions can optimise the measurement and produce a maximal HGS. Therefore, variations in the protocols used to assess HGS, as part of the diagnosis of sarcopenia and frailty, may lead to the identification of different individuals with low HGS, introducing bias. This can occur even when the same cut-off points are adopted, which consequently can lead to differences in the number of individuals identified with sarcopenia and frailty. The American Society of Hand Therapists (ASHT) recommended, in 1981, that HGS should be measured with the individuals seated with their shoulders adducted, their elbows flexed 90° and their forearms in neutral position using the Jamar dynamometer [24]. This protocol has been updated with more details of the procedure in 1992 [25], and later in 2015 [26]. In 2011, a new protocol was proposed, the Southampton protocol [27], representing another step towards an improvement of the description of HGS measurement. Nevertheless, there is still a lack of consistency in the studies' protocols to evaluate HGS used over time.

This systematic review resulted from the need to evaluate the differences between the protocols used for the HGS measurement to diagnose sarcopenia and frailty in older adults. For this reason, this revision represents a step forward towards the standardisation of the procedure. Therefore, the aim of this article is to gather all the relevant studies that measure HGS and to identify the differences between the protocols used. To this end, the proposed systematic review will answer the following questions:

1. Which dynamometer was used for measuring HGS?
2. Which hand was used?
3. What was the individual's posture?
4. What was the arm position?
5. Which handle position was used?
6. How long did the HGS measurement take?
7. How long were the intervals between the measurements?

Methods

A systematic review was carried out following the recommendations for reporting systematic reviews and meta-analyses of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (The PRISMA Statement) [28]. PubMed and Web of Science were systematically searched until August 16, 2016, with no restriction on the year of publication. The search was limited to English, Portuguese, Spanish and French publications and to human subjects. The reference lists within the articles were scanned for any additional references missing from the databases' search. The following search terms were used: [1] ((hand OR handgrip OR grip OR grasp) AND (force OR strength)) AND (sarcopenia OR frail elderly OR frail OR frailty). Subsequently, search results were inserted in EndNote X7 and duplicates were excluded. All the titles and abstracts were screened based on the eligibility criteria and classified as "relevant" or "not relevant". Full texts of eligible articles were assessed and read. Those that met all criteria were included.

Eligibility criteria

Studies were included if [1] participants were aged 65 years or older within well-defined samples, with a clear description of the inclusion and exclusion criteria; [2] sarcopenia and frailty were considered as outcomes, in which HGS was used to identify this condition; [3] a description of the protocol used to measure handgrip strength was provided; [4] the outcome measures described are: type of dynamometer for the assessment of HGS, individual's position (including shoulder, elbow, arm and handle position and posture), hand dominance, number of repetitions, acquisition and rest time, encouragement and handgrip strength values.

Randomised control trials, cohort studies, case control studies and cross-sectional studies were included, and meta-analyses or review articles, case reports, case series, meetings' proceedings, conference summaries and duplicate records were excluded. Articles were not included if information about either the posture of the individual, or concerning the arm position (shoulder, elbow or wrist) was absent. When the complete procedure was not described but a reference was made to another article, we searched for the missing parts of the procedure. If the article did not add more details regarding the procedure, it was still excluded. In case of disagreement about the inclusion of a study, the reviewers discussed their opinions to reach consensus. The studies were divided into

two subgroups: [1] articles about sarcopenia and [2] articles about frailty. Final studies selected for inclusion in each category were independently compiled in data tables. Articles which presented the same data as an earlier study were still excluded.

Results

From the described search 4393 articles were identified. After removing duplicates, a total of 2753 articles remained. From these, after screening for title and abstract 2166 articles were excluded. Five hundred and eighty-seven full-text articles were assessed for eligibility and 515 references were excluded. Seventy-two studies were found eligible and, therefore, included in this systematic review. Figure 1 presents a flow diagram of the literature search and of the selection process.

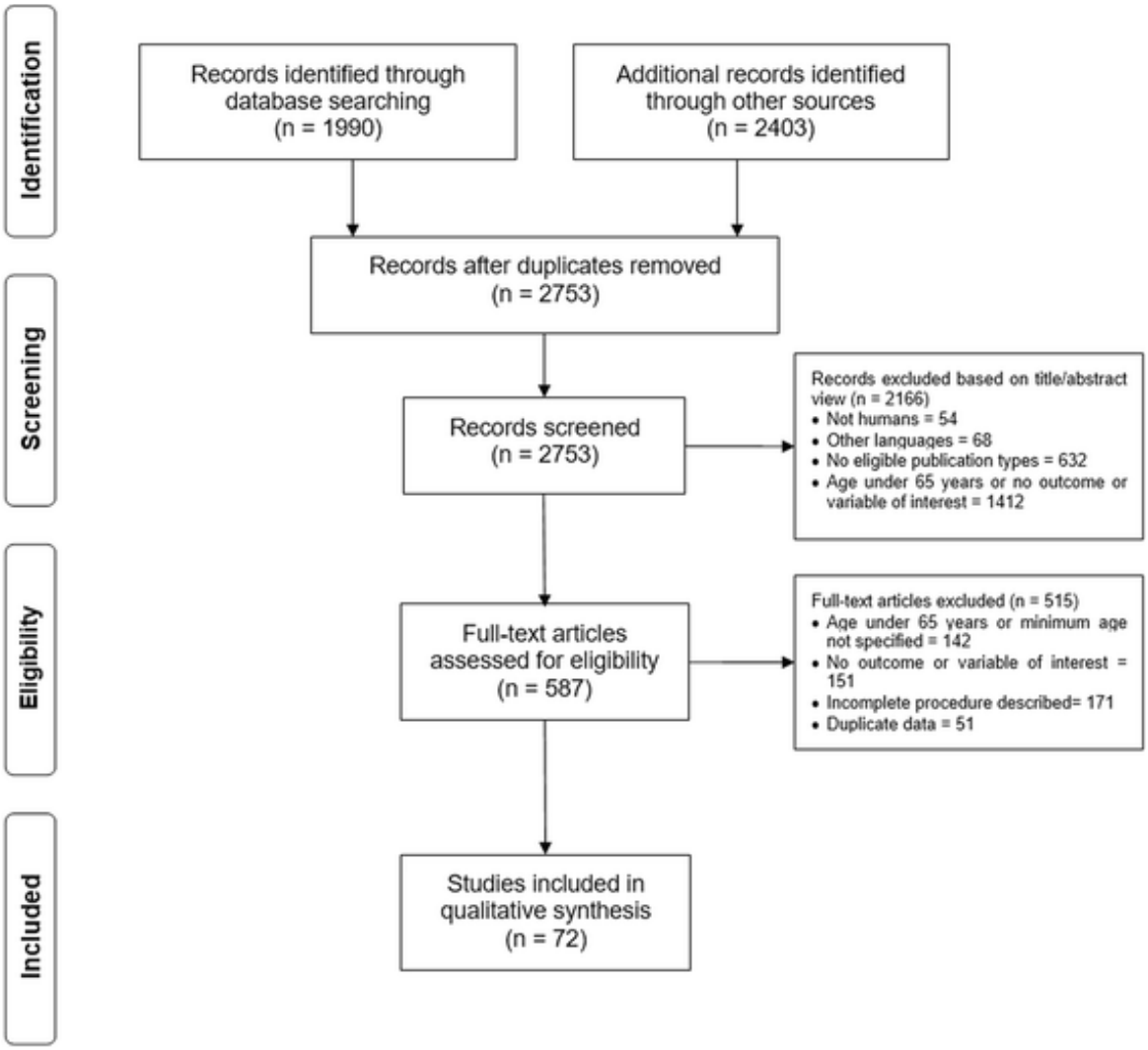

Figure 1. Flow diagram of the literature search and selection process.

The studies comprised in this systematic review were published between 2003 and 2016. Fifty-two were cross-sectional studies, 17 were cohorts, and three were clinical trials. The sample size ranged between 24 and 11844 individuals.

From the articles included, 37 studies referred to sarcopenia, 33 to frailty and two evaluated both conditions. The EWGSOP and the CHS definitions were used in the majority of studies to diagnose sarcopenia and frailty.

Description of HGS measurement

Most studies presented limited information regarding the protocols used. As shown in both Tables 1 and 2, all 72 studies described the dynamometer used, but only five specified if it was calibrated for the study. Although, there was a wide range of equipment used, the Jamar dynamometer was the most mentioned (n=35), followed by the Smedley dynamometer (n=10). Sixty-six studies described the posture of the individual, in which the majority was measured in a sitting position (n=47), and 19 were in a standing position. Three studies mentioned variations regarding the posture, depending on the ability of the individuals.

Most studies chose to measure HGS only in the dominant hand (n=33), in four studies measurement was obtained from the non-dominant, and in 25 in both dominant and non-dominant. In one study HGS was measured using the preferred hand while the right hand was used in two other studies. In seven articles information about the chosen limb was absent. The position of the shoulder and the elbow was indicated in 46 and 62 studies, respectively, and the wrist position was described in 39 studies. The dynamometer's handle was referred in 37 articles, while the second handle position was mentioned in 16 articles. Encouragement during the procedure was reported in 26 studies, only nine studies indicated the data acquisition time and, 19 studies specified the rest time. Most studies (n=42) used the higher HGS value for the analysis. The ASHT protocol was mentioned in 11 studies, of which the 1981 protocol was referred twice and the 1992 protocol was cited in five studies. The others did not specify the ASHT protocol used. The Southampton protocol was alluded to in eight studies.

Table 1. Details and HGS protocols of the studies that diagnose sarcopenia, included in this systematic review.

Study details	Author Year of publication	Sample	Size	Age	Dynamometer	Repetitions	Hand	Posture	Shoulder position	Elbow position	Wrist position	Handle position	Encouragement	Acquisition time	Rest time	HGS analysis	Cut-off values
Cross-sectional study Toulouse and Lyon, France	Abellan van Kan *et al.* [52]	Community-dwelling older women from the EPIDOS cohort	3025	≥75	Martin vigorimeter, Medizin Tecnik, Tuttlingen, Germany	3	Dominant	Standing upright	Adducted	180º	-	Adjusted to a comfortable position	-	-	-	Higher value	Lowest 25%
Cross-sectional study Turkey	Akin *et al.*[53]	Community-dwelling older adults from KEHES Study	879	≥60	Takei TKK 5401 digital handgrip dynamometer, Takei, Niigata-City, Japan	3	Dominant	Standing upright	Adducted	90º	-	-	-	-	-	Higher value	Fried's criteria*
Cross-sectional study S. Paulo, Brazil	Alexandre Tda *et al.*[54]	Older urban population from the SABE Study	1149	≥60	Takei Kiki Kogyo TK 1201, Tokyo, Japan	2	Dominant	Sitting position	-	Resting on the table (forearms too)	Palms facing up	Adjusted to a comfortable position	-	-	1 min	Higher value	M: <30 kgf W: <20 kgf
Cross-sectional study Milan, Italy	Barichella *et al.* [55]	Consecutive patients from a specialised tertiary care center	364	≥65	DynEx digital hand dynamometer, Akern/MD Systems, Florence, Italy	3	Dominant	Sitting position	Adducted and neutrally rotated	90º Forearm neutral	Neutral	-	-	-	-	Mean value	M: <30 kgf W: <20 kg
Cross-sectional study The Netherlands	Bastiaanse *et al.* [56] (a)	Adults with intellectual disabilities from the HA-ID study	884	≥50	Jamar hand dynamometer, Sammons Preston Rolyan, USA	6	Both	Sitting position	Adducted and neutrally rotated	90º Forearm neutral	Neutral	2nd	-	-	1 min	Higher value	M: <30 kgf W: <20 kgf
Cross-sectional study Liège, Belgium	Beaudart *et al.* [57] (d)	Consecutive outpatients from an osteoporotic and geriatric department of a clinic and community-dwelling older adults	250	≥65	Hydraulic and pneumatic dynamometer Saehan Corporation, MSD Europe, Bvba, Belgium (calibrated)	6	Both	Sitting position	-	Forearms resting on the arms of the chair	Neutral position, over the end of the arm of the chair, thumb facing upwards	Adjusted so that the thumb is round one side of the handle and the four fingers are around the other side	Yes	-	-	Higher value	M: <30 kgf W: <20 kgf
Cross-sectional study Liège, Belgium	Beaudart *et al.* [58] (d)	Community-dwelling older adults from the SarcoPhAge study	534	≥65	Hydraulic dynamometer Saehan Corporation,	6	Both	Sitting position	-	Forearms resting on the arms of the chair	Neutral position, over the end of the arm of the chair, thumb facing upwards	Adjusted so that the thumb is round one side of the handle and the four	Yes	-	-	Higher value	M: <30 kgf W: <20 kgf

Table 1. (continued).

Study details	Author Year of publication	Sample	Size	Age	Dynamometer	Repetitions	Hand	Posture	Shoulder position	Elbow position	Wrist position	Handle position	Encouragement	Acquisition time	Rest time	HGS analysis	Cut-off values
					MSD Europe, Bvba, Belgium (calibrated)							fingers are around the other side						
Cross-sectional study The Netherlands	Bijlsma *et al.* [59]	Young and healthy older Europeans from the Leiden Longevity Study	654	38-82	Jamar hand dynamometer, Sammons Preston Inc, Bolingbrook, IL, USA	3	Dominant	Standing upright	Abducted	180º	-	Adjusted to hand size (middle phalanx rested on the inner handle)	-	-	-	Higher value	M: <30.3 kgf W: <19.3 kgf
Cross-sectional study Leiden The Netherlands; Jyvaskyla, Finland; Tartu, Estonia; Paris, France and Manchester, United Kingdom (UK)	Bijlsma *et al.* [60]	Middle to older participants from the MYOAGE study	452	18-30/ 69-81	Jamar hand dynamometer, Sammons Preston, Inc., Bolingbrook, IL, USA	6	Both	Standing upright	Abducted	180º	-	Adjusted to hand size	-	-	-	Higher value	**
Cross-sectional study Guelph, Ontario, Canada	Campbell *et al.* [61]	Assisted-living older adults	40	≥65	Vernier digital hand dynamometer and collected using LoggerPro software, Vernier, OR, USA; 60 Hz	6	Both	Sitting position	Adducted	90º	Dynamometer vertical	-	Yes	Self-selected pace	-	Higher value	M: <30 kgf W: <20 kgf
Prospective cohort study Northern Italy	Cerri *et al.* [62]	Consecutively admitted older inpatients of an Acute Geriatric Clinic, S. Gerardo University Hospital	103	≥65	Jamar hand dynamometer	3	Dominant	Sitting position	Adducted	90º Forearm neutral	Between 0 and 30º extension	-	-	-	1 min	Higher value	M: <30 kgf W: <20 kgf
Cross-sectional study Madrid and Barcelona, Spain	Cuesta *et al.*[63] (a)	Geriatric outpatients from the ELLI study	298	≥70	Jamar hand dynamometer	3	Dominant	Sitting position	Adducted and neutrally rotated	90º Forearm neutral	Neutral	2nd	-	-	1 min	Higher value	M: <30 kgf W: <20 kgf
Cross-sectional study	Fukuda *et al.* [64]	Caucasian ambulatory individuals	107	65-89	DHS-176 digital handgrip dynamometer,	3	Dominant	Standing upright	Adducted	90º	-	-	-	3 to 5 s	-	Mean value	**

Table 1. (continued).

Study details	Author Year of publication	Sample	Size	Age	Dynamometer	Repetitions	Hand	Posture	Shoulder position	Elbow position	Wrist position	Handle position	Encouragement	Acquisition time	Rest time	HGS analysis	Cut-off values
Midwestern United States of America (USA)					Detecto, Webb City, MO												
Cross-sectional study Spain	Garatachea *et al.* [65]	Caucasian community-dwelling older adults from two geriatric nursing homes	81	71–93	Smedley digital hand dynamometer, Sportstek,VIC, Australia	3	Non-dominant	Standing upright	Abducted	180º	-	Adjusted to hand size	-	-	30 to 60 s	Higher value	**
Prospective cohort study Spain	Gonzalez-Montalvo *et al.* [66]	Consecutive patients hospitalized for hip fracture in a public 1300-bed university hospital	509	≥65	Jamar hydraulic dynamometer, Sammons Preston, Bolingbrook, IL, USA	3	Dominant	Sitting position	-	Forearms resting on the arms of the chair	Neutral, over the end of the arm of the chair, thumb facing upwards	Adjusted so that the thumb is round one side of the handle and the four fingers are around the other side	Yes	-	-	Higher value	M: <30 kgf W: <20 kgf
Cross-sectional study USA	Gray *et al.* [67]	Community-dwelling older adults	43	≥65	Takei Scientific Instruments digital grip strength dynamometer, Niigata City, Japan	3	Preferred hand	Standing upright	-	Arms down by the side	Neutral	Interphalangeal joint of the index finger maintained at 90°	Yes	Minimum of 3 s	1 min	Higher value	**
Cross-sectional study Taipei, Taiwan	Han *et al.* [68]	Healthy volunteers from the Taiwan Fitness for Seniors Study	878	≥65	Baseline hydraulic dynamometer, Fabrication Enterprises Inc., Irvington, NY, USA	3	Dominant	-	Adducted	90º Forearm neutral	-	-	-	-	-	Higher value	M: <30 kgf W: <20 kgf
Cross-sectional study 6th district of Tehran, Iran	Hashemi *et al.* [69] [c]	Community-dwelling individuals from the SARIR study	300	≥55	Baseline pneumatic squeeze bulb dynamometer, Jamar, Inc. USA: c7489-02 Rolyan (calibrated)	6	Both	Sitting position	Adducted and neutrally rotated	90º Forearm neutral	Neutral	2nd	-	-	30 s	Mean value	Compared with normative data from Merkies *et al.*[70]

Table 1. (continued).

Study details	Author Year of publication	Sample	Size	Age	Dynamometer	Repetitions	Hand	Posture	Shoulder position	Elbow position	Wrist position	Handle position	Encouragement	Acquisition time	Rest time	HGS analysis	Cut-off values
Cross-sectional study Northern Bavaria, Germany	Kemmler *et al.* [71]	Community-dwelling German women from the FORMoSA study	1325	≥70	Jamar hand dynamometer, Sammons Preston Inc, Bollington, USA	2	Both	Standing upright	-	Arms down by the side	-	Adjusted to hand size	-	-	-	Higher value	W: <20 kgf
Prospective cohort study I-Lan County, Taiwan	Lee *et al.* [72]	Young healthy volunteers and older adults from the I-Lan Longitudinal Ageing Study	508	20-40/ ≥65	Smedley hand dynamometer, TTM, Tokyo, Japan	3	Dominant	Standing upright	Abducted	180º	-	-	-	-	-	Higher value	M: <22.4 kgf W: <14.3 kgf
Cross-sectional study Korea	Lee *et al.* [73] (b)	Ambulatory women from the University Hospital Menopause Clinic	196	≥65	Jamar hand dynamometer, Sammons Preston Inc., Bolingbrook, IL, USA	3	Dominant	Sitting position	Adducted and neutrally rotated	90º Forearm neutral	Between 0 and 30° dorsiflexion	2nd	-	-	-	Mean value	W: <18 kgf
Cross-sectional study Tamana, Japan	Maeda *et al.* [74]	Patients admitted to acute phase wards from Tamana Regional Health Medical Center	224	≥65	Smedley hand dynamometer, TTM, Tokyo, Japan	2	Dominant	Standing or sitting position, depending on their ability	-	-	-	-	-	-	-	Higher value	M: <26 kgf W: <18 kgf
Cross-sectional study Salvador, Bahia, Brazil	Martinez *et al.* [75]	Hospitalised elderly patients in a multi-specialty hospital	110	≥60	Saehan hydraulic dynamometer, Saehan Corporation, 973, Yangdeok-Dong, Masan 630–728, Korea	3	-	Sitting position	-	90º	-	-	-	-	1 min	Higher value	M: <30 kgf W: <20 kgf
Cross-sectional study Guelph, Canada	McIntosh *et al.* [76]	Community-dwelling older adults	85	≥65	Vernier digital hand dynamometer and collected using LoggerPro software, Vernier, OR, USA; 60 Hz	6	Both	Standing upright	Adducted	90º	-	-	Yes	-	-	Higher value	M: <30 kgf W: <20 kgf
Prospective cohort study	Mijnarends *et al.* [77]	Community-dwelling older adults from the AGES-Reykjavik Study	2309	66–93	Good Strength software, Metitur, Finland	3	Dominant	Sitting position	Relaxed	90º, neutral	Attached by belts to a strain-	-	Yes	4-5 s	30 s	-	M: <30 kgf W: <20 kgf

Table 1. (continued).

Study details	Author Year of publication	Sample	Size	Age	Dynamometer	Repetitions	Hand	Posture	Shoulder position	Elbow position	Wrist position	Handle position	Encouragement	Acquisition time	Rest time	HGS analysis	Cut-off values
Reykjavik, Iceland											gauge system, thumb up						
Prospective cohort study Seongnam, Korea	Moon *et al.* [78]	Community-dwelling older adults from the Korean Longitudinal Study on Health and Aging	297	≥65	Jamar hydraulic hand dynamometer, Sammons Preston, Bolingbrook, IL, USA	2	Dominant	Sitting position	Adducted	90º Forearm neutral	-	Adjusted to a comfortable position	-	-	1 min	Mean value	M: <26 kgf W: <16 kgf
Cross-sectional study London, Ontario, Canada	Morat *et al.* [79]	Healthy and independent living older adults from the Canadian Centre for Activity and Aging	24	≥65	Smedley hand dynamometer, TTM, Tokyo, 100 kg	6	Both	Standing upright	-	90º Forearm neutral	Neutral	-	-	-		Higher value	M: <30 kgf W: <20 kgf
Cross-sectional study Goiâna, Brazil	Pagotto *et al.* [80] (b)	Community-dwelling older adults	132	≥60	CROWN hydraulic dynamometer	2	Dominant	Sitting position	Adducted and neutrally rotated	90º	Extended between 0 and 30º dorsiflexion	2nd	-	6 s	1 min	Both values	M: <30 kgf W: <20 kgf and Fried's criteria*
Cross-sectional study UK	Patel *et al.* [81] (d)	Community-dwelling older adults from the Hertfordshire Sarcopenia Study	1890	68-77	Jamar hand dynamometer	6	Both	Sitting position	-	Forearms resting on the arms of the chair	Neutral, over the end of the arm of the chair, thumb facing upwards	Adjusted so that the thumb is round one side of the handle and the four fingers are around the other side	Yes	-	-	Higher value	M: <30 kgf W: <20 kgf
Cross-sectional study Pavia, Italy	Rondanelli *et al.* [82]	Older adults consecutively admitted to a physical medicine and rehabilitation division, in Santa Margherita institute	159	≥65	Jamar 5030J1 hydraulic hand dynamometer, Sammons Preston Rolyan, Bolingbrook, IL,USA	4	-	Sitting position	-	Comfortable arm position	-	-	Yes	5 s	1 min	Mean value of the last three efforts	**
Prospective cohort study Barcelona, Spain	Sanchez-Rodriguez *et al.* [83] (d)	Consecutive hospitalised patients from a postacute care geriatric unit	100	≥70	Jamar hand dynamometer, Nottinghamshire , UK	3	-	Sitting position	-	Forearms resting on the arms of the chair	Neutral, over the end of the arm of the chair, thumb facing upwards	Adjusted so that the thumb is round one side of the handle and the four fingers are	Yes	-	-	Higher value	Compared with normative data from Luna-Heredia *et al.* [16]

Table 1. (continued).

Study details	Author Year of publication	Sample	Size	Age	Dynamometer	Repetitions	Hand	Posture	Shoulder position	Elbow position	Wrist position	Handle position	Encouragement	Acquisition time	Rest time	HGS analysis	Cut-off values
												around the other side					
Retrospective cohort study Kuopio, Eastern Finland	Sjoblom *et al.* (84)	Finnish postmenopausal women from the OSTPRE study	590	65–72	Pneumatic hand-held dynamometer Martin Vigorimeter, Germany	3	-	Sitting position	-	-	-	-	-	-	-	Mean value	Lowest 25%
Cross-sectional study Porto, Portugal	Sousa *et al.* (85) (b)	Hospitalised adult patients from medical and surgical wards in a general and teaching hospital	608	≥18	Jamar hydraulic hand dynamometer, Sammons Preston, Bolingbrook, IL, USA (calibrated)	3	Non-dominant	Sitting position	Adducted and neutrally rotated	90º	Between 0 and 30° dorsiflexion	2nd	-	-	1 min	Higher value	M: <30 kgf W: <20 kgf
Cross-sectional study Berlin, Germany	Spira *et al.* (86)	Community-dwelling older adults from the BASE-II study	1405	60-80	Smedley hand dynamometer, Scandidact, Denmark	6	Both	Standing upright	Adducted and neutrally rotated	90º Forearm neutral	Neutral	-	-	-	-	Higher value	Fried's criteria*
Cross-sectional study Manchester, UK and Leuven, Belgium	Verschuere *et al.* (87) (d)	Men from the European Male Ageing Study	679	40-79	Jamar hand dynamometer, TEC Inc., Clifton, NJ	6	Both	Sitting position	-	Forearms resting on the arms of the chair	Neutral, over the end of the arm of the chair, thumb facing upwards	Adjusted so that the thumb is round one side of the handle and the four fingers are around the other side	Yes	-	-	Higher value	Fried's criteria*
Multicentre cohort study Italy	Vetrano *et al.* (88)	Older adults admitted to acute care wards, of seven Italian hospitals, from the CRIME study	770	≥65	North Coast hydraulic hand dynamometer, North Coast Medical Inc, Morgan Hill, CA	4	Both	Sitting position or lying at 30º in bed (when unable to sit)	-	90º or with elbows supported	Neutral	-	-	-	-	Higher value	M: <30 kgf W: <20 kgf
Cohort study Ankara, Turkey	Yalcin *et al.* (89)	Residents in Seyranbagları Nursing Home and Rehabilitation Center	141	≥65	Takei Scientific Instruments, Niigata, Japan	2	Dominant	-	Abducted (30º)	180º	Palm perpendicular to the shoulder line	-	-	5 s	-	Mean value	M: <30 kgf W: <20 kgf

Table 1. (continued).

Study details	Author Year of publication	Sample	Size	Age	Dynamometer	Repetitions	Hand	Posture	Shoulder position	Elbow position	Wrist position	Handle position	Encouragement	Acquisition time	Rest time	HGS analysis	Cut-off values
Cross-sectional study Obu, Aichi, Japan	Yoshida *et al.* [90]	Community-dwelling older adults from Obu Study of Health Promotion for the Elderly	4811	≥65	Grip-D hand dynamometer, Takei, Niigata, Japan	1	Dominant	Standing upright	-	-	-	-	-	-	-	Single value	M: <28.8 kgf W: <18.2 kgf
Cohort study North west regions and Western suburbs of Adelaide, Australia	Yu *et al.* [91]	Community-dwelling individuals, from the CASA, FAMAS and NWAHS studies	1123	≥18	Lafayette Instrument Company, IN, USA (CASA and NWAHS), Smedley, Chicago, IL (FAMAS)	3	Dominant	Sitting position	-	Arm supported by a horizontal surface	-	-	-	-	-	Mean value	M: <30 kgf W: <20 kgf

S, Seconds; Min, Minutes; M, Men; W, Women.
[(a)] Study cited the ASHT 1981 protocol.
[(b)] Study cited the ASHT 1992 protocol.
[(c)] Study cited the ASHT protocol, without specifying which protocol year was used.
[(d)] Study cited the Southampton protocol.
* Fried's criteria (Cut-off points for handgrip strength) Men: ≤29 kgf (BMI ≤ 24 kg/m^2); ≤30 kgf (BMI 24.1–26 kg/m^2); ≤30 kgf (BMI 26.1–28 kg/m^2); ≤32 kgf (BMI > 28 kg/m^2) / Women: ≤17 kgf (BMI ≤ 23 kg/m^2); ≤17.3 kgf (BMI 23.1–26 kg/m^2); ≤18 kgf (BMI 26.1–29 kg/m^2); ≤21 kgf (BMI > 29 kg/m^2).
** Not defined due to the type of analysis conducted by the study.

Table 2. Details and HGS protocols of the studies that diagnose frailty, included in this systematic review.

Study details	Author Year of publication	Sample	Size	Age	Dynamometer	Repetitions	Hand	Posture	Shoulder position	Elbow position	Wrist position	Handle position	Encouragement	Acquisition time	Rest time	HGS analysis	Cut-off values
Multicentric prospective cohort study Burgos, Albacete and Madrid, Spain	Abizanda *et al.* [92] (c)	Institutionalised older adults, in four nursing homes from the ACTIVNES study	91	≥70	Jamar hand dynamometer, Sammons Preston Rolyan, Bolingbrook, IL	3	-	Sitting position	Adducted and neutrally rotated	90º Forearm neutral	Neutral	2nd	-	-	-	Higher value	Fried's criteria*
Cross-sectional study Alexandria, Egypt	Abou-Raya *et al.* [93]	Consecutive patients with congestive heart failure	126	≥65	Jamar hand dynamometer	2	Dominant	Sitting position	Adducted	90º	Between 0 and 30º dorsiflexion and 0 and 15º ulnar deviation	2nd	Yes	-	-	-	M: ≤21 kgf W: ≤14 kgf
Cross-sectional study USA	Bandeen-Roche *et al.* [94]	Older adults from the 2011 baseline of the National Health and Aging Trends Study	7439	≥65	Jamar digital hand dynamometer	2	Dominant	Sitting position	Adducted	90º	Dynamometer or forearm resting on the table	2nd	Yes	-	-	Higher value	Lowest 20% within 8 sex and BMI categories
Cross-sectional study The Netherlands	Bastiaanse *et al.* [56] (a)	Adults with intellectual disabilities from the HA-ID study	884	≥50	Jamar hand dynamometer, Sammons Preston Rolyan, USA	6	Both	Sitting position	Adducted and neutrally rotated	90º Forearm neutral	Neutral	2nd	-	-	1 min	Higher value	Fried's criteria*
Cross-sectional study Liège, Belgium	Beaudart *et al.* [58] (d)	Community-dwelling older adults from the SarcoPhAge study	534	≥65	Hydraulic dynamometer Saehan Corporation, MSD Europe, Bvba, Belgium (calibrated)	6	Both	Sitting position	-	Forearms resting on the arms of the chair	Neutral position, over the end of the arm of the chair, thumb facing upwards	Adjusted so that the thumb is round one side of the handle and the four fingers are around the other side	Yes	-	-	Higher value	Fried's criteria*
Cross-sectional study England	Buttery *et al.* [95]	Consecutively patients from three elderly care wards of an urban teaching hospital	44	67-91	Jamar isometric hand dynamometer, Sammons Preston, Bolingbrook, Illinois, USA	6	Both	Sitting position	Adducted and neutrally rotated	90º	Between 0 and 30º dorsiflexion and 0 and 15º ulnar deviation	2nd	Yes	-	-	Higher value	Compared with normative data from Bohannon *et al.* [96]
Cross-sectional study Germany	Buttery *et al.* [97]	Community-dwelling older adults from the DEGS1	1843	65-79	Smedley hand dynamometer, Scandidact,	4	Both	Standing upright	-	-	-	-	-	-	-	Higher value	Fried's criteria*

Table 2. (continued).

Study details	Author Year of publication	Sample	Size	Age	Dynamometer	Repetitions	Hand	Posture	Shoulder position	Elbow position	Wrist position	Handle position	Encouragement	Acquisition time	Rest time	HGS analysis	Cut-off values
					Denmark, 100 kg												
Cross-sectional study Urban administrative section of Taipei, Taiwan	Chang *et al.* [98]	Community-dwelling older adults	234	≥65	Handgrip dynamometer, Fabrication Enterprises, Inc., Irvington, NY	-	Both	-	Adducted	90º	-	-	Yes	-	-	-	Lowest 20% at baseline
Cross-sectional study Saint Bruno,Québec, Canada and Santa Cruz, Rio Grande do Norte, Brazil	Da Camara *et al.* [99]	Community-dwelling older adults	124	65-74	Jamar hand dynamometer, Jamar, Irvington, NY, USA	3	-	Sitting position	Adducted and neutrally rotated	90º Forearm neutral	Neutral	Adjusted to a comfortable position between the 2nd or 3th handle	-	-	1 min	Mean value	Fried's criteria*
Cross-sectional study Chicago, USA	Danilovich *et al.* [100] (b)	Convenience sample of older adults	42	≥65	Jamar hand hydraulic dynamometer	4	Both	Sitting position	Adducted and neutrally rotated	90º	Between 0 and 30° dorsiflexion	2nd	-	-	-	Higher value	M: <30 kgf W: <20 kgf
Cross-sectional study Denmark	Dato *et al.* [101]	Community-dwelling older adults	3719	≥70	Smedley hand dynamometer TTM	3	Dominant	Sitting position	Adducted	-	-	-	-	-	-	Higher value	**
Cross-sectional study The Netherlands	Evenhuis *et al.* [102]	Individuals with borderline to profound intellectual disabilities of three care provider services from the HA-ID Study	848	≥50	Jamar hand dynamometer, 5030J1, Sammons Preston Rolyan, Dolgeville, NY	6	Both	Sitting position	Adducted and neutrally rotated	90º	Between 0 and 30º dorsiflexion and 0 and 15º ulnar deviation	2nd	Yes	-	-	-	Fried's criteria*
Prospective cohort study USA	Fried *et al.* [10]	Community-dwelling older adults from the Cardiovascular Health study	5317	≥65	Jamar hand dynamometer	3	Dominant	Sitting position	-	90º	-	2nd	Yes	-	-	Mean value	Fried's criteria*
Cross-sectional study The Kolpino district, St. Petersburg, Russia	Gurina *et al.* [103]	Community-dwelling older adults from the ''Crystal'' Study	611	≥65	Carpal dynamometer (DK-50, Nizhni Tagil, Russian Federation)	6	Both	Standing upright	Arms hanging down at the sides	-	-	-	-	-	30 s	Mean value	Lowest 20%, adjusted for sex and BMI

Table 2. (continued).

Study details	Author Year of publication	Sample	Size	Age	Dynamometer	Repetitions	Hand	Posture	Shoulder position	Elbow position	Wrist position	Handle position	Encouragement	Acquisition time	Rest time	HGS analysis	Cut-off values
Cross-sectional study Vienna, Austria.	Haider *et al.* (104) (d)	Pre-frail and frail community-dwelling older adults	83	≥65	Jamar hydraulic hand dynamometer, Lafayette, Louisiana	6	Both	Sitting position	-	Forearms resting on the arms of the chair	Neutral, over the end of the arm of the chair, thumb facing upwards	Adjusted so that the thumb is round one side of the handle and the four fingers are around the other side	Yes	-	1 min	Higher value	**
Cross-sectional and prospective cohort study The Netherlands	Hoogendijk *et al.* (105)	Older adults from the Longitudinal Aging Study Amsterdam	1115	≥65	Takei TKK 5001, Takei Scientific Instruments, Tokyo, Japan	4	Both	Standing upright or sitting position when the participant was not able to stand	-	180º	-	-	-	-	-	Sum of the highest values of each hand	Fried's criteria*
Cross-sectional study Seoul, Korea	Kang *et al.* (106)	Female outpatients from the department of family medicine at Kangbuk Samsung Hospital	121	≥65	Lavisen electronic hand grip dynamometer KS 301, Lavisen Co. Ltd., Namyangju, Korea	-	Right	-	Abducted	180º	-	Medial phalange of the third finger perpendicular to the handle	-	-	-	-	≤14.5 kgf
Cross-sectional study Seoul and Gyeonggi province, Korea	Kim *et al.* (107)	Older adults who registered at six senior welfare centers	486	≥65	Jamar hydraulic hand dynamometer; Sammons Preston, Bolingbrook, IL, USA	2	-	-	Abducted	180º	-	-	-	-	-	Higher value	Lowest 20%, adjusted for sex and BMI
Cross-sectional study Beaver Dam, Wisconsin	Klein *et al.* (108)	Adults and older adults from the Beaver Dam Eye Study	2962	≥53	Lafayette hand dynamometer, Model 78010, Lafayette Instrument Company, Lafayette, Indiana	4	Both	Standing upright	Abducted	180º	-	Adjusted to hand size	-	-	-	Mean value for the dominant hand	M: ≤ 34.5 kgf W: ≤ 18.5 kgf

Table 2. (continued).

Study details	Author Year of publication	Sample	Size	Age	Dynamometer	Repetitions	Hand	Posture	Shoulder position	Elbow position	Wrist position	Handle position	Encouragement	Acquisition time	Rest time	HGS analysis	Cut-off values
Randomised controlled trial Itabashi Ward, Tokyo, Japan	Kwon *et al.* [109]	Pre-frail community-dwelling older women	89	≥70	Smedley hand dynamometer, Yagami, Tokyo, Japan	2	Dominant	Standing upright	Arms hanging naturally at their sides	-	-	-	-	-	-	Higher value	W: ≤23 kgf at baseline
Cohort study Korea	Lee *et al.* [110]	Community-dwelling older adults from the Living profiles of Older People Survey	11844	≥65	Tanita, No. 6103, Japan	4	Both	-	Elbow by the side of the body	90º	-	-	-	-	-	Higher value	Lowest 20%, adjusted for sex and BMI M: ≤28 kgf (BMI ≤ 24.9 kg/m^2); ≤30 kgf (BMI 25.0-27.2 kg/m^2); ≤32 kgf (BMI > 27.2 kg/m^2)
Prospective cohort study Boston, Massachusetts, USA	Mohr *et al.* [111]	Community-dwelling men from the Massachusetts Male Aging study	646	50-86	Jamar hydraulic hand Dynamometer, Sammons Preston, Bolingbrook, IL	2	Dominant	Sitting position	Arms at their sides	90º Forearm neutral	Neutral	Adjusted to hand size	-	3 s	1 min	Higher value	
Prospective cohort study Barcelona, Spain	Mora *et al.* [112]	Community-dwelling women from the Mataró Ageing Study	110	≥70	Jamar hand dynamometer	3	Non-dominant	Sitting position	Adducted and neutrally rotated	90º Forearm neutral	Between 0 and 30º dorsiflexion and between 0 and 15º ulnar deviation	-	Yes	-	-	Mean value	Fried's criteria*
Cross-sectional study Belo Horizonte, Brazil	Moreira *et al.* [113] (b)	Community-dwelling older women with type 2 diabetes	99	65-89	Jamar hand dynamometer	3	Dominant	Sitting position	Adducted and neutrally rotated	90º Forearm neutral	Between 0 and 30° dorsiflexion	2nd	Yes	-	-	Mean value	Fried's criteria*
Double-blind, randomised, controlled trial Rotterdam, The Netherlands	Muller *et al.* [114]	Community-dwelling older men	100	≥70	Jamar hand dynamometer, Horsham, PA	3	Non-dominant	Sitting position	Adducted and neutrally rotated	90º Forearm neutral	Between 0 and 30º dorsiflexion and between 0 and 15º ulnar deviation	-	Yes	-	-	Mean value	**
Cross-sectional study Dimantina, Brasil	Parentoni *et al.* [115] (c)	Convenience sample of older women	106	≥65	Saehan dynamometer, SH5001 (calibrated)	3	Dominant	Sitting position	Adducted and neutrally rotated	90º Forearm neutral	Neutral	2nd	Yes	-	1 min	Mean value	Fried's criteria*
Cross-sectional study	Passarino *et al.* [116]	Community-dwelling older adults	369	65-85	Smedley hand dynamometer TTM	3	Dominant	Sitting position	Adducted	-	-	-	-	-	-	Higher value	**

Table 2. (continued).

Study details	Author Year of publication	Sample	Size	Age	Dynamometer	Repetitions	Hand	Posture	Shoulder position	Elbow position	Wrist position	Handle position	Encouragement	Acquisition time	Rest time	HGS analysis	Cut-off values
Calabria district, Italy																	
Cohort study Texas, New Mexico, Colorado, Arizona and California, USA	Samper-Ternent *et al.* (117)	Non-institutionalised Mexican Americans from the Hispanic Established Population for the Epidemiological Study of the Elderly	1370	≥65	Jamar hydraulic hand dynamometer, Model 5030J1, J.A. Preston Corp., Clifton, NJ	2	Dominant	Sitting position	-	Resting on the table	Palm facing up	Adjusted to a comfortable position	Yes	-	-	Higher value	Lowest 20%, adjusted for sex and BMI
Cohort study United States and Denmark	Sanders *et al.* (118)	Community-dwelling individuals from The Long Life Family Study	4875	32–105	Jamar hydraulic hand Dynamometer, Lafayette, IN	2	Dominant	Sitting position	-	-	-	-	-	-	-	Mean value	Lowest 25%, adjusted for sex and BMI
Cross-sectional study Saarland, Germany	Saum *et al.* (119) (d)	Community-dwelling adults from ESTHER study	3112	≥59	Jamar hand dynamometer, Lafayette Instrument Company, Lafayette, IN	3	Dominant	Sitting position	-	Forearm resting on the arm of the chair	Neutral, over the end of the arm of the chair, thumb facing upwards	Adjusted so that the thumb is round one side of the handle and the four fingers are around the other side	Yes	-	-	Higher value	M: <30 kgf W: <20 kgf and Fried's criteria*
Cross-sectional study Lausanne, Switzerland Randomised, Double-Blind, Placebo-Controlled Trial The Netherlands	Seematter-Bagnoud *et al.* (120)	Community-dwelling older adults from the Lc65+ study	861	65-70	Baseline hydraulic dynamometer	3	Right	Sitting position	Adducted and neutrally rotated	90º	Between 0 and 30º dorsiflexion and 0 and 15º ulnar deviation	2nd	Yes	-	-	Higher value	Fried's criteria*
	Tieland *et al.* (121)	Frail older adults	62	≥65	Jamar hand dynamometer, Jackson, MI, USA	6	Both	Sitting position	-	90º	-	-	-	-	-	-	Fried's criteria*
Cross-sectional study Portugal	Vieira *et al.* (122) (c)	Institutionalised older adults from three urban residential homes	50	68–99	Jamar hydraulic hand dynamometer, J00105	3	Dominant	Sitting position	Adducted and in extension	90º Forearm neutral	Extended between 0 and 30º	.	-	10 s	1 min	-	M:<30 kgf W: <18 kgf
Cross-sectional study Baltimore, Maryland, USA	Walston *et al.* (123)	Community-dwelling women from the Women's Health and Aging Studies I and II	463	70-79	Jamar hand dynamometer, model BK-74978, Fred Sammons, Inc., Burr Ridge, IL	6	Both	Sitting position	Adducted	90º	-	.	Yes	-	-	Higher value of the non-dominant hand	Fried's criteria*

Table 2. (continued).

Study details	Author Year of publication	Sample	Size	Age	Dynamometer	Repetitions	Hand	Posture	Shoulder position	Elbow position	Wrist position	Handle position	Encouragement	Acquisition time	Rest time	HGS analysis	Cut-off values
Cross-sectional study Southern Taiwan	Wu *et al.* [124]	Community-dwelling older adults and outpatients from a hospital-based outpatient clinic	90	≥65	Jamar hand dynamometer, Sammons Preston, Bolingbrook, IL	-	Dominant	Sitting position	-	-	-	-	-	-	-	-	Fried's criteria*

S, Seconds; Min, Minutes; M, Men; W, Women.
[a] Study cited the ASHT 1981 protocol.
[b] Study cited the ASHT 1992 protocol.
[c] Study cited the ASHT protocol, without specifying which protocol year was used.
[d] Study cited the Southampton protocol.
* Fried's criteria (Cut-off points for handgrip strength) Men: ≤29 kgf (BMI ≤ 24 kg/m^2); ≤30 kgf (BMI 24.1–26 kg/m^2); ≤30 kgf (BMI 26.1–28 kg/m^2); ≤32 kgf (BMI > 28 kg/m^2) / Women: ≤17 kgf (BMI ≤ 23 kg/m^2); ≤17.3 kgf (BMI 23.1–26 kg/m^2); ≤18 kgf (BMI 26.1–29 kg/m^2); ≤21 kgf (BMI > 29 kg/m^2).
** Not defined due to the type of analysis conducted by the study.

Discussion

The aim of this systematic review is to identify the HGS protocols used to diagnose sarcopenia and frailty. The heterogeneity in HGS protocols, the wide variability in the criteria used to identify either sarcopenia and frailty and the different inclusion and exclusion criteria in the evaluated studies is an issue in this research field. Indeed, these differences hinder comparison between the studies and hamper progress of the study of these conditions.

We observed that most studies which diagnose these conditions did not mention the protocol used in the measurement of HGS or did not include a full description of it. Although the ASHT and Roberts et al. proposed standardised protocols, the results of the present review showed high heterogeneity of the chosen procedure. Studies concerning sarcopenia and frailty did not differ in standardised protocols used. Plus, the complete description of the procedure is lacking in most studies. In trying to overcome this problem, some authors raise an additional difficulty when they cite the previous publication of their study protocol.

The parameters regarding the HGS procedure that were presented in the Tables 1 and 2 and its influence in HGS values were evaluated in several studies. As shown below, in spite of some results being similar between the studies, others present contradictory results.

Dynamometer

The ASHT recommends a calibrated Jamar dynamometer in the second handle position for the measurement of HGS [24-26]. While the Southampton protocol suggested the handle should be adjusted so that the thumb is round one side of the handle and the four fingers are around the other side and the instrument should feel comfortable in the hand [27].

The Jamar hydraulic dynamometer presents higher intra and inter-individual reliability [17]. Despite this being referred to as the most widely used and tested dynamometer [27], this review shows a great variability in the dynamometers used, regardless of Jamar's predominance. Present results exhibit a great number of studies which failed to describe if the instruments were properly calibrated for the measurements. A correctly calibrated dynamometer is highly reliable. Nevertheless, it should be recalibrated regularly [29].

Other dynamometers, such as Smedley dynamometer (mechanical) and Martin vigorimeter (pneumatic), measure HGS by a different mechanism [30]. Concerning the Smedley dynamometer, it has shown excellent results regarding its laboratory tested accuracy but, when applied among older adults, it did not produce comparable results to the Jamar hydraulic [31]. Low agreement between Jamar dynamometer and Takei dynamometer was observed [32]. Otherwise, the results of the comparison between the Jamar dynamometer and the Martin vigorimeter in a healthy elderly population, indicate a very high correlation between the two HGS data values [33]. When the hydraulic dynamometers, Baseline and Saehan, were tested they shown to be valid, reliable and comparable to the Jamar dynamometer [34,35].

Hand

A summary of the studies comparing HGS in dominant and non-dominant limbs, revealed that it is reasonable to expect greater grip strength in the dominant upper extremity in right-handed individuals [36]. Yet, it is important to consider that the difference between sides varies widely among studied samples and in a significant proportion of individuals the opposite is observed [37,38].

Posture and arm position (shoulder, elbow and wrist)

Most studies revised here, a standing or sitting position was selected. In some cases, the position was adapted to the individual's physical function. The influence of the standing versus sitting posture in HGS values was evaluated and no significant differences were found by several studies [39-41]. When comparing standing versus sitting position, Balogun et al. observed significant differences only between sitting with elbow at 90 degrees and standing with elbow at full extension [20]. These results were in agreement with one study that showed that grip strength is significantly greater when measured with the elbow in the fully extended position [42]. Additionally, even though the posture alone did not significantly influence HGS values, combined with the elbow position it could indicate the presence of an interaction between the elbow position at 180 degrees and a standing position. On the other hand, other results showed a stronger grip strength measurement in the 90 degrees elbow flexed position than in the fully extended position [41,43].

Su et al. also evaluated different shoulder and elbow positions. They observed that when the shoulder was positioned at 180 degrees of flexion with elbow in full extension

the highest mean grip strength measurement was recorded; whereas the position of 90 degrees elbow flexion with shoulder in zero degrees of flexion produced the lowest grip strength score [44]. While, De et al. did not find significant differences when shoulder joints varied between 90 and 180 degrees [41].

Regarding the wrist position, one study suggested that a minimum of 25 degrees of wrist extension was required for optimum grip strength [21]. Later, it was shown that HGS measured with wrist in a neutral position was significantly higher than that in the wrist ulnar deviation [41] and, in another study that the mean grip strength scores were higher for all the tested six positions when wrist was positioned in neutral than in extension position [45].

Handle position

Some researchers opted for HGS measurement in a standard handle position. However, in others, researchers adapted the handle to hand size or to a comfortable position for the individual. It was suggested that hand size and optimal grip span only correlated in women [46]. Other studies results have shown that the second handle position was the best position for the majority of the participants. Therefore, the authors suggested the use of a standard handle position (second setting) over multiple different positions [23,47]. This would provide accurate results and increase the comparability of the results [47].

Repetitions

Mathiowetz et al. suggested that the mean of three trials is a more accurate measure than one trial or even the highest score of three trials [48], while the latter was the most widely adopted by the studies included in this systematic review. In contrast, it was suggested that muscle fatigability might occur with each attempt and one trial is sufficient for the measurement of grip strength [49]. In another study, it was observed that the mean values of grip strength generated for each method of grip strength testing (one trial, the mean of three trials, and the best of three trials) produced comparable results [50].

Encouragement

To our knowledge, only one research described the effects of the encouragement during HGS measurement. It showed that instruction, verbal encouragement, and visual feedback had critical effects on the handgrip strength and, therefore it should be

mentioned in the articles [51]. More than half of the articles included here did not provide a full description of if and how the encouragement was made during the trials.

Analysis

As described above, most studies used the higher value for the HGS analysis, however other forms of HGS values chosen by the authors, such as the mean or the sum of the values obtained during the measurements was also observed. Hence, the diagnosis of sarcopenia and frailty between the studies is even less comparable.

Comparison of the protocols

Although the most recent ASHT protocol presents more details regarding the HGS measurement, this protocol has not been adopted by any of the studies included in this revision. Almost every aspect was described in the protocol, making the variations between the studies almost impossible, but also increasing the complexity of the measurement, and therefore the duration of the procedure. Despite the fact that the Southampton protocol referred to all the aforementioned aspects in Table 3, it did not describe in detail the joints position, which could lead to variations in HGS values between the studies.

Table 3. Recent HGS protocols proposed.

	ASHT protocol – 2015 [26]	Southampton protocol – 2011 [27]
Posture	Subject seated in a chair without arm rests, with feet fully resting on the floor, hips as far back in the chair as possible, and the hips and knees positioned at approximately 90°	Subject seated (same chair for every measurement)
Arm position		Forearms rested on the arms of the chair
-Shoulder	Adducted and neutrally rotated	-
-Elbow	Flexed to 90°, the forearm should be in midprone (neutral)	-
-Wrist	Between 15-30° of extension (dorsiflexion) and 0-15° of ulnar deviation	Just over the end of the arm of the chair, in a neutral position, thumb facing upwards
Trials	Three trials	Three trials on each side, alternating sides (start with the right hand)
Dynamometer		
-Model	Jamar dynamometer	Jamar hydraulic hand dynamometer
-Calibration	Yes	-
-Handle position	2nd	Thumb is round one side of the handle and the four fingers are around the other side
Acquisition time	At least 3 seconds	-
Rest time	At least 15 seconds	-
Instructions	"This test will tell me your maximum grip strength. When I say go, grip as hard as you can until I say stop. Before each trial, I will ask you 'Are you ready?' and then tell you 'Go'. Stop immediately if you experience any unusual pain or discomfort at any point during testing. Do you have any questions? Are you ready? Go!". "Harder... harder... harder...Relax"	'I want you to squeeze as hard as you can for as long as you can until I say stop. squeeze, squeeze, squeeze, stop' (when the needle stops rising)
HGS analysis	Mean of three trials	Maximal grip score from all six trials

Due to the great variability in the studies concerning sarcopenia and frailty, namely in the inclusion and exclusion criteria, and in the definition and procedures used to identify these conditions, it is difficult to evaluate the impact of each parameter of the procedure in HGS values. Therefore, to diminish the heterogeneity observed in the studies, the most recent ASHT protocol should be adopted. Variations in the procedure are strongly discouraged, however when it is impossible to fully implement this protocol, namely due to the individuals' health conditions, any variation should be reported.

Main topics

The mixed results above discussed reinforce the need to standardise HGS measurement. The difference between the protocols can influence the HGS results and, consequently, affect the comparability between the studies. A common approach would

be not only important for research purposes but also for clinical practice. For both sarcopenia and frailty, the major studies that suggested a diagnosis using HGS did not recommend a protocol for its measurement, neither referred to the protocols used to estimate the outlined cut-off points. There is a necessity to include guidelines concerning a standardised protocol in the consensus made by European and International societies. That will allow the results of the studies to be more comparable and more suitable for the application in clinical practice.

In order to describe with precision the handgrip strength protocol used, researchers should always make reference to which protocol was adopted (when applied). For a complete description of the protocol, we suggest that all the points addressed in Table 3 should be mentioned in the methods section of the articles, and therefore include the description of the posture, arm position (including shoulder, elbow and wrist positions), number of trials, characteristics of the dynamometer (brand, model, resolution, calibration and handle position), acquisition and rest time, the applied instructions and the HGS values used in the analysis. The cut-off points to identify low HGS for sarcopenia or frailty should also be stated. Additionally, deviations to the protocol must be described.

Strengths and limitations

Some strengths of this systematic review can be highlighted. Besides the original search, we additionally handsearched the references of the included articles for a broader research. Plus, for our knowledge there is no other review of literature that comprises a detailed description of the methods of HGS in observational and experimental studies about sarcopenia and frailty in older adults and that considered the most recent protocols proposed for HGS measurement.

This article also had a few limitations. Data was only searched in two databases (Pubmed and Web of Science) and the inclusion of other databases could increase the range of articles found. In addition, we identified three articles in which we could not locate the references made for the full procedure. The focus of the present revision was to gather information regarding HGS methods, hence, we have not evaluated the methodologic quality of the included studies. In our opinion, we do not consider that the limitations would substantially alter our results.

Conclusion

In conclusion, the majority of the studies included did not describe a complete procedure of HGS measurement. The high heterogeneity between the protocols used, in sarcopenia and frailty related studies, create an enormous difficulty in drawing comparative conclusions among them. Even though, there are suggested standardised procedures, present results reinforce the need to uniform the procedure not only in the studies that diagnose these conditions but also in studies which present normative data. Further studies should evaluate which factors contribute to higher HGS values. Meanwhile, we suggest the adoption of the most recent ASHT protocol. In our opinion, this is the most detailed one and, thus, it is less probable to generate differences in HGS values between the studies. Nevertheless, we embrace that the complexity of this protocol may increase the difficulty in its application, especially in clinical practice. Future studies of these issues should include a complete description of the procedure, mentioning the deviations to the protocol.

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4.2.

Which is the best alternative to estimate muscle mass for sarcopenia diagnosis when DXA is unavailable?

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Abstract

Background: Dual-energy X-ray absorptiometry (DXA) is widely adopted to estimate muscle mass for research, but for daily practice is only available in a limited number of facilities.

Aim: To elucidate if it is anthropometry or bioelectrical impedance analysis (BIA) the method more concordant with DXA in estimating muscle mass for sarcopenia diagnosis among older adults, and to investigate the impact of several cut-off points in sarcopenia frequency.

Methods: 159 older adults (≥65 years) were included in a cross-sectional analysis. Sarcopenia was identified using the 2018 EWGSOP2 definition, plus previous definitions for muscle mass. Estimation of muscle mass by DXA (appendicular skeletal muscle mass (ASM) and ASM/height^2), by BIA (skeletal muscle mass/height^2 (SMM/height^2) and skeletal muscle mass index (SMI)), and anthropometry (calf and mid-arm muscle circumferences (CC and MAMC, respectively)) was carried out, as well as measurements of handgrip strength and gait speed.

Results: Sarcopenia frequency varied from 5.0 to 42.1% depending on the method and cut-off point applied. All surrogate diagnostic criteria had a higher agreement with the DXA defined criterion ASM over ASM/height^2. A substantial agreement was also found with BIA SMM/height^2 (κ=0.67), and with BIA SMI (κ=0.65), and a moderate agreement with MAMC (κ=0.42), p<0.001. Using the DXA ASM and ASM/height^2 criteria as reference, CC showed a specificity of 100% and 94%, respectively.

Conclusions: BIA is a suitable method to evaluate muscle mass in sarcopenia diagnosis when DXA is unavailable. Furthermore, CC showed to be a valid indicator to rule in the presence of sarcopenia.

Keywords: anthropometry, appendicular skeletal muscle mass, bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DXA), older adults.

Introduction

Sarcopenia definition has evolved over the years. Since 2016, sarcopenia is recognized as a muscle disease with a specific ICD-10-CM code [1], and later in 2018, updated guidelines were proposed to define and diagnose sarcopenia [2]. Contrary to the previous definition, this revised European Working Group on Sarcopenia in Older People (EWGSOP)2 consensus brought to the forefront low muscle strength as the primary parameter of sarcopenia diagnosis [2]. Sarcopenia diagnosis is now confirmed by the presence of low muscle quantity or quality when low muscle strength is present, and poor physical performance only indicates the severity of the disease [2].

There are several tools available to estimate muscle mass for the diagnosis of sarcopenia. Magnetic resonance imaging (MRI) and computed tomography (CT) are considered the gold standards to evaluate muscle mass [2], however, the lack of recommended specific cut-off points by scientific societies, their high cost and complexity, and the large amount of radiation involved in CT limits their use [3]. Despite being unable to evaluate muscle quality, dual-energy X-ray absorptiometry (DXA) has been alternatively recommended to assess muscle mass quantity both in the research area and in clinical practice [2], because the amount of exposure radiation is low, it is a relatively inexpensive technique, and more importantly, it provides a fairly accurate estimation of body composition [4]. Indeed, a systematic review found DXA to be highly correlated with the gold standards [5]. However, recently, its importance in sarcopenia diagnosis has been questioned [6].

In the 2010 EWGSOP consensus, it was suggested that muscle mass should be measured using DXA or, alternatively, by bioelectrical impedance analysis (BIA), while estimation of muscle mass by anthropometry was not recommended [7]. On the other hand, BIA was not recommended in the consensus from the Society of Sarcopenia, Cachexia and Wasting Disorders [8].

Even though DXA has been widely adopted in the research area, it remains a challenge in large-scale studies in the community and in clinical practice, because it is only available in a limited number of facilities. BIA and anthropometry are attractive methods to be applied in a wide range of clinical and research settings because they are portable, easy to use, and less expensive alternatives to assess muscle mass [3,4,7]. Nonetheless, their validity to provide accurate results has been questioned [3,4,7]. Although

DXA is preferred over both BIA and anthropometry, there is still no evidence on the best alternative measure to evaluate muscle mass when DXA is impossible to perform.

Several studies compared different methods to assess muscle mass for sarcopenia diagnosis. Yet, to our knowledge, only two studies included anthropometric measures in the comparison. A study carried out in fifty-nine patients with liver cirrhosis revealed a significant but weak correlation between CT and mid-arm muscle circumference (MAMC) and also between CT and DXA [9]. Other, performed in older patients in maintenance hemodialysis showed a higher agreement between DXA and BIA over anthropometry [10]. However, these studies were carried out in specific clinical patients, and it remains to be determined what is the best alternative method when the reference is unavailable.

While it is of utmost importance to standardise sarcopenia diagnostic procedure, the use of different methods to evaluate muscle mass hamper the comparison between studies. On the other hand, establishing the most accessible alternative when the reference methods are unavailable is imperative not only to access this condition but also to reduce the variability observed in the literature. However, it is acknowledged that current evidence is insufficient to support alternative means for sarcopenia diagnosis in older adults [11].

Therefore, in light of the above considerations, we intend to explore the agreement between BIA and anthropometric measures with the reference method (DXA) in the diagnosis of sarcopenia among older adults and to clarify the best alternative measure to assess muscle mass. In addition, we aim to investigate the impact of the use of several cut-off points for low muscle mass identification in sarcopenia diagnosis.

Materials and methods

A cross-sectional study was conducted in the city of Porto, Portugal. Subjects were recruited from several ongoing research programs developed at the Faculty of Sport of the University of Porto. A convenience sample of older adults aged ≥65 years, or if they completed 65 years in the year of the evaluation, was recruited. Individuals with the ability to sign an informed consent form (or their legally designated representative in the case of incapacitated subjects), able to mobilise independently with or without the use of gait aids, diagnosed with dementia or other neurocognitive disorder that do not exhibit significant motor/functional limitations were included. On the other hand, subjects with

a serious medical illness, cardiac or renal insufficiency, an amputated limb, medical devices, such as prosthetics, pacemakers, or metal implants, with a very advanced stage of dementia that could affect physical performance or that show the inability to understand the instructions were excluded from the current study. Hence, a total of 159 older adults were eligible for this study.

Data were collected between November 2017 and February 2020. Participants were submitted to anthropometric, BIA, and DXA examination on the same day. They were asked to refrain from vigorous exercise in the 24 hours before their clinic assessments.

DXA

Appendicular skeletal muscle mass (ASM) was obtained through a whole-body scan using DXA (Hologic Explorer QDR 4500, Bedford MA/USA). The DXA quality control procedures were followed according to manufacturer guidelines and the scanner was calibrated daily using a Spine phantom and a Step phantom whenever required by the system according to the manufacturer's instructions. All DXA scans were carried out by the same trained technician. Participants were asked to wear light clothes and all external metallic items were removed. They were then placed in a supine position in the centre of the scanning table, with the arms at each side slightly separated from the trunk, and hands in a pronated position. The legs were positioned together with the feet relaxed held in slight internal rotation by a strap and toes pointed upwards. During body scans, subjects were asked to remain motionless. Scans lasted approximately 7 min. Afterwards, the trained technician analysed each scan to adjust software-determined regions of interest prior to producing the total and segmental body composition reports. Appendicular skeletal muscle mass (ASM) was calculated as the sum of upper and lower limb lean mass of lean soft tissue, and then adjusted for the height of the individual ($ASM/height^2$).

BIA

Bioelectrical impedance analysis was measured using a Tanita Body Composition Analyzer BC-418MA (Tanita Corporation, Tokyo, Japan), using a constant frequency current source (50kHz, 90μA). Subjects were asked to stand upright with light clothes and barefoot with the heel and toe of each foot in contact with the metal footpads, with arms hanging to each side slightly away from their body, lightly holding the analyser

handgrips. Metal objects were removed before the test. Participants removed their socks, stood on two metallic electrodes on the floor scale barefoot, and held metallic grip electrodes placed in the palm of each hand with the fingers wrapped around the handrails. Whole-body impedance was measured using eight electrodes.

Skeletal muscle mass (SMM) was then calculated using the following BIA equation suggested by Janssen *et al.*, 2000 [12]: Skeletal muscle mass (kg) = [(height^2/BIA-resistance × 0.401) + (gender × 3.825) + (age × 0.071)] + 5.102, where height is in cm; BIA-resistance is in ohms; for sex, men = 1 and women = 0; and age is in years. Additionally, skeletal muscle index (SMI) was estimated according to Janssen *et al.*, 2002 [13] as: SMI (kg) = skeletal muscle mass (kg)/body mass (kg) × 100.

Anthropometry

All anthropometric measurements were taken using standardised procedures by the same trained investigator to ensure the consistency of the measurements throughout the study [14]. Body weight (in kilograms) and standing height were measured with the participants wearing light clothes, using a calibrated stadiometer and electronic scale (SECA 803, SECA GmbH, Hamburg, Germany) with 0.1 kg and 0.1 cm resolution, respectively. Mid-arm (MAC), waist, and calf (CC) circumferences were measured with a metal tape measure (Lufkin W606 PM, Lufkin®, Sparks, Maryland, USA) with 0.1 cm resolution. Triceps skinfold (TSF) thickness was obtained using a Holtain Tanner/Whitehouse (Holtain, Ltd., Crosswell, United Kingdom) skinfold calliper with 0.2 mm resolution.

Muscle mass was estimated, as suggested by Landi *et al.* [15], by MAMC, in cm, calculated using the formula suggested by Jelliffe [16]: MAMC = MAC - (3.14×TSF).

Body mass index (BMI) was calculated according to the formula: BMI = weight (kg)/ height^2 (m). The World Health Organization (WHO) criteria were applied, and individuals were classified as underweight for BMI <18.5 kg/m^2, as normal weight for BMI between 18.5 and 24.9 kg/m^2, as overweight for BMI between 25.0-29.9 kg/m^2 and as obese for BMI ≥30.0 kg/m^2 [17]. The only underweight participant was included in the reference group ("normal weight"). Waist circumference (WC) was categorised into the following categories: low WC for values ≤94 cm for men and 80 cm for women; high WC for values between]94-102] cm for men and]80-88] cm for women; and abdominal obesity for values >102 cm for men and >88 cm for women [18].

Functional measures

Muscle strength

Handgrip strength (HGS) was measured as recommended by the American Society of Hand Therapists most recent protocol [19,20]. Participants were asked to sit in a chair without an armrest, with feet fully resting on the floor, hips as far back in the chair as possible, and the hips and knees positioned at approximately 90°. Arms were adducted and neutrally rotated, elbow flexed to 90°, the forearm in midprone position (neutral), and wrist between 15 and 30° of extension (dorsiflexion) and 0–15° of ulnar deviation. The following instructions were followed: "This test will tell me your maximum grip strength. When I say go, grip as hard as you can until I say stop. Before each trial, I will ask you 'Are you ready?' and then tell you 'Go'. Stop immediately if you experience any unusual pain or discomfort at any point during testing. Do you have any questions? Are you ready? Go!". "Harder... harder... harder...Relax". The test was performed using calibrated Jamar Plus Digital Hand Dynamometer (Sammons Preston Inc., Bolingbrook, Illinois, USA), in the second handle position. Test time was at least 3 seconds, followed by a rest period of at least 15 seconds between trials. The mean of six trials, recorded in kilogram-force (kgf), was used for the analysis. Individuals unable to perform the measurement with both hands were asked to use the functioning hand.

Physical performance

Gait speed (GS) was measured over a distance of 4.57 meters, in an unobstructed corridor. Individuals were instructed to walk at the usual pace and walking time was recorded in seconds by a stopwatch (School electronic stopwatch, Dive049, Topgim, Portugal).

Sarcopenia status

Sarcopenia was diagnosed according to the EWGSOP2 guidelines [2], as the presence of low muscle strength (pre-sarcopenia) measured by HGS, plus low muscle quantity. Sarcopenia severity was determined by low physical performance [2]. The recommended EWGSOP2 guidelines were followed, however previous cut-off points used to define low muscle mass using BIA and anthropometry were also included, as displayed in Table 1. Sarcopenia was also identified using the 2010 EWGSOP guidelines, as the presence of low muscle mass (ASM/height^2 <7.26 kg/m^2 and <5.5 kg/m^2 for men

and women, respectively), plus low muscle strength (measured by HGS) or low physical performance (measured by usual gait speed) [7]. Low muscle strength was classified as HGS <30 kgf for men and <20 kgf for women and a gait speed of ≤0.8 m/s identified subjects with low physical performance [7]. Severe sarcopenia was identified when all three criteria were present [7].

Table 1. Cut-off points used to ascertain low muscle strength, low muscle quantity and low physical performance in sarcopenia diagnosis.

Criteria	Cut-off points		References
	Men	Women	
Low muscle strength			
Handgrip strength	<27 kgf	<16 kgf	Dodds *et al*., 2014 [21]
Low muscle quantity			
DXA defined criteria			
ASM	<20.0 kg	<15.0 kg	Cruz-Jentoft *et al*., 2019 [2]
ASM/height^2	<7.0 kg/m^2	<5.5 kg/m^2	Cruz-Jentoft *et al*., 2019 [2]
BIA defined criteria			
SMI (%)			
Class I	<37%	<28%	Janssen *et al*., 2002 [13]
Class II	<31%	<22%	
SMM/ height^2			
Class I	≤10.75 kg/m^2	≤6.75 kg/m^2	Janssen, Baumgartner, Ross, Rosenberg, & Roubenoff, 2004 [22]
Class II	≤8.50 kg/m^2	≤5.75 kg/m^2	
Anthropometry defined criteria			
Calf circumference	<31 cm		
MAMC	<21.1 cm	<19.2 cm	Landi *et al*., 2012 [15]
Low physical performance			
Gait speed	≤0.8m/s		Cruz-Jentoft *et al*., 2010 [7] Studenski *et al.*, 2011 [23]

DXA, Dual-energy X-ray absorptiometry; ASM, Appendicular skeletal muscle mass; BIA, Bioelectrical impedance analysis; SMI, Skeletal muscle mass index; SMM: Skeletal muscle mass; MAMC, Mid-arm muscle circumference.

Ethics

This research was conducted according to the guidelines established by the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of the Faculty of Sport from the University of Porto (CEFADE 26.2016, CEFADE 04.2018, CEFADE 22.2018), and by the Subcommission of Life and Health Sciences of University of Minho (SECVS 120/2016). All study participants signed an informed consent form.

Statistical analysis

Numerical data are expressed as mean ± standard deviation (SD). The frequency of sarcopenia in our sample was estimated using all eight different diagnostic criteria as described in Table 1. Pearson's correlation coefficients were used to calculate the association between muscle mass estimated using different definitions and also with the functional measures (HGS and GS). For the purpose of comparing the magnitude between correlations, the *cocor* package was used [24].

Inter-rater reliability was assessed using Cohen's kappa (κ) coefficient to evaluate the level of agreement between sarcopenia definitions depending on muscle mass assessment method and cut-off points. The strength of agreement was evaluated by κ value interpretation according to Landis and Koch, 1977 [25], as follows: <0 as indicating no agreement; 0-0.20 as slight; 0.21-0.40 as fair; 0.41-0.60 as moderate; 0.61-0.80 as substantial; and 0.81-1.0 as almost perfect agreement.

Moreover, sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) were determined to evaluate the performance of surrogate muscle mass measures for correctly identifying sarcopenia in older adults using DXA as the reference method. A high sensitivity refers to a better ability to correctly identify individuals with low muscle mass, while a high specificity test is important to correctly identify subjects without low muscle mass and is the ideal property of a rule in test [26].

All analyses were performed using SPSS 26 (SPSS, Inc., Chicago, IL, USA). A *p*-value of <0.05 was considered statistically significant.

Results

The sample was composed of 159 older adults, the majority were women (n = 120, 75.5%). Age ranged from 64 to 93 years, and the median age was 78 [interquartile range (IRQ): 11] years. Description of muscle strength, mass, and physical performance values, according to sex is displayed in Table 2. Considering the criteria presented in Table 1, in the present sample, men's mean values for HGS and muscle mass using both BIA defined criteria were below the cut-off point. Regarding women, the same was observed for DXA defined criterion ASM and for both BIA defined criteria.

Table 2. Participants characteristics, including anthropometric, muscle mass, muscle strength and physical performance values, according to sex.

	Mean ± SD	
	Men (n=39)	**Women (n=120)**
Age (years)	77.5 ± 7.1	77.8 ± 7.3
Weight (kg)	74.3 ± 10.3	63.4 ± 11.5
Height (m)	1.63 ± 0.06	1.50 ± 0.06
BMI (kg/m^2)	27.9 ± 3.7	28.2 ± 4.7
WC (cm)	99.0 ± 10.4	91.2 ± 12.9
Muscle mass measures		
DXA defined criteria		
ASM (kg)	20.4 ± 2.0	14.7 ± 2.3
ASM/height^2 (kg/m^2)	7.7 ± 0.7	6.5 ± 0.9
BIA defined criteria		
SMI (%)	31.6 ± 3.4	23.4 ± 3.5
SMM/height^2 (kg/m^2)	8.7 ± 0.7	6.5 ± 0.9
Anthropometry defined criteria		
Calf circumference (cm)	34.5 ± 2.9	33.6 ± 3.4
MAMC (cm)	23.1 ± 2.7	21.4 ± 3.5
Functional measures		
Handgrip strength (kgf)	25.9 ± 6.9	17.3 ± 4.3
Gait speed (m/s)	0.96 ± 0.42	0.95 ± 0.36

SD, Standard deviation; BMI, Body mass index; WC, Waist circumference; DXA, Dual-energy X-ray absorptiometry; ASM, Appendicular skeletal muscle mass; BIA, Bioelectrical impedance analysis; SMI, Skeletal muscle mass index; SMM, Skeletal muscle mass; MAMC, Mid-arm muscle circumference.

According to WHO BMI categories, 30.2% of the older adults were obese (n=48), 46.5% were overweight (n=74), 22.6% were normal weight (n=36), and only one individual was underweight (0.6%). Regarding abdominal obesity, very high WC was observed in 54.1% of the older adults (n=86) and a high WC in 23.9% (n=38). Furthermore, both general and abdominal obesity was identified in 28.9% of the sample (n=46).

Sarcopenia frequency varied from 5.0 to 42.1% depending on the method and cut-off point applied. More cases of sarcopenia were identified using BIA Janssen 2002 class I criterion, while the lowest frequency was obtained for ASM/height^2 by DXA. Sarcopenia frequency varied greatly for the different cut-off points, even when the same method was used. In more depth, for DXA defined criteria, ASM identified a larger proportion of individuals as sarcopenic (30.8%) than ASM/height^2 (5.0%), whereas for

BIA, Janssen 2002 criterion SMI identified more sarcopenic individuals over Janssen 2004 criterion, for both class I and class II sarcopenia (Figure 1).

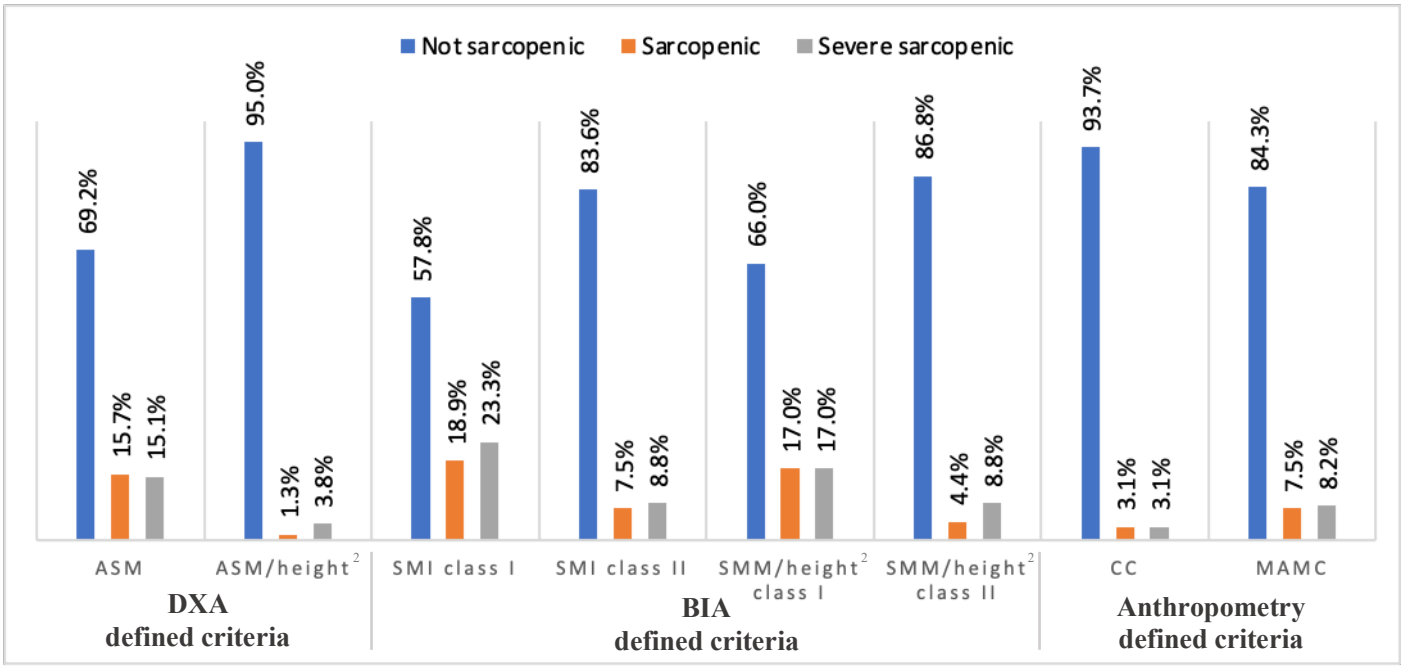

Figure 1. Frequency of sarcopenia according to the criteria used to evaluate low muscle mass.

ASM, Appendicular skeletal muscle mass; DXA, Dual-energy X-ray absorptiometry; SMI, Skeletal muscle mass index; SMM, Skeletal muscle mass; BIA, Bioelectrical impedance analysis; CC, Calf circumference; MAMC, Mid-arm muscle circumference.

Sarcopenia severity was also evaluated, and for DXA defined criteria it was observed that 15.1% (n=24) and 3.8% (n=6) of the older adults were classified as severe sarcopenic, for ASM and ASM/height^2, respectively (Figure 1). According to the EWGSOP 2010 guidelines, 14.5% (n=23) of the older adults were considered sarcopenic, in which 7.5% (n=12) were severe sarcopenic.

The correlation between DXA, BIA and anthropometry defined criteria is shown in Table 3. A very strong positive correlation was found between ASM with ASM/height^2 and SMM/height^2 (p<0.001). There was a strong correlation between SMM/height^2 and ASM/height^2, and also with SMI (p<0.001). Furthermore, a strong correlation was found between ASM/height^2 and both anthropometric measures, CC and MAMC (p<0.001). DXA criterion ASM correlated moderately with CC, MAMC and SMI (p<0.001). However, a very weak correlation was observed between ASM/height^2 and SMI (p=0.018). Although not statistically significant, a negative correlation was observed between SMI estimated by BIA and both CC and MAMC. Concerning DXA defined criteria, the comparison between correlations revealed statistically significant differences

for all the studied pairs, except for MAMC with SMI (regarding ASM) and CC (regarding both ASM and ASM/ height^2).

Table 3. Pearson correlation coefficients between muscle mass and functional measures.

	ASM	**ASM/height^2**	**SMI**	**SMM/height^2**	**CC**	**MAMC**
Muscle mass measures						
ASM	-	**0.87***	**0.43***	**0.81***	**0.57***	**0.54***
ASM/height^2	-	-	**0.19**	**0.77***	**0.66***	**0.61***
SMI	-	-	-	**0.66***	-0.15	-0.09
SMM/height^2	-	-	-	-	**0.43***	**0.44***
CC	-	-	-	-	-	**0.60***
Functional measures						
Handgrip strength	**0.64***	**0.52***	**0.41***	**0.53***	**0.28***	**0 .32***
Gait speed	0.04	0.06	0.03	0.01	0.10	0.06

ASM, Appendicular skeletal muscle mass; SMI, Skeletal muscle mass index; SMM, Skeletal muscle mass; CC, Calf circumference; MAMC: Mid-arm muscle circumference.
Bold indicates statistical significance at $p<0.05$.
*$p<0.001$

In addition, Table 3 also displays the correlation results between muscle mass and functional measurements. HGS was directly correlated with all muscle mass measures. A strong correlation was only observed for ASM estimated by DXA. Overall, DXA and BIA defined criteria showed higher correlation coefficients than anthropometric measures (CC and MAMC), which was considered weak (Table 3). However, statistically significance between pairs of correlations was not found for ASM/height^2 with both BIA defined criteria, for SMI with CC and MAMC, and between both anthropometric defined criteria. Despite GS not being significantly correlated with all muscle mass measurements, a statistically significant correlation was found with HGS (r=0.437; $p<0.001$).

Agreement between the two DXA defined criteria muscle mass measures with BIA and anthropometry is displayed in Table 4. More information regarding sarcopenia diagnosed by DXA (reference) and by BIA or anthropometry muscle mass criteria among study participants is also presented in Supplementary Table 1. In general, all studied diagnostic criteria presented a higher agreement with the DXA defined criterion ASM over ASM/height^2. Interestingly, the agreement of all these indicators was better than between both DXA defined criteria, which revealed to be fair ($p<0.001$). Kappa results concerning ASM showed a substantial agreement with class I SMI and SMM/height^2, and

a moderate agreement with MAMC (p<0.001). The lowest agreement besides ASM/height^2 was observed for CC, which was considered fair (p<0.001). Conversely, agreement was not found between ASM/height^2 and anthropometry defined criteria, CC (p=0.458) and MAMC (p=0.083). Moreover, a slight agreement was observed for class I BIA defined criteria SMI (p=0.001) and SMM/height^2 (p<0.001) (Table 4). Furthermore, the degree of agreement between BIA defined criteria and anthropometry defined criteria was fair (κ ranged from 0.33 to 0.40; p<0.001), except for class I SMI and SMM/height^2 with CC (κ=0.14; p=0.002 and κ=0.16; p=0.001, respectively), and for SMI (class II) with both MAMC and CC which Cohen's kappa was not statistically significant (p>0.05) (data not shown).

In general, sensitivity and specificity were higher when the ASM cut-off for DXA was considered as the reference. All measures showed high specificity in this case, with a particular emphasis on CC which showed a perfect specificity and PPV in this sample (Table 4). However only class I BIA defined criteria exhibited more satisfactory results regarding sensitivity. Sensitivity was 91.8% and 81.6%, indicating that these percentages of the participants identified with low muscle mass by DXA ASM criterion were also identified with low muscle mass by SMI and SMM/height^2 (class I), respectively. Moreover, the probability that individuals classified as non-sarcopenic by both BIA defined criteria (class I) were also considered non-sarcopenic by DXA ASM/height^2 criterion (NPV) was 100% (Table 4).

Considering the 2010 EWGSOP and 2018 EWGSOP2 definitions using ASM/height^2 as muscle mass criterion, agreement in sarcopenia diagnosis was found for 90.6% of the sample (n=144). Kappa results revealed a moderate agreement between these definitions (κ=0.48; p<0.001).

Table 4. Agreement between sarcopenia diagnosed by DXA, BIA and anthropometry muscle mass criteria.

Criteria	ASM by DXA						ASM/height^2 by DXA					
	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Agreement (%)	κ	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Agreement (%)	κ
Low muscle quantity												
DXA defined criteria												
ASM (kg)					-	**1**					74.2	**0.21***
ASM/height^2 (kg/m^2)					74.2	**0.21***					-	**1**
BIA defined criteria												
SMI (%)												
Class I	91.8	80.0	67.2	95.7	83.6	**0.65***	100.0	60.9	11.9	100.0	62.9	**0.14****
Class II	32.7	90.9	61.5	75.2	73.0	**0.27***	37.5	84.8	11.5	96.2	82.4	0.11
SMM/height^2 (kg/m^2)												
Class I	81.6	87.3	74.1	91.4	85.5	**0.67***	100.0	69.5	14.8	100.0	71.1	**0.19***
Class II	34.7	96.4	81.0	76.8	77.4	**0.37***	75.0	90.1	28.6	98.6	89.3	**0.37***
Anthropometry defined criteria												
Calf circumference (cm)	20.4	100.0	100.0	73.8	75.5	**0.26***	12.5	94.0	10.0	95.3	89.9	0.06
MAMC (cm)	40.8	95.5	80.0	78.4	78.6	**0.42***	37.5	85.4	12.0	96.3	83.0	0.11

ASM, Appendicular skeletal muscle mass; DXA, Dual-energy X-ray absorptiometry; PPV, Positive predictive value; NPV, Negative predictive value; BIA, Bioelectrical impedance analysis; SMI, skeletal muscle mass index; SMM, skeletal muscle mass; MAMC: Mid-arm muscle circumference.
Bold indicates statistical significance level of $p<0.05$.
*$p<0.001$; **$p=0.001$

Discussion

Using the 2018 EWGSOP2 criteria and also previous definitions to ascertain low muscle mass in sarcopenia diagnosis by surrogate methods, we found a wide range in sarcopenia frequency, from 5.0 to 42.1%. Furthermore, we have not only observed that sarcopenia frequency is highly dependent on the method used to evaluate muscle mass, but also on the chosen cut-off for each method. Likewise, results show a limited overlap in sarcopenia diagnosis between definitions, indicating an enormous variability depending on the muscle mass diagnostic criteria.

The considerable variability observed here is in line with current evidence from several systematic reviews reporting sarcopenia prevalence [27–29]. Furthermore, results from several studies which aimed to investigate the impact of the 2018 EWGSOP2 definition on sarcopenia diagnosis show a wide variability in sarcopenia frequency when compared with the 2010 EWGSOP guidelines [30–33]. The largest study conducted among 2256 older adults revealed that sarcopenia prevalence according to EWGSOP and EWGSOP2 was 31.9 % and 12.0 %, for men, and 4.9 % and 6.1 %, for women, respectively [30]. In our sample, similar results were found for men as the frequency of sarcopenia was 33.3% (EWGSOP) and 10.3% (EWGSOP2), while higher values were found for women, 8.3% (EWGSOP) and 10.3% (EWGSOP2). Despite the methodologic differences observed, a lower frequency of sarcopenia for men across all studies using EWGSOP2 definition was still observed, whereas conflicting results were seen for women [30–33].

Concerning muscle mass assessment methods, a systematic review highlighted a higher prevalence of sarcopenia when muscle mass was assessed by BIA over DXA [29]. Also, other studies reported an overestimation of muscle mass evaluated by BIA in comparison with DXA [34–37]. The highest sarcopenia estimates were indeed obtained here when using both BIA defined criteria (class I). However, when DXA defined criteria were applied, the use of adjusted or unadjusted cut-off values for ASM led to very distinct sarcopenia frequencies. Since sarcopenia prevalence is highly dependent on the diagnostic criteria [28,38,39], in 2018, the EWGSOP2 consensus tried to standardise the criteria for sarcopenia diagnosis. Yet, two cut-off points to evaluate low muscle mass by DXA were suggested [2]. Regardless of all the efforts to improve sarcopenia definition, currently, muscle mass assessment by DXA is still challenging in most situations [3]. In these cases, other surrogate indicators of muscle mass should be considered. Indeed, an

international survey aimed to assess the tools used for the diagnosis of sarcopenia in clinical practice revealed that 53.3% of the clinicians stated that they assessed muscle mass in their daily practice, and that anthropometry played a major role as a diagnostic tool. In fact, CC was the most reported tool by 57.5% of the practitioners [40].

As previously reported [28], comparison with alternative methods to identify low muscle mass showed different results depending on the chosen cut-off point for DXA. In general, the present study shows a higher agreement between all muscle mass measures and ASM, in comparison with ASM/height^2. Interestingly, the agreement between ASM and all surrogate methods was even higher than between both DXA defined criteria (ASM and ASM/height^2). Moreover, both BIA defined criteria performed above all other measures showing a substantial agreement with ASM. Considering anthropometry defined criteria, MAMC agreement with ASM was better than CC, which was still higher than ASM/height^2. The worst results between sarcopenia definitions were observed using muscle mass assessed by ASM/height^2 and both anthropometry defined criteria.

While the suggested ASM cut-off point was based on data from nine sources which included European older adults [41], the ASM/height^2 cut-off for DXA was only based on a sample of the Australian population [42], therefore the validity of these cut-offs for European older adults may be questionable, namely when adjustment for height is applied. Even though the EWGSOP2 consensus cut-off points were slightly different from the cited source [2,42], when Gould *et al.* cut-off points of 6.94 kg/m^2 for men and 5.30 kg/m^2 for women were used in the present sample, sarcopenia frequency was identical (data not shown), despite previous evidence showing slight differences in sarcopenia prevalence [30]. Also, in the present sample, the mean values of height of both female and male older adults were approximately 12 cm shorter in comparison to the sample where ASM/height^2 cut-off for DXA was generated [42]. Therefore, the adjustment for height produced higher ASM/height^2 values and potentially resulted in less individuals diagnosed with sarcopenia. Even in a study that developed cut-off points for ASM/height^2 in European older adults [43], the mean height of the participants was higher than in the current study. Moreover, ASM showed a stronger correlation with HGS than ASM/height^2, which was only moderate. This could indicate that the adjustment for height with the current cut-off points may not be appropriate for these older adults. Consequently, it would be important to develop longitudinal studies to obtain a more in-depth understanding and clarify which diagnostic criteria is better at identifying adverse clinical outcomes in older adults.

Age-related changes in body composition, namely FFM, can limit the use of surrogate methods to estimate muscle mass [7,44]. Even though several limitations have been pointed out for BIA regarding the diagnosis of sarcopenia [45], the results of the present study which used a single-frequency device showed that it can be alternatively used to identify low muscle mass when Janssen *et al.* criteria [13,22] was used and the ASM cut-off point for DXA was considered. Considering sensitivity and specificity results, the present study suggests that both BIA defined criteria (class I) may be a valid tool for sarcopenia diagnosis, in the absence of the reference method (DXA).

Regarding anthropometry, the results showed that MAMC was the best indicator to identify low muscle mass. However, the fact that CC is an easily obtainable measure in any setting and the 100% specificity results observed in our data, suggests it may be a valid screening tool for ruling in sarcopenia in older adults. This evidence further supports the position adopted by the EWGSOP2 consensus, which stated CC may be used as a diagnostic proxy for older adults in settings where no other muscle mass diagnostic methods are available [2].

Although previous studies have compared different methods to estimate muscle mass in sarcopenia diagnosis, most did not study both anthropometry and BIA as surrogate indicators of muscle mass in the same sample [36,37]. Besides this, these studies took place prior to the revised EWGSOP2 consensus [9,10,36,37], which proposed a new sarcopenia definition that also included different cut-off points for low muscle mass and low muscle strength. As previously mentioned, sarcopenia frequency diverges with the use of this new updated definition. Moreover, the present results indicate that the chosen cut-off points for DXA influence the agreement results with the other surrogate methods.

This study also raises the important question regarding which cut-off point would be more appropriate to identify low muscle mass in older adults. As observed here, the unadjusted ASM cut-off identified more sarcopenic individuals. Moreover, the agreement between both cut-off points for DXA was lower than for all the other surrogate muscle mass measures. Therefore, consensus should be made regarding the appropriate DXA cut-off points for sarcopenia diagnosis.

In this study, the gold standards for measuring muscle mass (MRI and CT) were not performed, instead, DXA was used as the reference. Even though specific cut-off points were not suggested for MRI and CT for sarcopenia diagnosis, it is important to take into account that although DXA is considered the reference method to evaluate

muscle mass [2,7], it has some limitations. In fact, it may overestimate FFM in older adults with extracellular fluid accumulation [2,11,46] and high levels of fibrous tissue [11]. Moreover, it does not allow to estimate muscle quality, due to its inability to measure intramuscular adipose tissue [3]. The fact that, as inclusion criteria, older adults had to be able to stand in order to perform BIA assessment, may have led to the selection of individuals with better functional status and overall health. Additionally, a convenience sample was used which can limit extrapolation of the results. Present results should be validated in a larger sample of older adults with sarcopenia. This sample only included a limited number of male participants, which hamper further evaluation regarding differences in the results according to sex. Hydration status of the individuals was not strictly controlled in the present study, which may impact body composition results. Nevertheless, older adults with decompensated chronic diseases were not included in this study. Also, all subjects were evaluated in the same equipment (DXA and BIA), and anthropometric measures were taken by the same trained investigator throughout the study.

It is also essential to acknowledge that with advancing age, FFM, total body water and bone mass tend to decrease, and there is also a redistribution and increase in fat mass [47]. These changes in body compartments and hydration status can affect the accuracy of body composition methods [48]. Adding to this, the disease states and mobility problems often observed among older adults can make the approach even more challenging. The International Clinical Practice Guidelines for Sarcopenia (ICFSR) for screening, diagnosis and management recommends that if DXA, CT, and MRI are not available, the health practitioner use his or her own clinical judgement to assess muscle mass [11]. Recently, a discussion has emerged regarding the use of DXA to evaluate muscle mass, since DXA-derived measures of lean mass (ASM and ASM/height^2) were not consistently associated with clinical adverse outcomes, such as incident fall, self-reported mobility limitation, hip fracture, and mortality [49]. However, despite the use of DXA for lean mass assessment in sarcopenia diagnosis has recently been questioned [6], it was also stated that the panelists disagreed about excluding lean mass from sarcopenia definition.

Future work should consider evaluating which cut-off point is better at identifying adverse clinical outcomes in older adults.

Conclusions

Taken together, the present results confirm that there is great variability in sarcopenia frequency depending on the method used to estimate muscle mass, and suggest that BIA is a suitable method to evaluate muscle mass in sarcopenia diagnosis when DXA is unavailable. Interestingly, this study has highlighted that even when the same muscle mass assessment method was used, the chosen cut-off points influenced sarcopenia diagnosis rates. Furthermore, CC showed to be a valid measure to rule in the presence of sarcopenia.

Supplemental material

Supplemental material for this article can be found online:

https://ars.els-cdn.com/content/image/1-s2.0-S0167494321001801-mmc1.docx

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Chapter 5

Summarising discussion, concluding remarks, and future challenges

Summarising discussion

The overall purpose of the present work was to increase the knowledge about age-related and nutritional problems often observed in older adults. The major focus was on sarcopenia and frailty, while other nutrition-related conditions such as undernutrition, obesity, and vitamin D deficiency were also studied.

Since world population longevity is increasing, there is a rising awareness of these health problems associated with ageing. Although there is an increasing interest concerning sarcopenia and frailty in recent years, these conditions remain under-recognised and poorly managed. Increasing the knowledge regarding the nutrition state of the Portuguese older population is essential for preventing and managing these conditions and create strategies to improve health status and quality of life during this period. Because data concerning these health conditions in Portuguese older adults are scarce, the Nutrition UP 65 Project aimed to address these shortcomings. So, the frequency of sarcopenia and frailty, and also undernutrition in the Portuguese older population was ascertained and the association with several sociodemographic and lifestyle factors was quantified (Chapters 2). Hence, this thesis represents an important step towards the characterisation of the Portuguese older population, regarding their nutritional and functional status. In more depth, the present work was the first to address the absence of information on the frequency of frailty, sarcopenia, and undernutrition in a nationwide sample of Portuguese older adults. By applying the most widely used definitions to evaluate age-related and nutritional problems, it aimed to fill the gap and increase the knowledge about these conditions, and the factors associated with them. These results are of major relevance to plan public health interventions.

Frailty status and obesity have been linked to lower vitamin D levels. However, in the present thesis, we decided to further explore this association by studying the influence of frailty and obesity on 25(OH)D levels accounting for a possible interaction effect. A special emphasis was also provided to several anthropometric obesity indices that may be useful for clinical practice and, besides the traditional obesity anthropometric indicators, we decided to look into further detail other adiposity indices, such as BRI and ABSI, and investigate if they could provide useful information for older adults. To date, this was the only work to explore the association of BRI and ABSI with serum 25(OH)D levels and clarify the association of both obesity and frailty status with vitamin D status.

Furthermore, the use of a cluster approach to combine BMI and WC into obesity phenotypes allowed to elucidate the link between frailty status and its criteria with different levels of general and abdominal adiposity (Chapter 3).

As we know, ageing is a state of increased vulnerability, and older adults often accumulate more than one health problem at the same time. These conditions are often studied separately despite current evidence showing that they are frequently identified in older adults. We found it important to evaluate the co-occurrence of these conditions and the factors that were associated with the presence of multiple of these conditions (Chapter 3). By studying all four conditions (sarcopenia, physical frailty, undernutrition, and obesity) in the same sample of older adults, the present work provides important insights into older adults' nutritional and functional status.

In this thesis, sarcopenia and frailty diagnostic methods were reviewed, namely the protocols followed by researchers to measure HGS (Chapter 4). This idea came up during my early literature review about the subject, where I noticed discrepancies between the methods used by several studies to identify both sarcopenia and frailty. Due to some similarities in the diagnostic tools shared by sarcopenia and physical frailty, and the fact that HGS is a strong indicator of muscle strength, we decided to ascertain the differences observed in HGS measurement protocols used in research and discuss the influence of these variations on HGS values. Hence, this work contributed to the awareness about the major variation observed in HGS procedures during frailty and sarcopenia assessment and suggested some guidelines to take into consideration by future studies.

In the course of this work, we also came across the difficulty of using the reference method (DXA) to identify low muscle mass for the diagnosis of sarcopenia, because of the lack of available equipment. We took advantage of the limitations experienced in the Nutrition UP 65 Project, regarding the measurement of muscle mass according to what was proposed by the EWGSOP guidelines, by designing a study to evaluate these limitations. As sarcopenia diagnosis often relies on more easily accessible techniques which are highly criticised, such as BIA and anthropometry, we intended to evaluate if these measurements could be alternatively used when the reference method is unavailable. Therefore, outside of the Nutrition UP 65 Project, we decided to develop a cross-sectional study to investigate the difference between the alternative methods to assess muscle mass in the diagnosis of sarcopenia in comparison with the reference method (DXA) and evaluate which procedure should be recommended as an alternative

(Chapter 4). Unfortunately, data collection was terminated earlier due to COVID-19 situation, and the analysis was carried out with the sample gathered by that time.

Strengths and limitations

Several strengths of the present work can be highlighted. The Nutrition UP 65 Project included a large nationwide sample, representative of the Portuguese older population in terms of age, sex, education, and regional area, which comprised 1500 individuals, with 65 or more years. Plus, an effort was made to minimise the exclusions in some of the analyses hence, statistical tests such as multiple imputation were performed to handle missing values for some variables.

Another strength of this study is the use of well-recognised tools to evaluate nutritional and frailty status, such as MNA-SF [186] and Fried's frailty phenotype [60]. In addition, serum 25(OH)D levels were dosed in the same laboratory, using the same method and the same equipment, minimising the possibility of errors.

While the results of this thesis provide important insights about older adults' health and nutritional status, we do acknowledge some limitations of the present work. First, the cross-sectional nature of this study did not allow us to ascertain the evolution of these conditions over time, and to establish cause-effect relationships. Also, even though we have adjusted our analyses for multiple covariates the possible occurrence of residual confounding cannot be ruled out.

Concerning the conditions evaluated, some limitations can be enumerated. In the original frailty phenotype, the Minnesota Leisure Time Activities Questionnaire was proposed to assess physical activity, but in the Nutrition UP 65 Project the International Physical Activity Questionnaire was used instead, and the impact of this modification in the final results is undetermined. Additionally, for sarcopenia diagnosis, anthropometric measurements (MAMC and CC) were used to estimate low muscle mass, as the recommended methods were unfeasible to be applied in the Nutrition UP 65 Project. Also, since sarcopenia and frailty share similar criteria, and both were evaluated at the same time, it was adopted the distance of 4.6 metres to perform gait speed test, instead of the 4 metres suggested by the EWGSOP, to avoid the repetition of identical tests. Still, we acknowledge that even though the velocity would theoretically be the same, this modification could result in slightly slower or faster gait speeds, and consequently influence the results of sarcopenia and sarcopenia severity.

Aside from the criticism on anthropometry as an assessment method to quantify muscle mass, the use of anthropometry for obesity diagnosis in older adults is also a rather controversial topic. The age-related changes in body composition and the use WHO BMI categories are often the reasons why BMI is considered unsuitable for this age group. Therefore, the combination with WC or the use of other anthropometric indicators of body adiposity might be a way to overcome this issue. Also, electrochemiluminescence immunoassay was used for dosing serum 25(OH)D instead of the golden standard (liquid chromatography-tandem mass spectrometry). Moreover, participants' sun exposure levels were not assessed, which would be interesting to evaluate since individuals with frailty and obesity are frequently less exposed to sunlight, namely due to the mobility issues frequently present, and that may influence serum 25(OH)D levels.

Lastly, data for Nutrition UP 65 Project were collected between December 2015 and June 2016, therefore the results presented here may not portrait the current reality regarding these conditions.

Concluding remarks

Our findings

In general, the present work investigated age-related and nutritional health conditions frequently associated with the ageing process. The results of the papers written along with this thesis show the following:

- Sarcopenia status was first evaluated following the 2011 EWGSOP guidelines, and 11.6% of the older adults were diagnosed with sarcopenia (4.4% had severe sarcopenia). Later, using the 2018 EWGSOP guidelines, sarcopenia frequency was again estimated, and a lower number of individuals (4.4%) were identified with this muscle disease. It was interesting to see that, although sarcopenia frequency was low, a large proportion (36%) of the older adults presented the primary parameter of sarcopenia diagnosis (low muscle strength). So, these individuals may still develop sarcopenia over time. An important aspect highlighted in the recent consensus is that intervention should start at this point, when weakness is observed, to prevent further deterioration of functional status.
- A low frequency of undernutrition was observed however, together with undernutrition risk it affected 16% of the older adults.
- Association between sarcopenia and undernutrition/undernutrition risk was only identified when muscle mass quantity was assessed by CC, and not by MAMC.
- Pre-frailty and frailty were highly prevalent in this sample of older adults. More than half were pre-frail and one-fifth were frail. Pre-frail and frail Portuguese older adults manifest weakness more frequently over any other frailty criterion.
- Throughout this thesis, educational level and alcohol consumption were the factors that more commonly showed an association with the conditions evaluated here. Indeed, higher education and particularly moderate alcohol consumption often showed an inverse association with these conditions.
- A higher BMI ($\geq$25 kg/m^2) was inversely associated with both sarcopenia and undernutrition or undernutrition risk, but on the other side, it was also directly associated with frailty.

- It was observed an association between frailty and obesity with lower 25(OH)D levels. Despite median 25(OH)D levels were lower in individuals presenting both frailty and obesity, the associations between frailty and obesity concerning 25(OH)D levels were independent, as no interaction effect was found.
- We found that besides the commonly used obesity indicators (BMI and WC), BRI and ABSI showed an inverse association with serum 25(OH)D concentrations, and their use should be considered.
- Overweight, general, and abdominal obesity rates were high among Portuguese older adults. While women presented higher frequencies of general and abdominal obesity, men were more often classified as overweight. Moreover, older adults with frailty had higher odds of presenting general and abdominal obesity.
- Within this large sample of older adults, almost three out of five older adults presented at least one, and one-fifth had two or more of these health conditions (sarcopenia, physical frailty, undernutrition, and obesity). When all pre-conditions were considered, almost all older adults presented at least one of these pre-conditions or conditions.
- It was found a high heterogeneity in HGS protocols used by the studies to identify sarcopenia and frailty. Furthermore, it was also observed that numerous papers presented limited information about the procedure used, which creates an enormous difficulty in comparing results between studies. To overcome this problem, it was advised the adoption of a standardised procedure (the 2015 ASHT protocol), with a strong encouragement to mention any deviations to the initial protocol.
- In a sample of 159 older adults, sarcopenia frequency showed a great variability depending on the method used to estimate muscle mass and the cut-off point applied, from 5.0 to 42.1%. The substantial agreement found between BIA and DXA defined criteria indicate that BIA is a suitable alternative method to evaluate muscle mass for the diagnosis of sarcopenia. Furthermore, CC showed to be a valid indicator to rule in the presence of sarcopenia, due to the high specificity observed regarding DXA defined criteria.

In conclusion, our findings suggest that some of these age-related and nutritional conditions are highly prevalent in Portuguese older adults and emphasise the need to

screen these individuals. However, the low coexistence between sarcopenia, physical frailty, undernutrition, and obesity found here reinforces the need to assess them all individually during geriatric assessment. Furthermore, the enormous differences observed concerning sarcopenia and frailty diagnostic criteria may hamper the comparison with other studies.

Future challenges

With the present work, we were able to capture the panorama of the Portuguese older population regarding these age-related and nutritional problems. However, longitudinal studies are needed to evaluate the incidence and progression of these health conditions and confirm the direction and the magnitude of the identified associations. Moreover, one of the biggest challenges faced in the study of these conditions was the great variability found in the methods to evaluate particularly sarcopenia and frailty. For that reason, comparison with other studies is often hampered by the differences in their diagnostic criteria. Future directions for research in this field could be taken from this thesis, as follows:

- Nutrition UP 65 Project represented an important step towards the study of age-related and nutritional health problems in Portugal however, a follow-up study would be important to appraise the evolution of these conditions over time.
- Several tools have been suggested in the literature for sarcopenia and frailty screening, translation and validation for the Portuguese older population would be important.
- Screening for sarcopenia and frailty in older adults should be considered routinely during geriatric assessment. Special focus in individuals with obesity and low serum 25(OH)D levels must be pondered for frailty screening.
- An agreement between international societies is needed to reach a universally accepted definition for use in the diagnosis of sarcopenia and frailty. Hence, more emphasis should be put on uniformise and standardise the methods used to identify these conditions and their cut-off points. Reliable and easily accessible procedures should be recommended alternatively when reference methods are unavailable.
- To ascertain the appropriate tools to easily evaluate obesity in older adults, namely by the use of other anthropometric adiposity indicators, and consider the inclusion of these indices routinely in clinical practice.
- Longitudinal studies are also needed to investigate the outcomes of the co-occurrence of these conditions and determine the cumulative effects on older adults' health status and quality of life.

Despite the major evolution observed in recent years in the study of these conditions, particularly for sarcopenia and frailty, the difficulties faced in their diagnosis are still significant. It would be of special interest that researchers continue to try to overcome these limitations, provide evidence to identify individuals at risk, and develop strategies aiming to reduce the burden of these health problems in a near future. In Portugal, undernutrition screening is routinely carried out in hospital settings, whereas sarcopenia and frailty remain poorly identified. The large proportion of pre-frail or frail older adults observed in the present work, which was largely superior to the number of undernourished individuals emphasise the need to implement screening tools to identify these age-related health problems in the community. Moreover, evidence indicates that transition between states can occur, and frailty can be reversible. Therefore, targeting those in the early stages of frailty could be essential to prevent a further deterioration in physical function, or even promote a transition towards a robust state and hamper worse health consequences.

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