UNIVERSIDADE ESTADUAL DE CAMPINAS
Faculdade de Educação Física

HÉLIO JOSÉ COELHO JUNIOR

FRAILTY: PREVALENCE, ASSOCIATED FACTORS AND TREATMENT THROUGH RESISTANCE TRAINING

FRAGILIDADE: PREVALÊNCIA, FATORES ASSOCIADOS E TRATAMENTO ATRAVÉS DO TREINAMENTO DE FORÇA

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Thesis presented to the Faculty of Physical Education of the University of Campinas in partial fulfillment of the requirements for the degree of Doctor, in the area of adapted physical activity.

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Co-supervisor: BRUNO RODRIGUES

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Au lieu de le garder dans des coffres rouillés.

Il restera de toi de ton jardin secret,

Une fleur oubliée qui ne s'est pas fanée.

Ce que tu as donné, en d'autres fleurira.

Celui qui perd sa vie, un jour la trouvera.

Il restera de toi ce que tu as offert

Entre les bras ouverts un matin au soleil.

Il restera de toi ce que tu as perdu

Que tu as attendu plus loin que les réveils,

Ce que tu as souffert, en d'autres revivra.

Celui qui perd sa vie, un jour la trouvera.

Il restera de toi une larme tombée,

Un sourire germé sur les yeux de ton coeur.

Il restera de toi ce que tu as semé

Que tu as partagé aux mendiants du bonheur.

Ce que tu as semé, en d'autres germera.

Celui qui perd sa vie, un jour la trouvera

Simone Weil

RESUMO

A fragilidade é um estado potencialmente reversível de maior vulnerabilidade à desfechos de saúde negativos, o qual ocorre como resultado do comprometimento biológico multissistêmico e aspectos socioambientais. A prevalência de fragilidade na Europa e na Ásia já foi estabelecida e, mais recentemente, pesquisadores sugeriram que a incidência de fragilidade em três anos ao rendo do mundo é de 13,6%. Embora os países da América do Sul sejam uma economia emergente, ainda sofrem com a pobreza, desnutrição, moradia precária, falta de informação e baixa qualidade de vida, todas variáveis associadas ao desenvolvimento da fragilidade. No entanto, a prevalência de fragilidade na América do Sul ainda é pouco explorada**. Portanto, o presente projeto de doutorado investigou a prevalência de fragilidade na América do Sul.** A gênese e a progressão da fragilidade estão associadas à muitos desfechos negativos relacionados à saúde, como limitações da mobilidade e anormalidades cardiovasculares. Em contraste, o alto consumo proteico parece estar associado negativamente ao status de fragilidade. Notavelmente, a definição operacional de fragilidade ainda é difícil pela ausência de uma definição unívoca, e mais de 60 instrumentos diferentes para a sua avaliação estão atualmente disponíveis. Algumas investigações observaram que esses instrumentos não capturam necessariamente o mesmo construto, o que permite supor que a associação entre fragilidade e outros fatores possa ser dependente do instrumento utilizado. **Com base nessas premissas, este projeto investigou a relação entre o status de fragilidade e a ingestão de proteínas, função física e parâmetros relacionados à hipertensão arterial sistêmica usando 4 instrumentos diferentes.** O estabelecimento da fragilidade como um problema de saúde pública levou pesquisadores a examinar terapias para colaborar com o tratamento dessa condição. Muita atenção tem sido dada ao exercício físico, principalmente ao treinamento de força (TF), dados os inúmeros estudos que relataram melhorias nos parâmetros relacionados à fragilidade em resposta aos programas de TF. No entanto, mesmo que os programas tradicionais de TF, ou também chamados treinamento de resistência a baixa velocidade (LSRT), pareçam ser uma ferramenta poderosa para melhorar a força muscular, seus efeitos da mobilidade são menos pronunciados. Nesse contexto, evidências que a potência muscular, a capacidade de exercer força em um curto intervalo de tempo, diminui precocemente e está mais associada à tarefas de mobilidade do que a força muscular, levou à suposição de que os protocolos de RT de alta velocidade (HSRT) poderiam causar maiores melhorias na mobilidade do que o LSRT. Ensaios clínicos randomizados, revisões sistemáticas e metanálises testaram essa hipótese e os resultados ainda são controversos. Além disso, as investigações são baseadas em idosos robustos, de modo que os efeitos dos programas de TF no status de fragilidade e no desempenho

físico de idosos frágeis não foram descritos anteriormente. **Assim, o presente projeto investigou os efeitos do HSRT e LSRT no status de fragilidade. Secundariamente, foi examinado os efeitos de ambos os programas de TF no desempenho físico, função cognitiva e pressão arterial, dada sua estreita associação com à fragilidade.**

Palavras-chave: Fragilidade; Sarcopenia; Treinamento de Força; Força Muscualr; Teste de Caminhada;

ABSTRACT

Frailty is a potentially reversible state of increased vulnerability to negative health-related outcomes that occurs as a result of multisystem biological impairment and environmental aspects. The prevalence of frailty in Europe and Asia has been estimated and more recently researchers suggested that the average 3-year incidence of frailty worldwide is 13.6%. Although South America countries an emerging economy, they are still suffering with the poverty, malnutrition, poor housing, lack of information, and low quality of life, all variables associated with frailty development. Nevertheless, the prevalence of frailty in South America is still poorly explored. **Therefore, the current Ph.D. project investigated the prevalence of frailty in South America.** The genesis and progression of frailty is associated with many negative health-related outcomes, such as mobility limitations and cardiovascular abnormalities. In contrast, high protein consumption seems to be negatively associated with frailty status. Notably, the operational definition of frailty is still hampered by the absence of a univocal definition, and more than 60 different instruments for the assessment of frailty are currently available. Some investigations have observed that these instruments not necessarily capture the same construct, which allows the assumption that the association between frailty and associated factors may be instrument-dependent. **Based on these premises, this project investigated the relationship between frailty status and protein intake, physical performance, and hypertension-related parameters using 4 different frailty instruments.** The establishment of frailty as a public health problem led researchers to examining therapies to collaborate with management of frailty. Much attention has been paid to exercise training, mainly to resistance training (RT), given the numerous studies that have reported improvements in frailty-related parameters in response to RT programs. However, even if traditional RT programs, or also called low-speed resistance training (LSRT), seem to be a powerful tool to improve muscle strength, its effects of mobility are less pronounced. In this context, evidence has found that muscle power, the capacity to exert force in a short time interval, declines faster and is more associated with mobility tasks than muscle strength, which lead to the assumption the high-velocity RT (HSRT) protocols could cause greater improvements in mobility than LSRT. Randomized clinical trials and systematic reviews and metanalyses have tested this hypothesis and findings are still controversial. Furthermore, investigations are based on robust older adults the effects of both RT programs on frailty status and physical performance have not been described before. **Thus, the present project investigated the effects of HSRT and LSRT on frailty status.**

Secondarily, we examined the effects of both RT programs on physical performance, cognitive function, and blood pressure, given its close association with frailty.

Keywords: Frailty; Sarcopenia; Resistance Training. Muscle Strength; Walking Speed

LISTA DE ABREVIATURAS E SIGLAS/ LIST OF ABBREVIATIONS

10RM= 10-Repetition Maximum Test

1RM= 1-Repetition Maximum Test

6MWT= 6-Min Walking Test

AA= Amino Acids

ABPM= Ambulatory Blood Pressure Monitoring

ACEI= Angiotensin-Converting Enzyme Inhibitor

ACSM= American College Of Sports And Medicine

Ang1= Angiotensin

ANOVA= One-Way Analysis Of Variance

BCAA= Branched Chain Amino Acids

BDNF= Brain-Derived Neurotrophic Factor

BIA= Bioelectrical Impedance Analysis

BW= Body Weight

CA= Chronological Age

-COOH= Carboxyl

CDM= Cumulative Deficit Model

CDT= Clock Drawing Test

CFS= Clinical Frailty Scale

CG= Control Group

CHD= Coronary Heart Disease

CHS= Cardiovascular Health Study

CI= Confidence Intervals

CKD= Chronic Kidney Disease

CPOD= Chronic Obstructive Pulmonary Disease

CRP= C Reactive Protein

CS= Control Session

CTX= Terminal Collagen Crosslinks

CV= Coefficient Of Variance

DBP= Diastolic Blood Pressure

DBP= Diastolic Blood Pressures

DHEA= Dehydroepiandrosterone

DS= Down Syndrome

DXA= Dual X-Ray Absorptiometry

EAA= Essential AA

EFS= Edmonton Frailty Scale

ER= Endoplasmic Reticulum

ES= Effect Size

ESHEUGMS= European Society Of Hypertension-European Union Geriatric Medicine Society

EWGSOP= European Working Group On Sarcopenia In Older Persons

FFQ= Food-Frequency Questionnaires

FRAIL= Fatigue, Resistance, Ambulation, Illnesses, & Loss Of Weight

FS= Forgetting Speed

FTI= Free Testosterone Index

GUG= Get-Up And Go

Hcl= Hydrochloric Acid

HDI= Human Development Index

HF= Heart Failure

HR= Heart Rate

HSRT= High-Speed Resistance Training

HYVET= Hypertension In The Very Elderly Trial

IGF=1 Insulin-Like Growth Factor-1

IGF-1 Insulin-Like Growth Factor 1

IGFBP= IGF Binding Protein

IHG= Isometric Handgrip

IL-6= Interleukin

ILAS= I-Lan Longitudinal Aging Study

IPAQ= International Physical Activity Questionnaire

IRS-1= Insulin Receptor Substrate 1

Itug= Instrumented TUG

JNC7= VII Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure

KCL= Kihon Checklist

LBM= Lean Body Mass

LRST= Low-Speed Resistance Training

LV= Left Ventricular

MAP= Mean Arterial Pressure

MCEP= Multicomponent Exercise Programs

MCID= Minimal Clinically Important Difference

MI= Myocardial Infarction

MMSE= Mini-Mental State Examination

MPB= Muscle Protein Breakdown

MPS= Muscle Protein Synthesis

Mtor= Mammalian Target Of Rapamycin

MU= Motor Units

-NH2= Amine

NOS= Newcastle Ottawa Quality Assessment Scale

OA= Osteoarthritis

OR= Odds Ratio

PEH= Post-Exercise Hypotension

PI= Proactive Interference

PI3K= Phosphatidylinositol 3-Kinase

PRISMA= Primary Reporting Items For Systematic Reviews And Meta-Analyses

PW= Pulse Wave (PW)

PWV= Pulse Wave Velocity

RALVT= Rey's Auditory Verbal Learning Test

RCTS= Randomized-Clinical Trials

RDA= Recommended Dietary Allowance

RI= Retroactive Interference

ROM= Range Of Motion

RPE= Rating of Perceived Exertion

RT= Resistance Training

RW= Reflected Wave

SBP= Systolic Blood Pressure

SD= Standard Deviation

SHBG= Sex Hormone Binding Globulin

SMD= Standard Mean Difference

SMI= Skeletal Muscle Index

SOF= Study Of Osteoporotic Fracture

SPPB= Short Physical Performance Battery

SPRINT= Systolic Blood Pressure Intervention Trial

SQFFQ= Semi Quantitative-Food Frequency Questionnaire

STROBE= Strengthening The Reporting Of Observational Studies In Epidemiology

TF1I= Tilburg Frailty Indicator

Trna= Transfer RNA

TSH= Thyroid-Stimulating Hormone

TUG= Timed “Up And Go”

TUT= Time Under Tension

UPS= Ubiquitin-Proteasome System

VL= Verbal Learning

WHAS= Women's Health And Aging Study

WHI-OS= Women’s Health Initiative Observational Study

WHO= World Health Organization

WS= Walking Speed

X2= Chi-Square

SUMÁRIO

INTRODUCTION

Aging process and frailty: a brief perspective

The aging process and mainly the old age have gone through many perceptions during human history. In ancient Greek, the god of old age was Geras (*Senectus* in ancient Rome), represented as a sad person who walked using a cane and accompanied the actions of Thanatos, the god of death (HAMILTON, 2019). Heh (i.e., million in Egypt) was the personification of eternity for Egyptians. He is commonly represented as a man holding one palm stem in each hand and with a palm stem in his head, indicating longevity (WILKINSON, 2003). African polytheists adore Oxalufan as the representation of "old age". This divinity is described as a wise old man with mobility limitations who wears white clothes and walks using a sacred cane (paxorô) (BARBOSA, 2014).

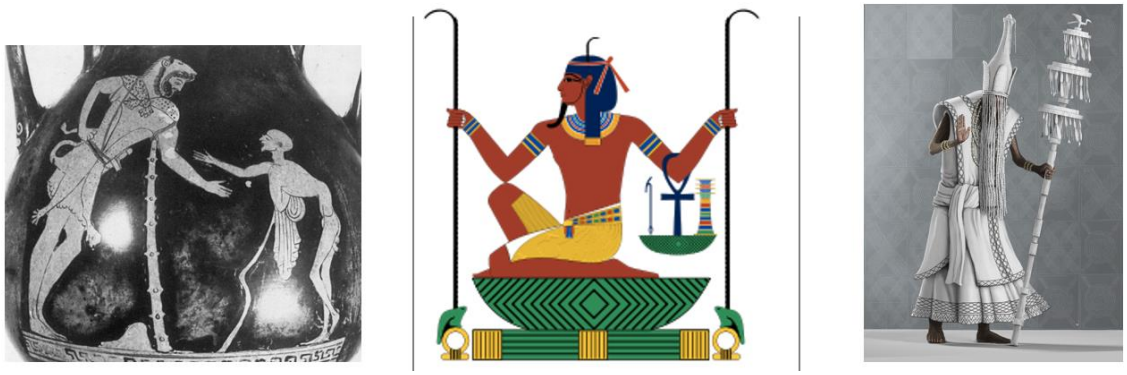

Figure 1. Representation of a) Geras, b) Heh, and c) Oxalufan. In the first picture, a representation of Heracles who would have won Geras; Heh, in the middle, holds palm stems, representing longevity; in the last picture, Oxalufan is represented by a thin old man who walks hunched.

In the bible, grow old is described as a divine blessing. Adam (930 years) and Moses (120 years), for example, lived more than 100 years, and Methuselah (969 years) is considered the oldest person in human history. According to psalms 91, longevity will be a gift for those who follow God's footsteps: *With long life, I will satisfy him and show him my salvation*. More than that, long life would be a representation of morality, *Gray hair is a crown of splendor; it is attained in the way of righteousness* (Proverbs, 16:31).

Nevertheless, also in the psalms, people showed their despair to not be abandoned by god when they become old and weak: *"Do not cast me away when I am old; do not forsake me when my strength is gone"* (psalms 71:9).

Being old in ancient Rome allowed some perks. The Law of the Twelve Tables, *Duodecim Tabulae*, gave to the breadwinner permission to decide on the life of his slaves and

children (*patres familias*). Older men also composed the *senatus*, a council responsible for political decisions.

At that moment, thinkers started to reflect on the aging process. Cicero, one of the most famous Roman thinkers, wrote a book expressing his ideas about how to grow old (CICERO, 103AD). According to him, four main problems are associated with getting old: 1st) that it withdraws us from active pursuits; 2nd) that it makes the body weaker; 3rd) it deprives us of almost all physical pleasures; and, 4th) that it is not far removed from death.

In his point of view, remain intellectually active, instead of being worried about the decline in physical function may propitiate successful aging and counteract most problems associated with growing old. Nevertheless, the possible negative outcomes of aging have been described by many writers, philosophers, and poets throughout the centuries.

In King Lear, Shakespeare recognizes that the old age may a moment of expressing wisdom (SHAKESPEARE, 1606). In the first act, Lear asks the fool about his behavior with his daughter, given that he showed signals of dementia, and the footman comments: "*If thou wert my fool, nuncle, I'd have thee beaten for being old before thy time"*. Samuel T Coleridge shares this perspective and portrays his ancient Mariner as an old man who learned with his mistakes. Dona Benta, character created by Monteiro Lobato who took care of children, was known to be old and wise.

However, Gabriel García Márquez in *Memories of My Melancholy Whores* genially identified that be smart and cultured may not be enough for a complete old age and suggests that loneliness may trigger serious problems (MÁRQUEZ, 2004).

Physical changes arising from old age are a common topic in the literature and many times a problem for the characters. In the *magnun opus* of Oscar Wilde (1890), Doryan gray, *Prince Charming*¸ remains young and handsome thanks to a full-length portrait in oil, which gets old instead of him. When he stabs the painting, Doryan died and his body became old, withered and decrepit. Would Wilde be indicating that evil makes us old? Is old age a punishment?

In the myth of Tithonus, Eos, Goddess of the Dawn, asked Zeus to make her beloved immortal but forgot to ask that he be granted eternal youth. As a result, Tithonus kept growing old, lost his physical function and became a cicada.

Santiago, Ernest Hemingway's fisher, is described as *thin and gaunt with deep wrinkles in the back of his neck* and the author concludes that *everything about him was old* (HEMINGWAY, 1952).

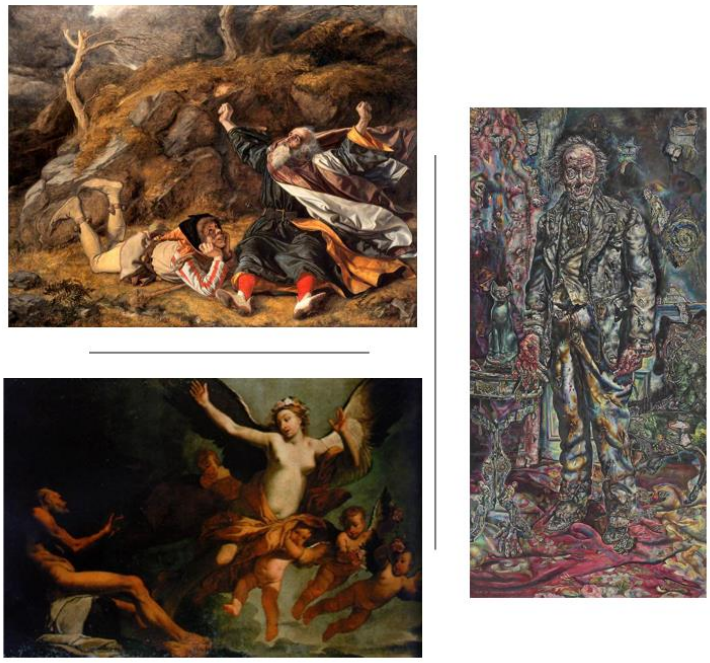

Figure 2. King lear, Eos and Tithonus, and Doryan Gray. In the upper left corner of the figure, King Lear and his fool by William Dyce (1806–1864); In the picture below, Eos and Tithonus by Giulio Carpioni (Italian, 1613–1679); In the right corner of the figure, the picture of Doryan Gray by Ivan Albright (1897–1983).

Aging was not forgotten by great painters. After dissecting the corpse of an older man, Leonardo da Vinci stated that *muscles were consumed and reduced to the state of a thin membrane so that the cords, instead of being transformed into muscle were converted into a wide sheet* (TONELLI, 2014).

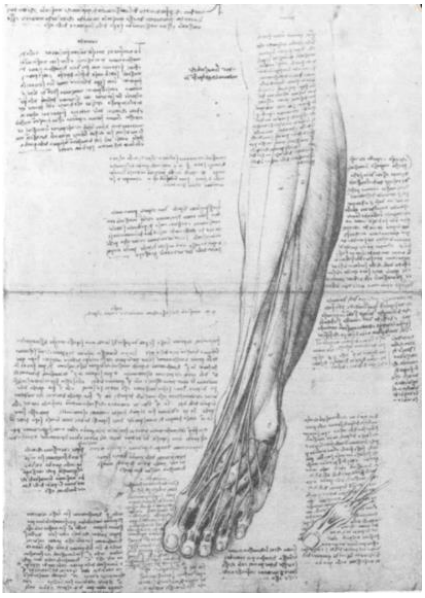

Figure 3. Dissected leg by Leonardo da Vinci (1452-1519).

The demographic transition made aging become a hot topic in science. Reports from the earlier 20's indicated that become old was treated as a disease by some scientists. In the article *The Pathology of the Aging Process*, Warthin A. (1928) termed old age as "the period of involution", given that men have fulfilled their biological duty and the human body slowly reduces the functioning of its vital functions. During the second world war II, Nazis performed secret experiments with hormones in an attempt to slow aging and make the Fuher and the so-called Aryan race immortal (DE NÁPOLI, 2012).

The first papers talking about frailty started to be published in the 80's and recognized this condition as possible characteristic inherently associated with the aging process (GADOW, 1983) or a state associated with long-term hospitalization and high prevalence of comorbidities (WILLIAMS et al., 1989). However, there was the notion that aging could be a heterogeneous process (GADOW, 1983). In the 90's, researchers (SPEECHLEY; TINETTI, 1991; BORTZ, 1993; ROCKWOOD et al., 1999) had in mind that frailty was apparently associated with some elements, like aging, diseases, and behavioral factors, but a conceptual framework was not yet established.

However, still in this period, some investigations (SPEECHLEY; TINETTI, 1991; ROCKWOOD et al., 1999) reported that be frail, according to definitions based on mobility, disability, and dementia, to quote a few, were associated with higher risk of falls and institutionalization.

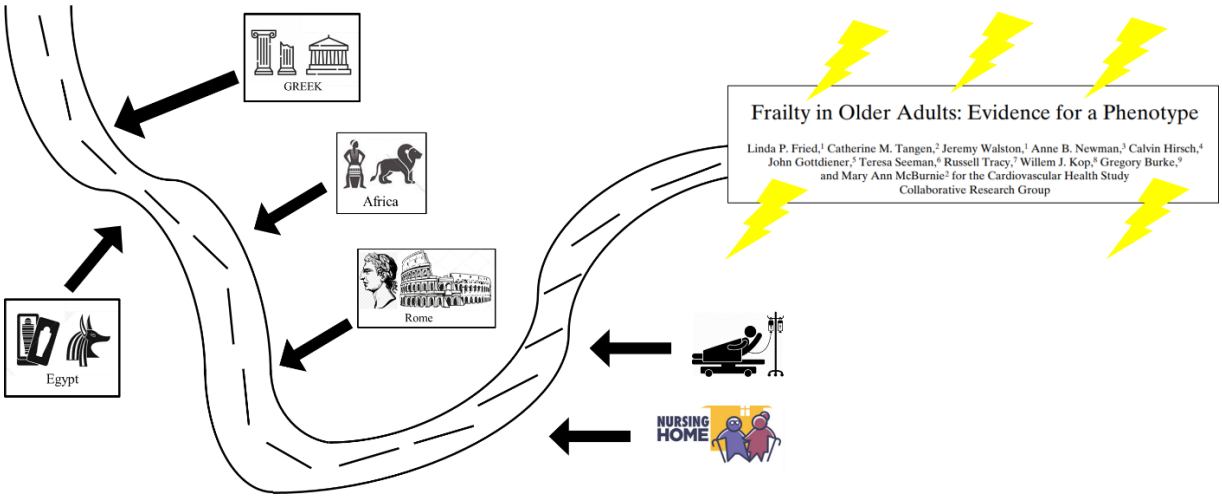

Figure 4. A long road to frailty**.**

These compendia of evidence motivated researchers in the early 2000s to look for a conceptual framework and a clinical definition of frailty. The turning point occurred with the

investigation of Fried et al. (2001). First, researchers identified that a) weight loss, b) weakness, c) exhaustion, d) slowness and e) sedentary behavior were five elements fundamentally associated with frailty and could be used to clinically identify it. Subsequently, they used data from the Cardiovascular Health Study (CHS) to test the hypothesis that older adults with three or more of the five abovementioned features were at higher risk of adverse health outcomes.

Figure 5. Five cardinal features of frailty according to Fried et al., 2001

Baseline results deconstructed preliminary views by suggesting that frailty was not necessarily accompanied by disability or diseases, given that 27% of the frail participants had none of the conditions. Authors observed that their proposal of frailty phenotype was an independent predictor of incident falls, worsened mobility or activities of daily living disability, incident hospitalization, and death over 3 or 7 years, after adjustment for many covariates.

This study opened an avenue for exploring the physiopathology of frailty (CLEGG et al., 2013; COELHO-JUNIOR et al., 2019b (Article 1); MARZETTI et al., 2019; PICCA et al., 2019), its associated factors (BEASLEY et al., 2010; BOLLWEIN et al., 2013; NADRUZ et al., 2016; GOBBENS, 2019), its development and adverse outcomes (KOJIMA, 2016a, 2016b, 2017a, 2017b, 2018; KOJIMA et al., 2016), the best instruments for its identification (BUTA et al., 2016; APRAHAMIAN et al., 2017; LIN et al., 2018a), and the possible treatments (NEGM et al., 2017; JADCZAK et al., 2018). Indeed, many observational studies (NERI et al., 2013; PIRES CORONA et al., 2015) and randomized clinical trials (MARZETTI et al., 2018) have been performed to study the several strands of frailty around the world.

It should be mentioned that alternative phenotypes of frailty including other domains (e.g., social, religious, cognition) were proposed by research groups (ROCKWOOD et al., 2005; SEWO SAMPAIO et al., 2016a; BRECCIA et al., 2018; CHECA-LÓPEZ et al., 2019), and have been exhaustively tested. However, the Fried frailty phenotype, also called physical frailty, is still the most used in research and clinical practice (CLEGG et al., 2013; MORLEY et al., 2013a).

Nowadays, frailty is defined as a reversible state of increased vulnerability to negative health-related outcomes, including disability and mortality, which occurs separated and faster than normal aging process in response to a heterogenous multisystem impairment of the human body that presents high within-individual variability (FRIED et al., 2009; VAN KAN et al., 2010; CLEGG et al., 2013; MORLEY; MALMSTROM, 2013; CHOI et al., 2015; STOLZ; MAYERL; FREIDL, 2019). It means that frail patients are at higher risk for many unfavorable outcomes and early death. Their clinical presentation is composed of numerous age-related components (e.g., weakness), but not represent a product of the aging process. Its cause may and probably do vary across individuals so that two frail older adults might show a different combination of biological impairments and social issues. Finally, frail individuals will present fluctuations in their state, which has important implications in the treatment.

Investigations have estimated the prevalence of frailty worldwide. In Europe, the overall prevalence was estimated at 7.7%, with lower occurrences identified in countries with higher Human Development Index (HDI), such as Switzerland, Sweden and Denmark (MANFREDI et al., 2019). Similar findings were found in Japan, where frailty accounts for 7.4% (KOJIMA et al., 2017). A recent systematic review and meta-analysis identified that around 21.7% of older adults in South America are frail (Article 2). In Brazil, specifically, the mean prevalence of frailty is estimated in 26.1%, with the highest prevalence observed in nursing-home residents (55.8%), followed by hospitalized (39.6%), and community-dwelling people (24.8%).

Frailty and associated factors: protein consumption, physical performance, and hypertension-related parameters

The main concern regarding frailty progression is its close association with adverse outcomes. Frail people are at higher risk for mobility limitations (VERMEIREN et al., 2016; LIN et al., 2018b), cardiovascular abnormalities (NEWMAN et al., 2001; NADRUZ et al., 2016), cognitive impairment (GRANDE et al., 2019; MIYAMURA et al., 2019), falls (VERMEIREN et al., 2016), fractures (ENSRUD et al., 2008; KOJIMA, 2016b, 2017b),

hospitalization (LIN et al., 2018b), and death (VERMEIREN et al., 2016; LIN et al., 2018b), which collaborates to a poor quality of life and high prevalence of depressive symptoms in this population (VAUGHAN; CORBIN; GOVEAS, 2015). This state of susceptibility increases private and public costs (BOCK et al., 2016). As such, frailty represents a major public health problem.

On the other hand, good life habits, such as adequate nutrients intake (LORENZO-LÓPEZ et al., 2017) and high physical activity levels (DE SOUTO BARRETO, 2010) may postpone or even prevent frailty's development.

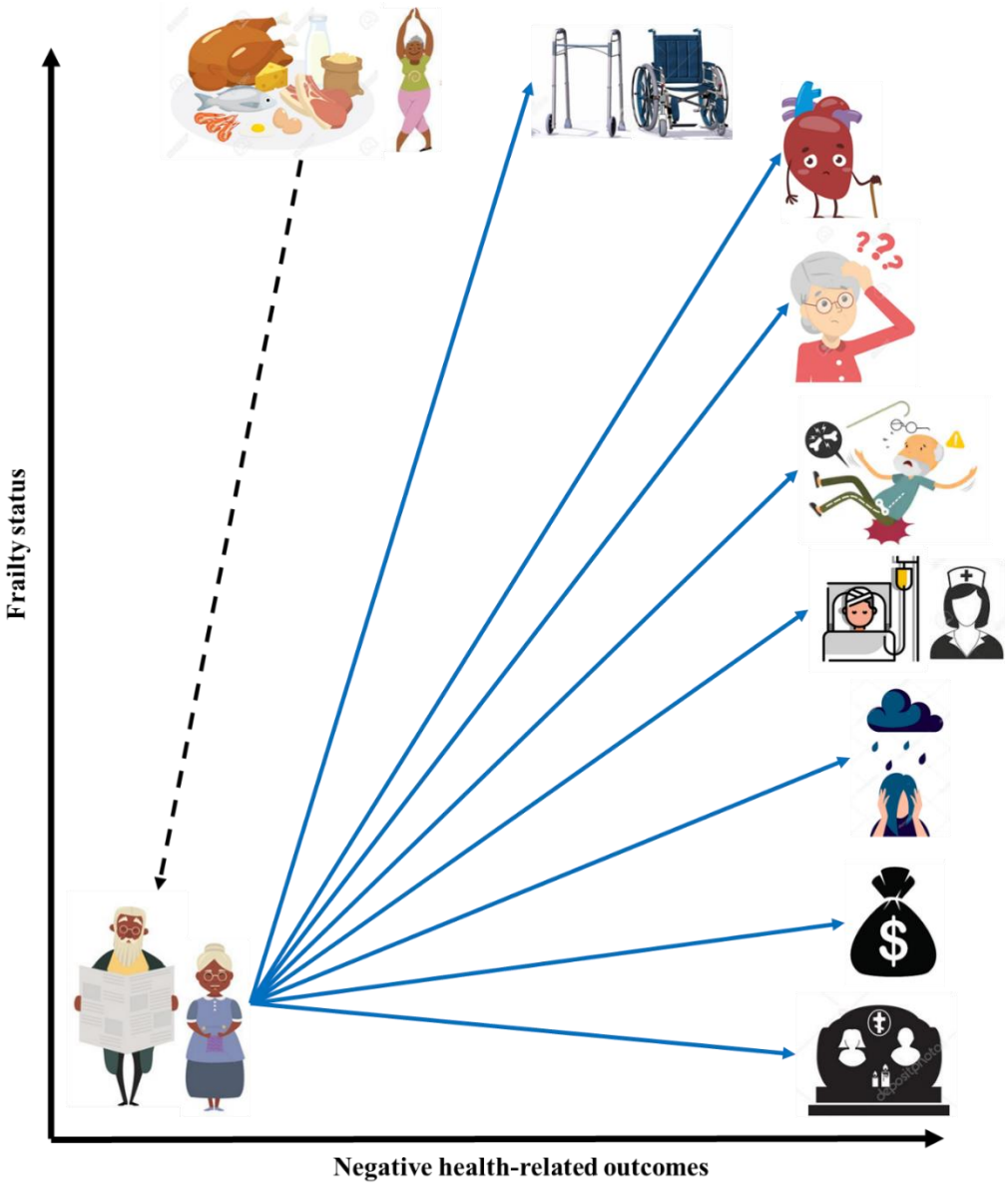

Figure 6. Frailty and negative health-related outcomes.

The relationship between frailty and some of its associated factors will be discussed below.

Frailty and protein consumption

Proteins are macromolecules consisting of a linear polymer of amino acids (AA), which are responsible for numerous biological processes in the human body, including DNA replication, cell structure, enzymatic reactions, and transporting of molecules. Different from other macronutrients, protein has no inactive compound to serve as a reservoir and protein dietary intake must be kept constant so that skeletal muscle contractile proteins are rapidly utilized to supply the lack of AA during fasting and stress.

The building of proteins begins with the acquisition of AA derived from dietary protein, given that the human body is not able to synthesize all essential AA (EAA). Different from carbohydrates, protein degradation, proteolysis, begins in the stomach, where the hydrochloric acid (HCl) exposes the peptide bonds to digestive enzymes and activates and converts pepsinogen into pepsin, which acts cleaving peptide bonds into small AA molecules. In the duodenum, the AA chains are metabolized into shorter molecules of AA (i.e., tripeptides and dipeptides) by digestive enzymes produced by the pancreas, such as trypsin, chymotrypsin, elastase, and carboxypolipeptidase. Finally, tripeptides and dipeptides are converted into AA and reach target tissues through the bloodstream.

AA are organic compounds that contain amine (-NH2), carboxyl (-COOH) and R groups (side chain), which varies according to each AA. These variations on R groups have a key role in the structure of proteins by influencing the combination of AA during polymerization. Protein synthesis begins after DNA's transcription into a messenger RNA (mRNA). This molecular structure involves a recipe with the sequence of AA to produce the protein. A complex composed by ribosomes adhered to the endoplasmic reticulum (ER), mRNA, and transfer RNA (tRNA) will produce proteins by dehydrating each single AA, forming a peptide bond, which results in an amide group, a functional group essential to connect many residues during polymerization in which nitrogen is close to a carbonyl.

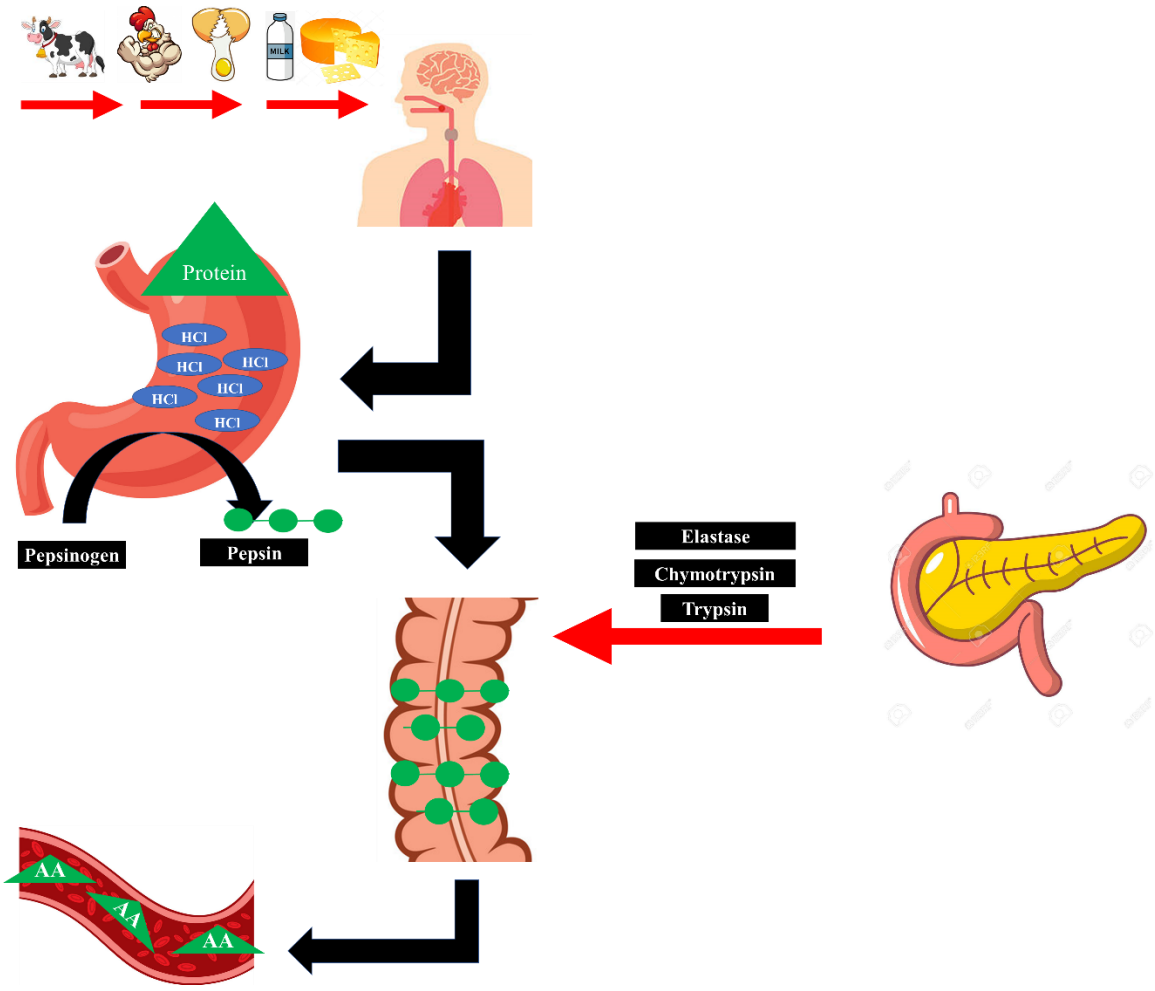

Figure 7. Protein digestion.

The current Recommended Dietary Allowances (RDA) of proteins for adults is 0.8 g/kg body weight (BW)/d. However, RDA is under intense criticism (DREYER; VOLPI, 2005; BAUER et al., 2013; VOLPI et al., 2013; BAUER; DIEKMANN, 2015; DEER; VOLPI, 2015; LANDI et al., 2016a; PHILLIPS; CHEVALIER; LEIDY, 2016), given that it is based on nitrogen balance studies and does not include specific recommendations for older adults, who seem to need higher amounts of protein to maintain basic functions of some biological process.

In particular, muscle protein anabolism is blunted in the old muscle due to a reduced muscle protein synthesis (MPS) in response to hyperaminoacidemia (VOLPI et al., 2000; KATSANOS et al., 2005, 2006; WALL et al., 2015), which is known as anabolic resistance. Evidence have demonstrated that the rate of phenylalanine, an essential AA not produced in the body and not oxidized in the muscle tissue, taken up by the muscle after essential/mixed AA infusion (VOLPI et al., 2000) or ingestion (KATSANOS et al., 2005, 2006; WALL et al., 2015) is higher in young than in older adults. This phenomenon was accompanied by a reduced MPS

in the post-prandial, but no post-absorptive state (VOLPI et al., 2000; KATSANOS et al., 2005, 2006; WALL et al., 2015).

Moore et al. (2014) added to the aforementioned studies by observing that older adults required a 140% greater protein intake to maximally stimulate postprandial rates of MPS in comparison to young adults.

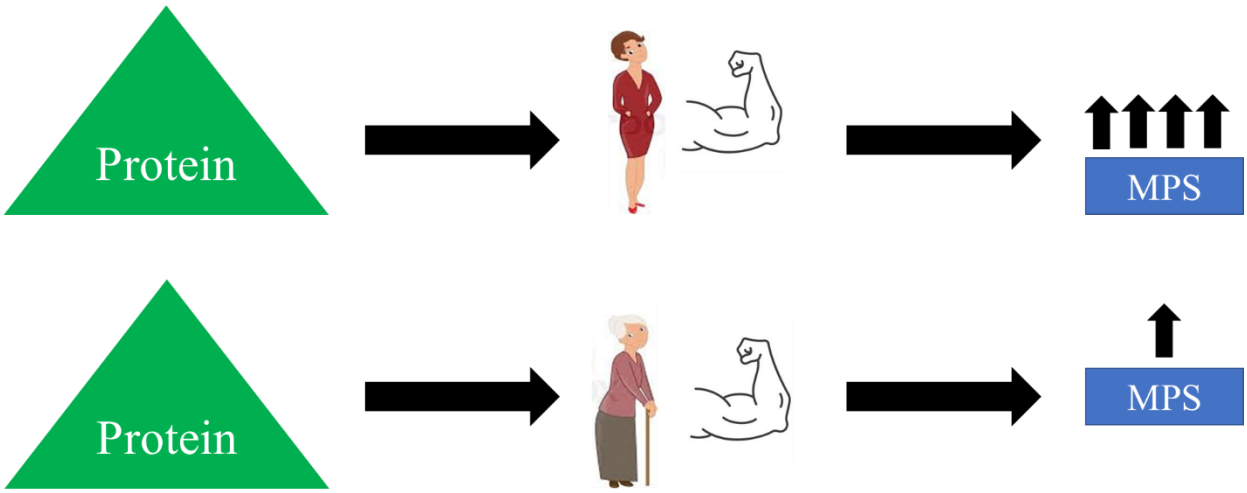

Figure 8. Anabolic resistance.

These premises lead researchers to propose that muscle loss with aging may be at least partially attributed to anabolic resistance to protein intake, given that skeletal muscle mass is maintained by the balance between MPS and muscle protein breakdown (MPB). Age-related muscle wasting is an important clinical aspect of older adults due to its close relationship with the development of sarcopenia.

Sarcopenia, or also called muscle failure (SUETTA; MAIER, 2019), is a chronic neuromuscular degenerative disease involving substantial muscle loss, dynapenia, and reduced physical function (CRUZ-JENTOFT et al., 2019). This condition has been considered a public health problem, given its possible adverse outcomes (e.g., disability, institutionalization, death) (HIRANI et al., 2015; LOCQUET et al., 2019), high prevalence in older adults (ETHGEN et al., 2017; SHEN et al., 2019; SU et al., 2019) and people with premature aging (COELHO-JUNIOR et al., 2019a; Article 3), and costs for public health (BEAUDART et al., 2014).

The atrophic process is characterized by a significant reduction in muscle area and preferably occurs in type II muscle fibers (LEXELL; TAYLOR; SJÖSTRÖM, 1988; KLITGAARD et al., 1990; NILWIK et al., 2013). These fibers are the main responsible for the production of maximal force and power, which occurs due to the larger availability and higher

activity of myosin ATPase and glycolytic enzymes, in comparison to type I muscle fibers (SCOTT; STEVENS; BINDER-MACLEOD, 2001).

Notably, the clinical presentation of sarcopenia encompasses some of the criteria diagnosis for frailty (LANDI et al., 2015; CESARI; NOBILI; VITALE, 2016), such as weakness, slowness, and body shrinking, while exhaustion and sedentary behavior are common consequences of sarcopenia progression (ZIAALDINI et al., 2017). Researchers have suggested that sarcopenia might be envisioned as a substrate for the development of frailty (LANDI et al., 2015; CESARI; NOBILI; VITALE, 2016). In other word, physical frailty may be the final pathway of sarcopenia progression (LANDI et al., 2015; CESARI; NOBILI; VITALE, 2016). This idea is further supported by the higher prevalence of sarcopenia in pre-frail and frail older adults when compared to robust people (FRISOLI et al., 2011; MIJNARENDS et al., 2015).

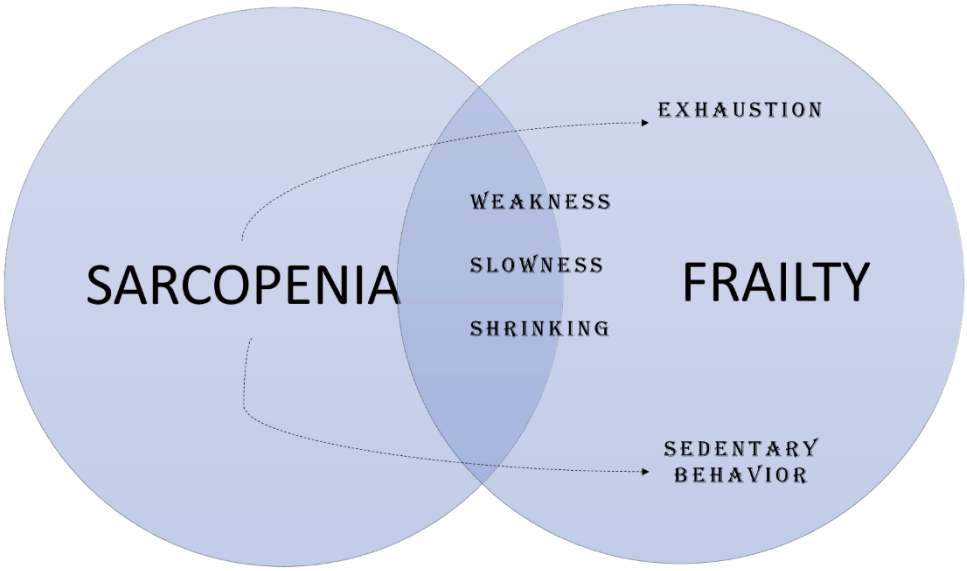

Figure 9. Sarcopenia and frailty.

In this context, insufficient dietary protein intake could be intended as a risk factor for the development of frailty by modulating sarcopenia-related parameters. On the other hand, opinion articles and consensus statements have argued that greater amounts of protein than the RDA (1.0–1.5 g/kg) can prevent or postpone age-related neuromuscular decline (DREYER; VOLPI, 2005; BAUER et al., 2013; VOLPI et al., 2013; BAUER; DIEKMANN, 2015; DEER; VOLPI, 2015; LANDI et al., 2016a; PHILLIPS; CHEVALIER; LEIDY, 2016), given the number of evidence that found higher physical function in older adults who had a protein intake higher than the RDA (GREGORIO et al., 2014; LAROCQUE et al., 2015; ISANEJAD et al., 2016; RAHI et al., 2016a; COELHO-JUNIOR et al., 2018a, Article 4; TEN HAAF et al., 2018).

Observational studies have reported a negative relationship between protein intake and frailty status in older adults. Beasley et al. (2010), Rahi et al. (2016b), Sandoval-Insausti et al. (2016), Nanri et al. (2018) found that higher protein intake was significantly associated with a lower frailty prevalence in older adults. These findings were supported by a systematic review and metanalysis that investigated more than 18,000 community-dwelling older adults from five different countries (COELHO-JUNIOR et al., 2018b, Article 5).

Although these findings indicate the need for increased protein intake in older adults to avoid frailty development, we clarified in the systematic review and metanalysis that data should be carefully interpreted due to some limitations (COELHO-JUNIOR et al., 2018b, Article 5). First, the use of different instruments to asses frailty (e.g., frailty phenotype, Kihon checklist [KCL]) may mean that studies are capturing different frailty domains (CHECA-LÓPEZ et al., 2019). Second, some studies (BOLLWEIN et al., 2013; SHIKANY et al., 2014; NANRI et al., 2018) have not observed a significant relationship between protein intake and frailty prevalence, and authors (BOLLWEIN et al., 2013) have suggested that protein distribution over the day may be more crucial in muscle anabolism. Third, protein quality, an index of the amount of EAA that is provided by a determined quantity of protein (MILLWARD et al., 2008), has been suggested as another important aspect of this paradigm.

Indeed, animal-derived proteins (e.g., meat, eggs) are thought to have a higher content of EAA, mainly branched-chain amino acids (BCAA; i.e., isoleucine, leucine, and valine) and consequently evoke greater MPS than plant-based proteins (e.g., soya, beans, nuts) (VAN VLIET; BURD; VAN LOON, 2015a; LANDI et al., 2016b). Indeed, BCAA seems to have a key role on MPS, since it improved the phosphorylation of eIF4E-BP1 and $p70^{S6K}$ at rest (LIU et al., 2001) and further enhanced $p70^{S6K,}$ Thr^{389}, and ribosomal protein s6 phosphorylations in response to exercise (KARLSSON et al., 2004). In the work of van Vliet et al. (VAN VLIET; BURD; VAN LOON, 2015b), for example, whey protein stimulated greater aminoacidemia and MPS than soy at rest and after an acute session of exercise.

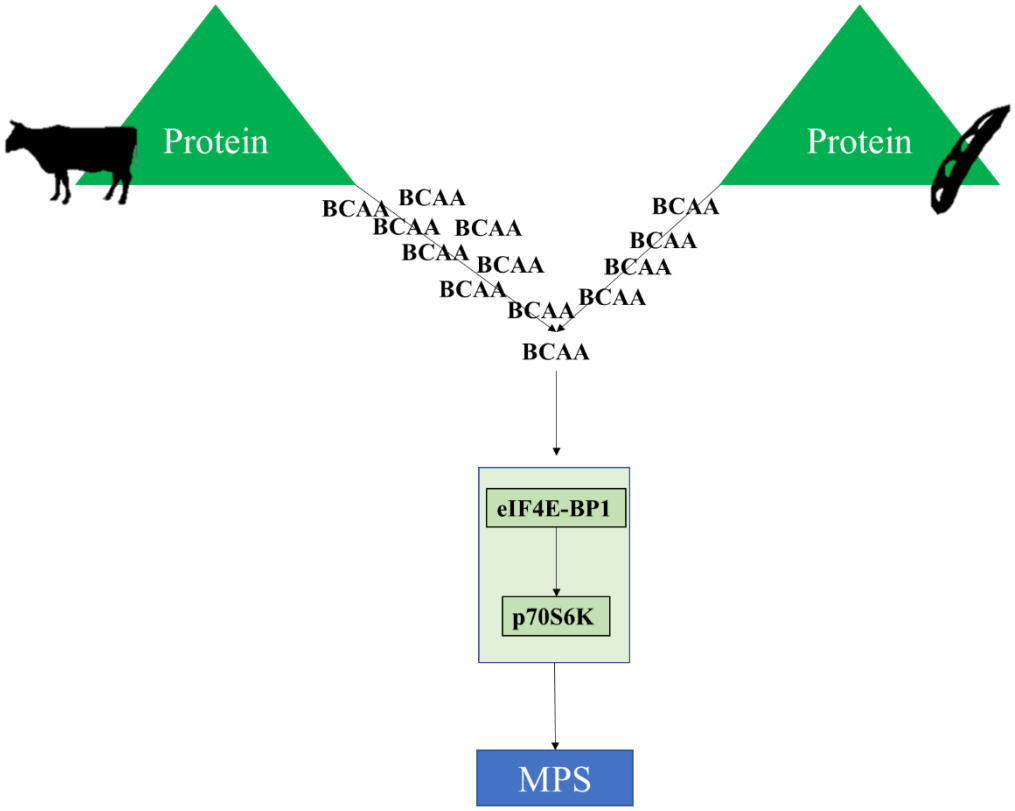

Figure 10. Animal- and Plant-Based Protein Sources.

These premises lead to the investigation (Article 6) if frailty status, identified using 4 different instruments, was associated with: a) daily protein consumption, b) daily body weight-adjusted protein consumption, c) BCAA consumption, d) evenness of protein distribution across the three main meals (i.e., breakfast, lunch, dinner), e) number of daily meals providing at least 0.30 g of protein per meal, and f) number of daily meals providing at least 0.4 g of protein/kg of body weight in community-dwelling older adults.

Some factors may limit the consumption of animal-based protein in older adults, such as oral health, price, and even lifestyle. Cultural and regional values and also associated with dietary patterns (MUKHERJEA et al., 2013; BROWN et al., 2019; RUGGIERO et al., 2019) and may negatively influence the adherence to diet recommendations (JUÁREZ-RAMÍREZ et al., 2019) and health-related outcomes (ZOU, 2017). In the study 7, the patterns of protein intake between Brazilian and Italian older adults were compared. Results indicated that Brazilians older adults had a higher intake of plant-based protein, while Italian older women consumed more animal-based protein. These differences were associated with different performances in physical tests among the groups. These data are supported by the study 8, in which higher plant-based protein intake was significantly associated with physical performance in community-dwelling Brazilian older women.

Taken together, these findings suggest that protein recommendations for counteracting frailty should take into consideration cultural values in an attempt to increase diet adherence.

Frailty and physical performance

Two main theoretical models of frailty have been proposed and tested for reliability: a) the frailty phenotype model, proposed by Fried et al. (2001), and b) the cumulative deficit model (CDM) or multidomain model (ROCKWOOD et al., 2005). The frailty phenotype model is the most utilized instruments for frailty characterization (CHECA-LÓPEZ et al., 2019), which has allowed the creation of a sketch of the mechanisms underlying its genesis and development (CLEGG et al., 2013; LANDI et al., 2015; CESARI; NOBILI; VITALE, 2016).

The frailty phenotype involves five cardinal factors (i.e., weakness, slowness, exhaustion, sedentary behavior, shirking) (FRIED et al., 2001) highly influenced by physical function, which lead researchers to alternatively referred to it as physical frailty model (CLEGG et al., 2013; MORLEY et al., 2013b), and proposed that sarcopenia should be considered a substrate for frailty's development and progression (LANDI et al., 2015; CESARI; NOBILI; VITALE, 2016).

This point of view may lead health professionals to the erroneous assumption that frail patients shown a reduced overall physical function. Nevertheless, physical function, as a construct, includes different physical capacities and abilities that may not necessarily be equally reduced in frailty. This information is important for exercise and rehabilitation prescribers since comprehend which are the main impairments on physical performance (e.g., reduced mobility) associated with frailty may collaborate with more specific exercise programs.

These premises are supported at least partially by evidence that found that physical capacities underlying mobility performance are sample-dependent (BENAVENT-CABALLER et al., 2016; ZARZECZNY et al., 2017; COELHO-JUNIOR et al., 2018b, Article 9). Benavent-Caballer et al. (2016) found that functional balance, but not other physical functions, was the most significant factor explaining timed "Up and Go" (TUG) performance in a sample composed by community-dwellers and institutionalized Spanish older adults. When Coelho-Junior et al. (2018a, Article 9) investigated only community-dwelling older women, researchers observed that high TUG performance was significantly associated with lower limb muscle strength, while low TUG performance showed an increased contribution of other physical capabilities, such as lower limb muscle power, balance, and aerobic capacity. Similarly,

Zarzeczny et al. (2017) reported a significant correlation between muscle strength/power and aerobic capacity in institutionalized older adults.

Therefore, the article 10 investigated the associations between frailty status identified using 4 different instruments and physical performance tasks in community-dwelling older adults.

Frailty and hypertension-related parameters

Frailty is commonly associated with physical adverse outcomes, such as falls, fractures, and disability. However, expert opinions have argued that frailty may be also significantly associated with hypertension-related parameters (ODDEN; BEILBY; PERALTA, 2015; BENETOS et al., 2016a), which may impose an extra risk for adverse outcomes in this population (RAVINDRARAJAH et al., 2017). Particularly, researchers suggest that specific attention may be necessary for the management of hypertension in frailty patients (ODDEN; BEILBY; PERALTA, 2015; BENETOS et al., 2016a).

Nevertheless, empirical studies testing this hypothesis have shown incongruent findings. Ricci (2014), Aprahamian et al. (2018), and Anker et al. (2019) observed a higher prevalence of hypertension among pre-frail and frail individuals in comparison to robust counterparts. In contrast, Basile et al. (2017) found an inverse relationship between frailty status and office systolic (SBP) and diastolic blood pressures (DBP). Fattory et al. (2013) detected that for every 1 mmHg reduction in office mean arterial pressure (MAP), the likelihood of being frail increased by 1.4%. Bastos-Barbosa et al. (2012) reported that frail older adults had higher SBP and DBP obtained by ambulatory blood pressure monitoring (ABPM), but not office blood pressure, in comparison to robust people. These findings were expanded by Gijón-Conde et al. (2018), who found that one additional frailty category was significantly associated with a 1.5442 mmHg low day time SBP and a 1.388 mmHg higher night-time SBP.

An interesting perspective was given by Rockwood and Howlett (2011), who proposed a U-shaped relationship between frailty and blood pressure, regardless of hypertension diagnosis. In this context, high blood pressure levels would be expected in robust and frail older adults, while prefrail individuals would show low blood pressure levels.

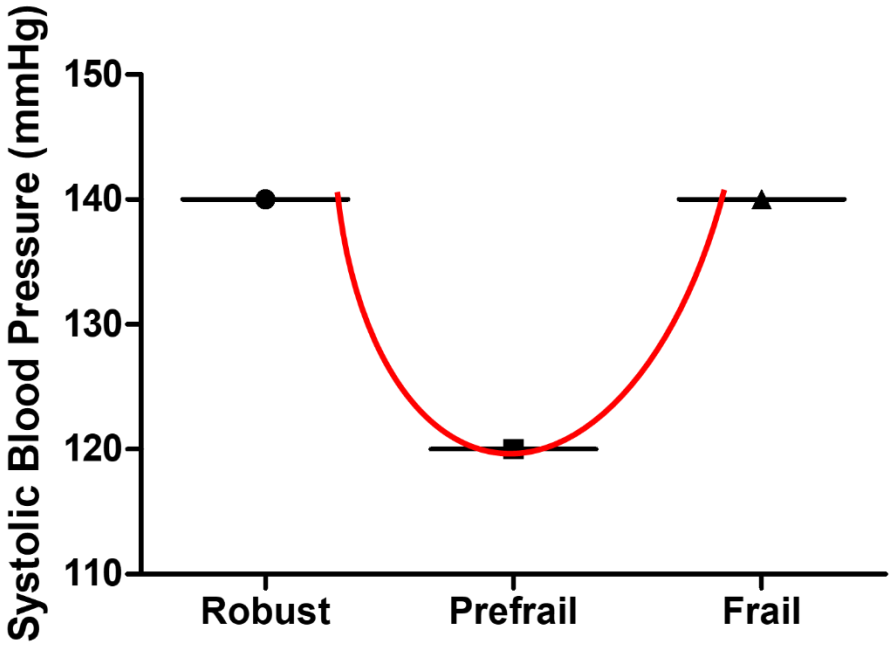

Figure 11. U-shaped relationship between frailty and blood pressure.

For the moment, only two clinical trials investigated if frailty status could modify the impact of antihypertensive treatment. Using data from the Hypertension in the Very Elderly Trial (HYVET), Warwick et al. (WARWICK et al., 2015) did not find a significant interaction between the effect of treatment for hypertension and frailty. Similarly, older adults from the Systolic Blood Pressure Intervention Trial (SPRINT) had increased risk for falls and all-cause hospitalizations, but not cardiovascular morbidity (PAJEWSKI et al., 2016).

The different results among the studies may be explained based on age, setting, hypertension diagnosis, time of hypertension, blood pressure measurement, frailty assessment, and comorbidities.

Age-related changes on cardiovascular structure and functioning have been argued as the main mechanisms underlying the possible relationship between frailty and hypertension (MULLER et al., 2014; ODDEN; BEILBY; PERALTA, 2015; BENETOS et al., 2016a), although conceptually frailty occurs separated from normal aging. In this context, studies have investigated other possible pathways mediating this phenomenon, including a) abnormalities on cardiovascular architecture and function; b) medication; and c) renal function.

Regarding abnormalities on cardiovascular architecture and function, a growing body of evidence suggests that frailty is associated with left ventricular (LV) hypertrophy (NEWMAN et al., 2001; NADRUZ et al., 2016), LV systolic and diastolic dysfunction

(NADRUZ et al., 2017), and arterial stiffness (NEWMAN et al., 2001; SINGH et al., 2012; AVILA-FUNES et al., 2014).

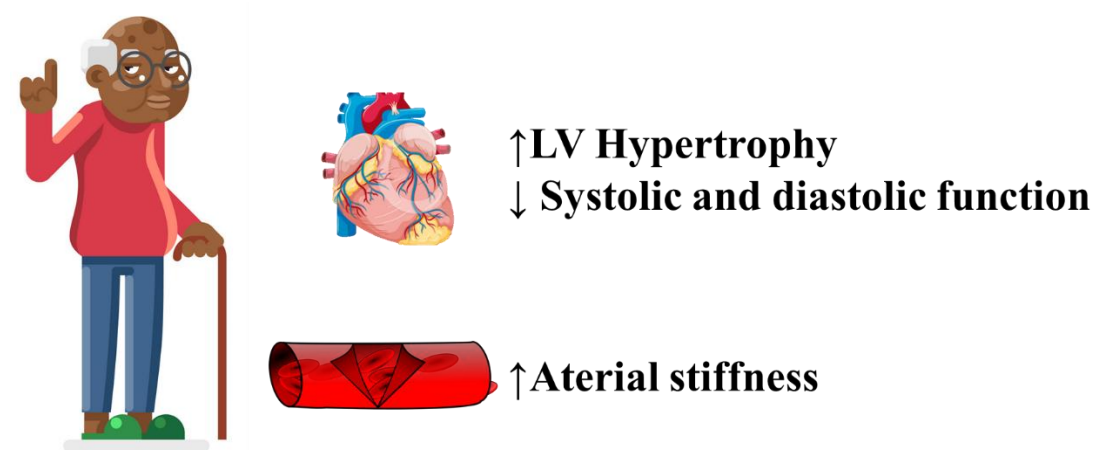

Figure 12. Cardiovascular abnormalities in frail older adults.

A possible scenario to associate the aforementioned cardiovascular abnormalities and blood pressure changes in frailty may be proposed beginning with arterial stiffness. Notably, arterial stiffness has not only been observed in frail older adults, but also in people showing one or more diagnostic criteria for frailty (e.g., weakness and slowness) (OCHI et al., 2010; ABBATECOLA et al., 2012; SAMPAIO et al., 2014; COELHO JUNIOR et al., 2015).

When the myocardial contracts, large elastic arteries, such as aorta and its down trunk, distend to store part of the stroke volume and subsequently drain this amount of blood to the periphery during cardiac diastolic, ensuring an adequate cardiac output and a continuous supply of blood to organs and tissues (SHIRWANY; ZOU, 2010; AVOLIO, 2013; SAFAR et al., 2018). During this phenomenon, the force of cardiomyocyte contraction generates a pulse wave (PW) that propagates along the vessel wall (SHIRWANY; ZOU, 2010). The velocity in which the forward and backward waves (PW velocity, PWV) propagate is dependent on the degree of impedance in conduit arteries, so that, in physiologic situations, large elastic arteries offer relatively low impedance and the wave returns toward the heart in late systole and early diastole (SHIRWANY; ZOU, 2010).

In contrast, stiffening of the central elastic vessels leads to a significant increase on PWV causing an early return of reflected wave (RW) to the aorta and heart during the early systole, increasing afterload (Laplace's law) (SHIRWANY; ZOU, 2010; AVOLIO, 2013; SAFAR et al., 2018). Observational studies have reported that arterial stiffness is a risk factor for increases in SBP and incident hypertension in normotensive people, even if after

adjustments for covariates (DERNELLIS; PANARETOU, 2005; KAESS et al., 2012; MITCHELL, 2014). This phenomenon can be perpetuated via positive feedback cycles, given that high blood pressure insults vascular structure by fragmenting elastin and increases collagen content (MITCHELL, 2014).

Elevated blood pressure causes an increase in LV wall stress and, over time, LV wall thickens and LV mass increases, as a compensatory mechanism to normalize wall stress and myocardial oxygen demand (NADRUZ, 2015). At this moment, blood pressure still remains elevated. As LV hypertrophy progress, chronic stress will result in ventricular dilation, fall in contractile function and eventually progress to heart failure (HF) (DRAZNER, 2011), which may be associated with low blood pressure levels.

In this context, it is conceivable to speculate that variations on blood pressure in studies investigating frail patients may occur in the function of the progression of cardiovascular abnormalities.

A second hypothesis is based on the antihypertensive therapy of frailty patients, given that researchers may have investigated patients under different pharmacological therapies. These premises seem to be important, given that some drugs may modify frailty development.

Angiotensin-converting enzyme inhibitor (ACEI), for example, is among the most widely used class of antihypertensive medication (BENETOS et al., 2016b), which acts inhibiting the action of ACE. The renin-angiotensin system is a major blood pressure regulating mechanism. After being released from the juxtaglomerular cells in the kidney, renin cleaves angiotensinogen, forming the decapeptide angiotensin (Ang I) that in turn is converted to the octapeptide Ang II by ACE. There is substantial and solid literature supporting the effects of Ang II on the cardiovascular system (KIM; IWAO, 2000; FERRARIO, 2006) and most recently studies started to suggest its role on muscle metabolism (BRINK et al., 2001; SONG et al., 2005; YOSHIDA et al., 2013), by proposing that Ang II causes protein degradation via an AT1 receptor-dependent mechanism by stimulating ubiquitin-proteasome system (UPS) and reducing insulin-like growth factor-1 (IGF-1) signaling, the main anabolic pathway in skeletal muscle (MUSARÒ et al., 2001).

Investigations in humans have reported positive (ONDER et al., 2002), negative (SPIRA et al., 2016), and null (SPIRA et al., 2016) associations between ACEI use and physical function (e.g., weakness and slowness). In addition, findings of a systematic review and metaanalysis did not identify differences in the aerobic capacity and upper limb muscle strength between ACEI users and non-users (ZHOU et al., 2015). Regarding muscle mass, which can be

associated with shrinking, most evidence has not indicated its associations with ACEI (DI BARI et al., 2004; SPIRA et al., 2016).

Potential explanations for this discordance among the studies may be the use of other drugs and the time using ACEI. Indeed, even though di Bari et al. (2004) proposed that longer ACEI use could be associated with larger lower extremity muscle mass, Spira et al. (2016) refuted this hypothesis and proposed that ACE inhibitor therapy in skeletal muscle decreases over time as negative effects of angiotensin II on muscle tissue become more prominent.

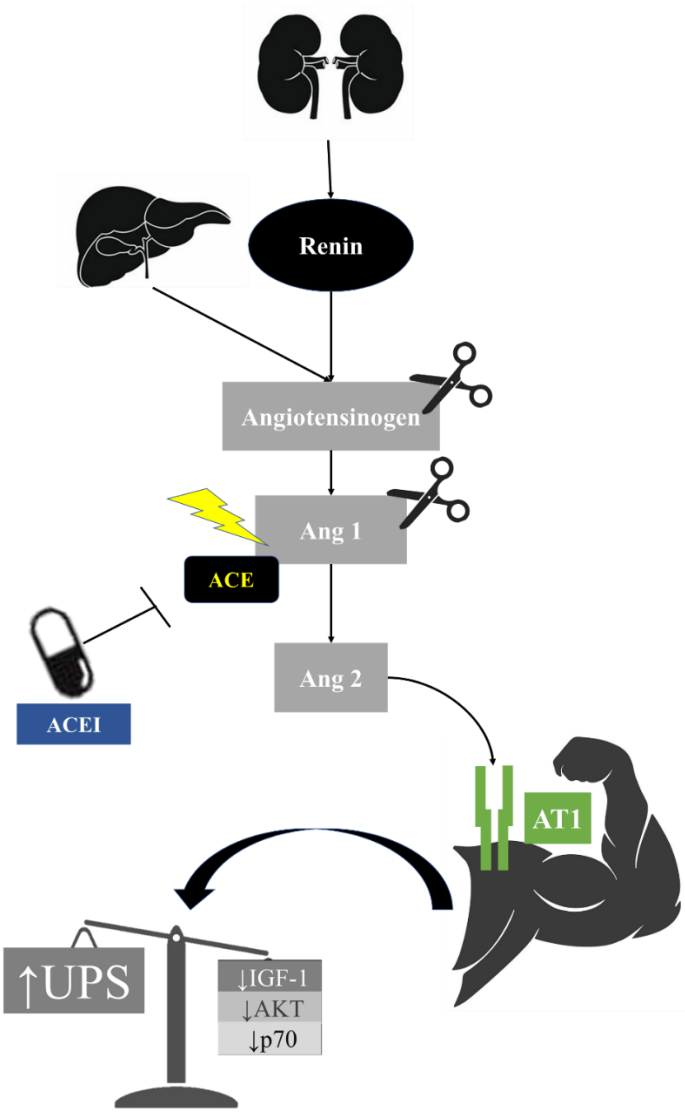

Figure 13. Renin-angiotensin system, ACEI, and skeletal muscle metabolism.

Another possible mechanism is based on subclinical renal injury. Indeed, renal damage may increase blood pressure levels by many mechanisms (e.g., increased sodium and

fluid retention, renin-angiotensin hyperactivation) (HUAN; COHEN; TOWNSEND, 2014) and reduced glomerular filtration rate has already been observed in frail patients (NADRUZ et al., 2016). Nevertheless, findings were based on secondary outcomes and more specific investigations are still necessary.

Low-grade inflammation, increased oxidative stress, and autonomic dysfunction are all present in the physiopathology of hypertension (BEEVERS; LIP; O'BRIEN, 2001) and observed in frail patients (VARADHAN et al., 2009; ALONSO-BOUZÓN et al., 2014; MARZETTI et al., 2019), so that other mechanisms than those abovementioned may be responsible for the association between hypertension and frailty. Furthermore, most studies are based on a cross-sectional design, and there is still a lack of longitudinal population-based studies.

To collaborate with the current knowledge, the article 11 investigated the relationship between frailty using 4 different instruments and office blood pressure, hypertension diagnosis, and antihypertensive treatment.

Exercise and Frailty

The growing knowledge regarding the adverse outcomes associated with frailty progression led many scientists worldwide to investigate possible therapies that could collaborate with frailty reversion. This topic is under intense debate and exercise training has been recognized as powerful tool to help clinicians in the management of frailty (DENT et al., 2017). Nevertheless, exercise training allows many combinations and is still not clear which could be the best exercise training design to counteract frailty.

In the last years, much attention has been paid to resistance training (RT), given the solid evidence on its effects on frailty-related parameters (LOPEZ et al., 2018). Nevertheless, most evidence did not investigate the effects of RT protocols on frailty status. In addition, studies combined RT with other types of exercise or other health interventions (SEINO et al., 2017), limiting inferences regarding the impact of RT alone on frailty status (NUNAN, 2019). Low-speed (LSRT) and high-speed resistance training (HSRT) are two types of RT, which differ in the velocity of concentric muscle contraction. As discussed in the subtopics below, both LSRT and HSRT have the potential to reverse frailty. However, this issue is still poorly explored in the literature.

Therefore, the present Ph.D. thesis had, as the main aim, investigate the effects of HSRT and LSRT on frailty status (Article 12). Secondarily, was examined the effects of both

RT programs on physical performance, cognitive function, and blood pressure, given its close association with frailty.

Low-Speed Resistance Training and High-Speed Resistance Training: Physical function

The importance of RT for the development of muscle strength has been known since ancient times (GRIVETTI; APPLEGATE, 1997). It is credited to Theseus the development of weightlifting as a sport, given the myth in which the hero had to move a heavy stone to recover his father's tokens to start a journey to Athens. However, the concept of RT, as well as the principles of overload and progression, are attributed to Milo of Croton, who won many of the most important athletic festivals. According to the legend, Milo walked one-hundred twelve steps per day with a four-year-old bull on his shoulders. As time went on, the animal got heavier and Milo, stronger. One of the first recommendations of RT for health and physical performance were performed by Galen, who argued that Gladiators should not perform too much RT to do not become heavy.

Figure 14. Theseus lifting the rock; Milo of Croton; and Cladius Galen (130-210 AD).

Throughout history, the prescription of RT persisted restricted to athletes who aimed to improve physical fitness or body shape, while its applications in health, mainly in older adults, was limited until the 80's and early 90's, when evidence started to report beneficial effects of RT programs on muscle mass and strength of older adults (MORITANI; DEVRIES, 1980; FRONTERA et al., 1988). Notably, such improvements were not only observed in community-dwelling older adults, but also in institutionalized patients with limited mobility (FIATARONE et al., 1990).

Since then, many studies have investigated and described the beneficial effects of RT or LSRT programs in older adults. These trials explored LSRT protocols based on different exercise intensities (KALAPOTHARAKOS et al., 2004) and models of organization

(NEWTON et al., 2002; PRESTES et al., 2015; COELHO-JUNIOR et al., 2019), to quote a few, enabling the creation of specific guidelines for health professional responsible for exercise prescription in older adults (CHODZKO-ZAJKO et al., 2009). According to the American College of Sports and Medicine (ACSM), RT is a potent intervention to improve muscle strength in older adults, if programs are performed at least 2 days per week at moderate-to-high intensity (CHODZKO-ZAJKO et al., 2009).

Evidence has supported investigations in robust older adults by demonstrating improved muscle strength in prefrail and frail older who performed LSRT programs (IKEZOE et al., 2005; HESS; WOOLLACOTT; SHIVITZ, 2006; LUSTOSA et al., 2011). Findings from a systematic review (LOPEZ et al., 2018) indicated that enhancements in muscle strength in frail older adults after RT ranged from 6.6 to 37.0% in the isometric knee extension, and from 13.1 to 20.5% in leg press.

Such enhancements in muscle strength in response to LSRT seem to occur in the function of improvements on neuromuscular control. According to the size principle of Henneman et al. (HENNEMAN; SOMJEN; CARPENTER, 1965), motoneuron and motor units (MU) are recruited from smallest to largest. In the light of LSRT, this means that exercise intensity and a reduced supply of adequate oxygenation to the muscle due to muscular contractions lead to recruitment of largest MU, which have a high content of type II muscle fibers, by increasing the number of active MUs (i.e., more type II muscle fibers working together) or a more rapid frequency of MU discharges (i.e., greater number of stimulus, in a shorter time frame) (MCKINNON et al., 2017).

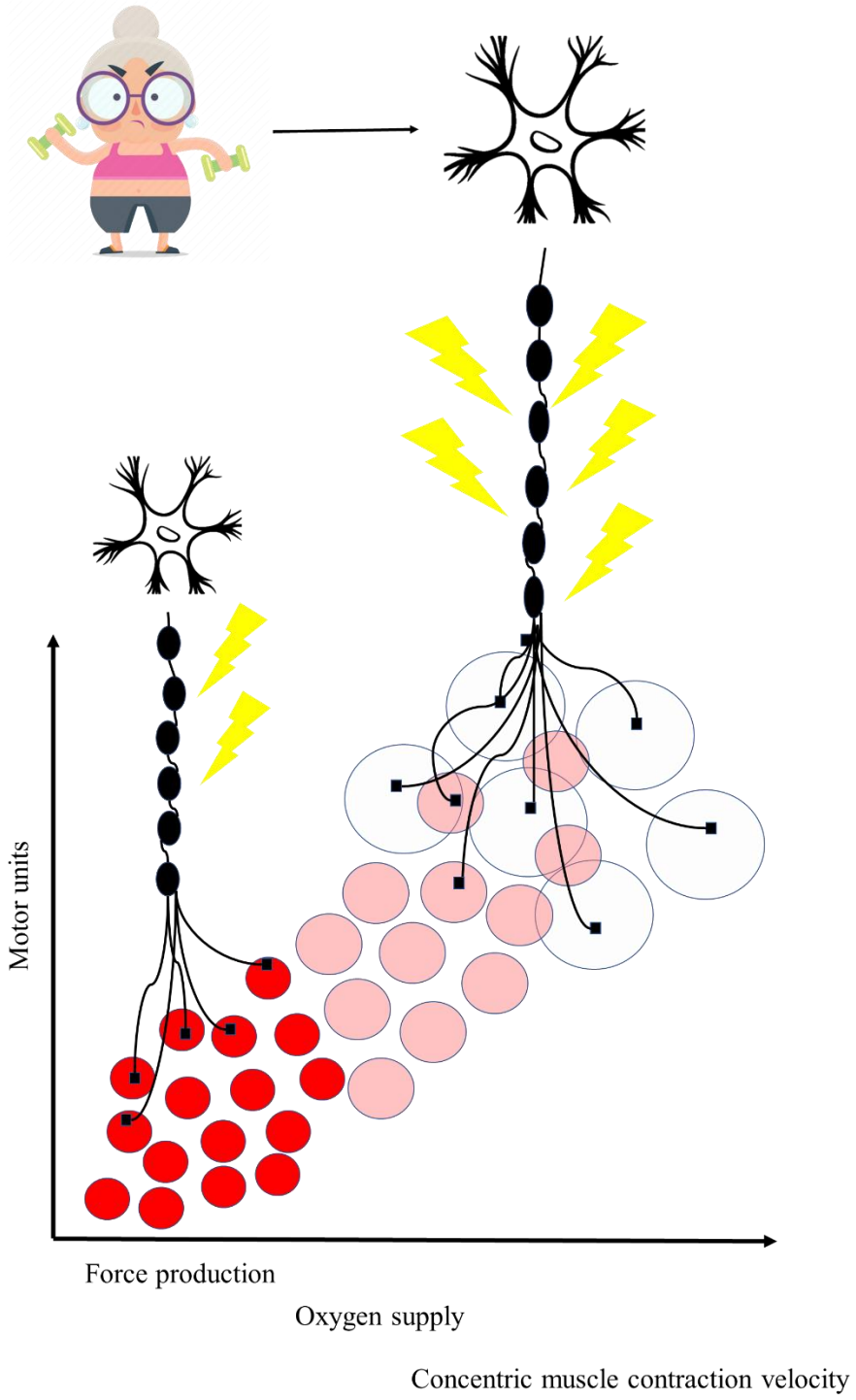

Figure 15. Size principle in the light of Resistance Exercise.

Although LSRT has an important influence on muscle strength, its effects on other criteria diagnosis for frailty, such as mobility (CHODZKO-ZAJKO et al., 2009) seem to be limited. Mobility, the individual's ability to transfer from a place to another as comfortable as possible with reduced risk of falls is one of the five cardinal points of frailty (FRIED et al., 2001) and is strongly associated with falls (PIAU et al., 2019) and mortality (STUDENSKI et

al., 2011), as well as part of the clinical presentation of many diseases, such as stroke and Parkinson's.

Notably, many investigations in the early 2000's began to suggest that muscle power, the capacity to exert force in a short time interval, declines earlier and faster and is more associated with mobility tasks than muscle strength (SUZUKI; BEAN; FIELDING, 2001; BEAN et al., 2003; LAURETANI et al., 2003). Findings from the InCHIANTI study, for example, indicated that women at 50-60 years of age had a 20-30% reduction on lower-limb muscle strength, while muscle power was reduced in ~50% (LAURETANI et al., 2003). Researchers also observed that lower limb muscle power showed a slightly higher discriminating power in the identification of poor mobility in women in comparison to upper limb muscle strength, lower limb muscle strength, and calf muscle area (LAURETANI et al., 2003). Bean et al. (2003) expanded this view by indicating that older adults with low lower limb muscle power had two- to threefold higher odds of limited mobility in comparison with those with lower limb muscle strength. In the investigation performed by Suzuki et al. (SUZUKI; BEAN; FIELDING, 2001), dorsiflexion peak power was stronger associated with chair rise and stair climb performance than plantarflexion and dorsiflexion isometric strength.

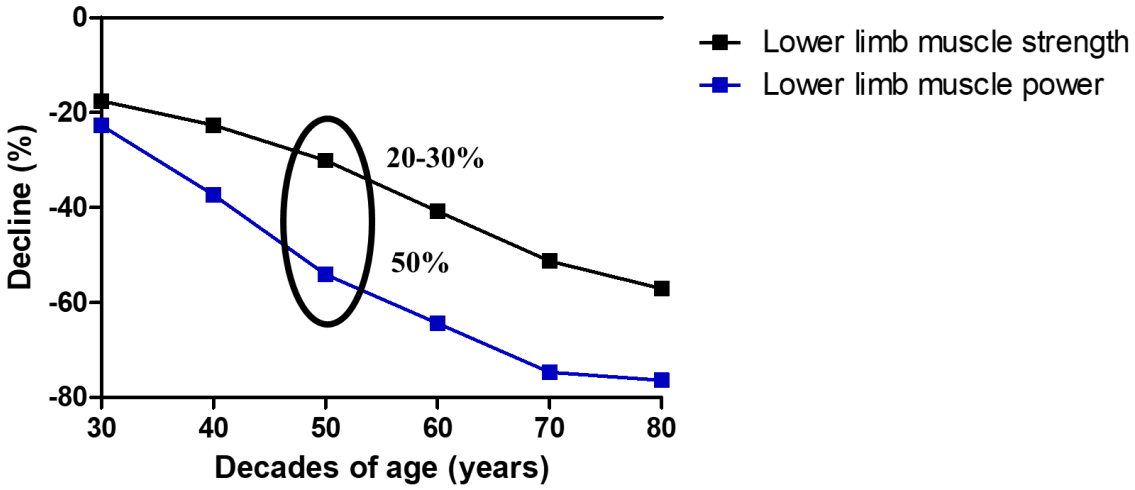

Figure 17. Age-related decline in muscle strength and muscle power. Adapted from Lauretani et al. (2003).

These premises led researchers (MISZKO et al., 2003; HENWOOD; RIEK; TAAFFE, 2008; RAMÍREZ-CAMPILLO et al., 2014; LOPES et al., 2016) to suggest that RT programs based on concentric muscle contractions performed as fast as possible, HSRT, could cause greater improvements in mobility tasks than LSRT in older adults. The first studies that investigated the effects of HSRT on older adults did not compare HSRT and LSRT but proposed

RT protocols composed by many stimuli, including concentric muscle contractions performed as fast as possible. In these articles, Professor Häkkinen's group (1998) found that this type of intervention improved many neuromuscular parameters (e.g., muscle strength, muscle power, neuromuscular activation).

Professor Bean's group was pioneer to compare the effects of HSRT and LSRT protocols on the physical function of older adults (BEAN et al., 2003). Researchers investigated independent and mobility-limited older adults who performed a traditional LSRT for important limb groups based on two sets of 10 repetitions or a HSRT based on task-specific movements performed as fast as possible during the concentric action. Similar improvements on Short Physical Performance Battery (SPPB) were observed after both LSRT and HSRT, while a post hoc analysis indicated that greater enhancements were observed in older adults with velocity limitations after HSRT. One major limitation of this study is that RT programs were not equalized according to exercise total volume, limiting extrapolations.

Subsequent studies found greater (MISZKO et al., 2003; RAMÍREZ-CAMPILLO et al., 2014; LOPES et al., 2016) or similar (HENWOOD; RIEK; TAAFFE, 2008) improvements in mobility tasks after HSRT in comparison to LSRT. Investigations compared equalized RT protocols (RAMÍREZ-CAMPILLO et al., 2014; LOPES et al., 2016) or HSRT using less total workload per exercise sessions (HENWOOD; RIEK; TAAFFE, 2008). The programs occurred from 12 to 16 weeks using exercise machines and weight vests and intensities ranged from 40% to 75% of 1RM.

Systematic review and metanalyses (TSCHOPP; SATTELMAYER; HILFIKER, 2011; ORSSATTO et al., 2019) supported these findings by indicating that HSRT caused slight greater improvements in mobility than LSRT, but authors indicated that both RT protocols seem to be clinically compatible. It is worth mentioning that investigations were based on physically healthy older adults, short-term RT protocols, and expensive exercise machines, limiting extrapolations for prefrail and frail older adults.

Indeed, evidence comparing LSRT and HSRT in frail people is still scarce, but studies investigated exercise programs using high-velocity muscle contractions have reported encouraging data (IZQUIERDO; CADORE, 2014). Nevertheless, expert opinions (CADORE; IZQUIERDO, 2018; FRAGALA et al., 2019) have encouraged the inclusion of HSRT on exercise programs for frail older adults. According to researchers, perform concentric muscle contractions as fast as possible would be crucial to improve mobility and restore independence.

The plausibility behind this hypothesis is based on a neuromuscular component summed to the biomechanical particularities of each mobility task. High-velocity muscle

contractions are supposed to recruit type II muscle fibers to a similar or greater extent as LSRT (MCKINNON et al., 2017). Regarding the biomechanical perspective, it is suggested that crucial moments of some mobility tasks (e.g., plantar flexion to lift from the chair) are more dependent of fast than strong movements.

However, it is still unknown if HSRT may cause greater improvements in mobility than LSRT in prefrail and frail older adults.

Low-Speed Resistance Training and High-Speed Resistance Training: Cognition

Cognition may be understood as the expression of brain activity by which the mind interacts with the world (ASSOCIATION, 2019). Although cognitive parameters are not part of the criteria diagnosis for physical frailty (FRIED et al., 2001), this variable has been included in other instruments (e.g., KCL)(SEWO SAMPAIO et al., 2016b), and observational studies have found that frail people are at higher risk for cognitive decline (GRANDE et al., 2019; MIYAMURA et al., 2019).

The effects of RT on cognitive function are still poorly explored and the few available studies have reported contradictory results. A systematic review and metanalysis of 18 studies reported that different adaptations in response to RT are observed according to cognitive levels, so that overall cognitive function is improved in demented older adults, while short-term memory was increased in cognitively intact older adults (Article 13).

Cardalda et al. (2019) and Yoon et al. (2017) observed improved overall cognitive function in frail older adults. This view was expanded by Van de Rest et al. (2014), who found increased digit span, attention, and working memory performances in prefrail and frail older adults after a 24-week LSRT program. To the best of our knowledge, only Yoon et al. (2018) compared the effects of HSRT and LSRT, and results demonstrated similar improvements in overall cognitive function after both protocols of RT.

The article 14 compared the acute effects of low-speed resistance exercise (LSRE) and HSRE (HSRE) on memory, inhibitory control, and attention. Findings suggested that both exercise protocols improved learning memory immediately after the exercise session, but transitory improvements were only sustained after LSRE after one hour.

Low-Speed Resistance Training and High-Speed Resistance Training: Blood Pressure

The effects of RT on the blood pressure of older adults has long been explored. Evidence has been accumulated that different designs of RT may reduce baseline blood pressure in hypertensive and normotensive older adults (FARIA TERRA et al., 2008; MORAES et al.,

2012; MOTA et al., 2013; COELHO-JUNIOR et al., 2018c). These findings are supported by systematic reviews and metanalyses (CORNELISSEN; SMART, 2013; MACDONALD et al., 2016).

The main concern regarding the prescription of LSRT for the management of blood pressure in older adults is based on the fact that this kind of intervention may elicit exaggerated blood pressure responses (FLECK; DEAN, 1987), increasing the risk of acute events during or after the exercise session. In contrast, authors (COELHO-JUNIOR et al., 2018d) have argued that HSRT protocols may elicit significant reductions on blood pressure, while individuals are submitted to low cardiovascular and osteoarticular stress.

Recent seminal observations made by our group reported significant post-exercise hypotension (PEH) in community-dwelling older women after an acute session of high-speed resistance exercise (COELHO-JUNIOR; AGING; 2017). These findings were supported by Machado et al. (2019), who observed lower SBP and DBP values in older adults with type II diabetes mellitus. On the other hand, Orsano et al. (2018) did not observe significant effects of HSRE on the blood pressure of community-dwelling older women. In frail people, the Article 15 reports that a longer time reduction in SBP and an exclusive decrease in MAP are observed after LSRE in comparison to HSRE.

To the best of our knowledge, only one study investigated the chronic effects of HSRT on the blood pressure of older adults. In this study, Coelho-Junior et al., (COELHO-JUNIOR et al., 2018d) did not observe significant changes in blood pressure values after a 22-week RT program composed by HSRT and LSRT sessions. However, there is no evidence in prefrail and frail older adults.

ARTICLES

ARTICLE 1

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Review

If my muscle could talk: Myokines as a biomarker of frailty

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ABSTRACT

Frailty is a potentially reversible state of increased vulnerability to negative health-related outcomes that occurs as a result of multisystem biological impairment and environmental aspects. Given the relevance of this condition in both clinics and research, biomarkers of frailty have been actively sought after. Although several candidate biomarkers of frailty have been identified, none of them has yet been incorporated in the assessment or monitoring of the condition. Over the last years, increasing research interest has been focused on myokines, a set of cytokines, small proteins and proteoglycan peptides that are synthetized, expressed and released by skeletal myocytes in response to muscular contractions. Myokines may act in autocrine, paracrine, and endocrine manner and regulate several processes associated with physical frailty, including muscle wasting, dynapenia, and slowness. This review discusses the rationale to support the use of myokines as biomarkers of frailty in older adults.

1. Introduction

Frailty is a highly prevalent condition among older adults, and is defined as a potentially reversible state of increased vulnerability to negative health-related outcomes (Collard et al., 2012). This condition occurs as a result of multisystem biological derangements that impact the organismal ability to maintain homeostasis after a stressor event (van Kan et al., 2010; Clegg et al., 2013; Morley and Malmstrom, 2013; Choi et al., 2015). Social factors may also have a role in frailty development, given that many environmental aspects, such as separation from both parents during early life (Haapanen et al., 2018), adult experiences with bad (e.g., social insecurity, noise neighborhood) and poor (e.g., lack of street lighting, recreation) neighborhoods (Desrichard et al., 2018), and difficult to cope with stressful events (Gobbens, 2019) are associated with this condition.

As frailty progresses, the individual may experience a number of negative events, such as fractures, disability, hospitalization, nursing home placement, and death (Kojima, 2016, 2017). As such, frailty represents a major public health problem (Collard et al., 2012).

The impact of frailty on older people's wellbeing and on the sustainability of healthcare systems has instigated intense research on its biological determinants. As a corollary to this, many research groups have been looking for biomarkers that could be used to predict the risk of frailty and its progression in attempt to prevent its development and avoid its negative outcomes (Calvani et al., 2015, 2017, 2018a; Wang et al., 2019). Despite the fact that several biomolecules have been proposed as frailty biomarkers, none of them has shown to capture the complexity of the condition, which indicates that there is still a long way to go and the need for a broad understanding of the possible candidates.

Recent evidence indicates that myokines, molecules that are expressed, synthetized and released by skeletal myocytes in response to muscular contractions (Pedersen et al., 2003, 2004, 2013), regulate several processes associated with physical frailty, including muscle wasting, dynapenia, and slowness (Pedersen and Hojman, 2012; Kim et al., 2019). However, few studies have reported empirical findings regarding the association between myokines and frailty. This review discusses the rationale to support the use of myokines as biomarkers of frailty in older adults.

2. Biomarkers of aging

The notion of time is commonly based on a measurement that can be expressed in seconds, minutes, hours, etc. In the ancient Greek, however, time could be expressed as Chronos (Χρόνος) or Caerus (Καιρός).

While Chronos is the personification of chronological time, linearity, quantification; Caerus represents favorable moments, moments of good feelings, opportunity, quality (Bulfinch, 2009; Buxton, 2004). Therefore, in a conversation about a train trip, Chronos would probably focus on the time spent sitting in the train, while Caerus would focus on the opportunity to talk and observe beautiful landscapes, even if for short periods of time.

Similarly, the current notion of aging avoids the simplistic view that this process is only determined chronologically and proposes that aging is a highly heterogenous, nonlinear phenomenon influenced by many factors, including the genetic background, environment, and diseases (Baker and Sprott, 1988; Bürkle et al., 2015; Bai, 2018; Levine and Crimmins, 2018). Indeed, although aging is observed in many species, it is not universal, since some species show no age-related increase in mortality or decline in fertility (Kirkwood, 2002). In most mammals, including humans, aging is determined by the capacity of the organism to cope with physical, chemical, and biological agents over the course of life (Franceschi et al., 2006, 2018), which is largely influenced by the genetic background and exposure to damage, causing the emergence of high heterogeneity within individuals of the same species (Levine, 2013).

Consequently, chronological age (CA), which is determined by the simple flow of time and expresses no more than for how long a person is alive, might not be the best indicator of body's age (Baker and Sprott, 1988; Bürkle et al., 2015; Mitnitski et al., 2016; Bai, 2018), and has been indicated only as a proxy for the rate of aging (Levine, 2013). On the other hand, biological age (BA), the sum of empirical biomarkers of health (e.g., DNA methylation, physical function, cytokines) into a single variable by a mathematic regression, is strongly influenced by environmental factors and genetic differences taking into account the heterogeneity of people with the same CA (Mitnitski et al., 2016; Levine and Crimmins, 2018). Hence, compared with CA, BA provides a more realistic representation of a person's biological health status. As a matter of fact, BA has shown to a better predictor of negative outcomes and death than CA independent of individual diseases and traditional risk factors (Levine, 2013; Soriano-Tárraga et al., 2017, 2018).

The concept of biomarker of aging, first proposed by Baker, in 1998, refers to a biological parameter able to predicts the functional status of an individual better than CA. Due to the variability of aging, it is unlikely that a single biomarker may provide a valid measure of BA (Wagner et al., 2016), which might instead be offered by the

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Abbreviations: AD, Alzheimer's disease; ADL, Basic activities of daily living; AFAR, American Federation for Aging Research; BA, Biological age; BDNF, Brainderived neurotrophic factor; CA, Chronological age; CFS, Clinical frailty scale; CHS, Cardiovascular Health Study; CSHA, Canadian Study of Health and Aging; CPOD, Chronic obstructive pulmonary disease; HF, Heart failure; HIMS, Health in Men Study; IADL, Instrumental activities of daily living; ILAS, I-Lan Longitudinal Aging Study; IGF-1, Insulin-growth factor 1; IGFBP, Insulin-growth factor binding protein; IL-6, Interleukin-6; IL-15, Interleukin-15; IRS-1, Insulin receptor substrate; KCL, Kihon checklist; mTOR, Mammalian target of rapamycin; P1K3, Phosphatidylinositol 3-kinase; PF, Physical frailty; SD, Standard deviation; SPPB, Short-physical performance battery; UPS, Ubiquitin proteasome system; WHO, World Health Organization; WHAS, Women's Health and Aging Study

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combined assessment multiple genes, proteins, metabolites, and even other markers, such as physical performance (Bai, 2018).

The criteria of the American Federation for Aging Research (AFAR) (2016) indicate that a biomarker of aging must: a) predict the rate of aging; b) monitor a basic process that underlies the aging process, not the effects of disease; c) be able to be tested repeatedly without harming the person (e.g., blood test); and d) be something that works in humans and in laboratory animals (e.g., mice). Nevertheless, some researchers argued that the last parameters might be questioned, given that preclinical models could show some biological differences in comparison to humans, limiting comparisons among the species (Bürkle et al., 2015).

Finding a robust and specific biomarker of aging according to AFAR criteria might be very a difficult mission, given that age is associated with many syndromes and diseases. To overcome such an obstacle, several investigations have started searching for biomarkers conditions intrinsic to the aging process, such as sarcopenia and frailty, instead of aging per se. Recent advances in the field of frailty biomarkers are briefly discussed in the following sections.

3. Challenges in frailty biomarker discovery

Frailty is defined as a reversible state of increased vulnerability to health-related negative outcomes, including disability and mortality, which occurs separated and faster than normal aging process in response to a multisystem impairment of the human body (van Kan et al., 2010; Clegg et al., 2013; Morley and Malmstrom, 2013; Choi et al., 2015). Although large agreement exists regarding the clinical relevance of frailty, its operationalization is still hampered by the absence of a univocal definition. Indeed, more than 60 different instruments for the assessment of frailty are currently available, with limited concordance across them (Buta et al., 2016; Faller et al., 2019).

Many theorical models of frailty have been proposed over the years (Morley et al., 2013), which are inspired by two seminal models: a) the phenotype model (Fried et al., 2001) and b) the cumulative deficit model or multidomain model (Rockwood et al., 2005).

Fried et al. (2001) developed and operationalized the phenotype model of frailty by analyzing 5317 older adults from the Cardiovascular Health Study (CHS). Researchers established the frailty phenotype based on five elements: 1) unintentional weight loss; 2) dynapenia; 3) fatigue; 4) poor mobility; and 5) inactive lifestyle. The classification is quantitative, so that people with three or more factors are classified as frail, while those with one or two factors are considered pre-frail. Alternatively, Rockwood et al. (2005) proposed the Clinical Frailty Scale (CFS), which is based on the cumulative deficit model. The scale is composed of 70 clinical deficits, including the presence and severity of diseases, ability to perform basic activities, and cognitive status, to quote a few. A score is assigned to each the 70 items, and then an overall score ranging from 1 (i.e., very fit) to 7 (i.e., severely frail) is eventually calculated.

The diversity of the two major frailty constructs is a major obstacle to the comprehension of the pathophysiology of frailty. Nevertheless, multiple biological hypothesis have been proposed to explain frailty, such as anemia, abnormal hormonal levels, dysregulation of inflammatory process, oxidative stress, mitochondrial dysfunction, and cellular senescence (Fried et al., 2009; Sieber, 2017). However, the time-course of the interaction between two or more biological systems over the course of life leading to frailty is currently unknown, and the most plausible explanation is that frailty occurs in response to a nonlinear and heterogenous process (Fried et al., 2009; Pijpers et al., 2012). Note that an illustration of this theory was provided by Fried et al. (2009), who observed that different combinations of three or more systems at abnormal level were significant predictors of frailty, regardless of the nature of individual systems.

Recently, the notion of heterogeneity in frailty has been expanded by the introduction of the concept of fluctuation in frailty, that is the within-individual variability in the frail state over the long-term frailty trajectory, which can be thought as a sign of loss of homeostasis (Stolz et al., 2019).

Based on these premises, frailty may be envisioned as a highly heterogeneous condition, with substantial variations inter- and withinsubjects, caused by a nonlinear decline in the function of some, but none in particular, inter-related biological systems. Although the pathophysiology of frailty is largely unclear and its clinical appraisal depends of the assessment tool used, a notable overlap in many clinical signs and frailty outcomes may be observed between frailty constructs, including increased risk of falls, disability, fracture, and death (Ensrud et al., 2008, 2009; Pilotto et al., 2012), which suggests that common elements work together in the development and progression of frailty. In this scenario, the search for biomarkers of frailty has been an emergent and active field of research, given that alterations in biological markers may precede the clinical manifestations of frailty, possibly allowing timely corrective interventions (Calvani et al., 2015, 2017, 2018a; Wang et al., 2019). Frailty biomarkers could also serve to comprehend the underlying pathophysiology, besides being relevant targets in clinical decision-making and randomized clinical trials (Calvani et al., 2015, 2017, 2018a; Wang et al., 2019).

Considerable research effort has been provided by different laboratories and many candidate biomarkers for frailty have been proposed, such as proinflammatory markers (e.g., TNF-alpha, C reactive protein [CRP]), neuroendocrine markers (e.g., testosterone, vitamin D), and metabolic markers (e.g., glycated hemoglobin [HbA1c]), to quote a few (Saedi et al., 2019). Nevertheless, the perspective of a single biomarker of frailty is unlikely, and it is argued that there is not one biological marker that reliably tracks the multitude of frailty (Calvani et al., 2015). In this sense, the identification of the largest number of possible molecules may collaborate to develop a model able to predict this condition and clarify its physiopathology.

4. Why could myokines be useful biomarkers of frailty?

The skeletal muscle is the largest organ of human body and constitutes about 40% of the total body mass in non-obese adults. Once regarded simply as the biological substratum of locomotion, the skeletal muscle is now recognized as the largest protein reserve in the body, the primary site for the regulation of glucose metabolism, and the major energy consumer, with a pivotal role in body metabolism (Fougère et al., 2015). Furthermore, the skeletal muscle tissue communicates with many other systems (e.g., nervous, endocrine, immune) by the synthesis and release of molecules collectively called myokines.

The existence of a muscle factor was first proposed by Goldstein (1961), based on the observation that a humoral factor could mediate exercise-induced hypoglycemia. However, this metabolic

perspective remained unexplored for decades, and many researchers in the 90's argued that the increased levels of circulating cytokines observed after exercise occurred due to the adherence and activation of neutrophils and macrophages recruited in response to exercise-induced muscle damage and fibers disruption (Drenth et al., 1995; Ostrowski et al., 1998b). This view was based on the fact that systemic concentrations of some inflammatory factors, mainly interleukin (IL)-6, increased exponentially during and after exercise to levels similar to those observed after a trauma (Ostrowski et al., 1998a). However, in the early 2000's, evidence began to emerge that contracting skeletal muscles were the major source of IL-6 produced during exercise (Jonsdottir et al., 2000; Steensberg et al., 2000). In the investigation by Jonsdottir et al. (2000), researchers observed that IL-6 mRNA levels were similarly increased (~20-fold) after concentric and eccentric contractions, but not after resting, in the calf muscles of rats. Similarly, Steensberg et al. (2000) found that contracting skeletal muscles were the major source of IL-6 production during exercise. These findings changed the assumption that systemic levels of cytokines during and after exercise were exclusively derived from immune cells and led to the hypothesis that IL-6 could be functioning in a hormone-like fashion to help regulate glucose homeostasis (Gleeson, 2000; Steensberg et al., 2000). According to Gleeson (2000), the depletion on muscle glycogen stores during exercise could be the triggering factor to the increase of IL-6 levels, which would signal the liver to increase hepatic glycogenolysis and glucose release in the attempt to maintain glucose homeostasis and avoid muscle fatigue. These premises were confirmed by the observation that muscular glycogen content was a critical determinant regulating the IL-6 response to exercise (Keller et al., 2001; Steensberg et al., 2001), and that glucose ingestion during exercise attenuated the exercise-induced increase in IL-6 levels (Henson et al., 2000; Nieman et al., 2003).

At that time, Pedersen and coworkers first proposed the term myokine (Pedersen et al., 2003, 2004), to identify any molecule, including IL-6, expressed, produced and released by active skeletal muscles and exerting either paracrine or endocrine effects. Nowadays, myokines are conceptualized as molecules, cytokines or signaling peptides expressed, synthetized and released by skeletal muscle fibers in response to muscular contractions with pluripotent effects (Pedersen and Hojman, 2012; Kim et al., 2019; Lee and Jun, 2019). Indeed, not only IL-6, but many other myokines (e.g., myostatin, irisin, IL-15) have been studied due to their possible autocrine, paracrine, and endocrine effects on numerous metabolic process, including energy expenditure, lipid (e.g., lipolysis, adipocyte browning, fat-free acids oxidation), muscular (e.g., glucose uptake) and liver (e.g., glycogenolysis and glycogenesis) metabolism, and insulin sensitivity (to review see Pedersen et al., 2007; Pedersen and Febbraio, 2008; Pal et al., 2014; Ahima and Park, 2015; Huh, 2018).

According to proteomic studies, approximately 60 myokines are regulated in response to muscle contraction (Raschke et al., 2013), while ~40 different myokines have a role in muscle differentiation (Ojima et al., 2014). Nevertheless, some research groups have argued that many muscle-derived factors need further evaluation regarding their biological activity and function to be appropriately characterized as myokines (Kim et al., 2019; Lee and Jun, 2019).

In addition, the identification of skeletal muscle as an active endocrine organ allows the investigation of the role of myokines in other important physiological process, such as muscle wasting and renewal, mitochondrial activity, and inflammation, to quote a few. Indeed, myokines have been suggested as a possible mediator for the positive effects of regular exercise training on human body (Pedersen and Hojman, 2012; Pratesi et al., 2013; Kim et al., 2019). Hence, myokines are possibly essential components of whole-body homeostasis. It follows that alterations in the synthesis, secretion and downstream signaling of myokines could potentially contribute to the development of metabolic (Carson, 2017; Garneau and Aguer, 2019), cardiovascular (Ouchi et al., 2016), kidney (Ebert and Kralisch, 2016), hepatic (Yang and Luo, 2017), and bone (Guo et al., 2017) diseases.

Furthermore, myokines may directly impact some variables associated with frailty, which allows the proposal of two theorical models: a) sarcopenia hypothesis and b) hypokinesia hypothesis.

4.1. The sarcopenia hypothesis

Sarcopenia, or, as recently suggested, muscle failure (Suetta and Maier, 2019), is a chronic degenerative neuromuscular disease (Anker et al., 2016) encompassing dynapenia, muscle atrophy, and low physical performance (Cruz-Jentoft et al., 2018). This condition has been considered a public health problem, given its possible adverse outcomes (e.g., disability, institutionalization, death) (Hirani et al., 2015; Locquet et al., 2019), high prevalence in older adults worldwide (Ethgen et al., 2017; Shen et al., 2019; Su et al., 2019), and costs for public health (Beaudart et al., 2014).

During aging, several biological processes, including inflammation (Marzetti et al., 2009; Coelho Junior et al., 2016), oxidative stress (Marzetti et al., 2009), and mitochondrial dysfunction (Marzetti et al., 2010, 2013; Picca et al., 2019), contribute to muscle protein breakdown and muscle atrophy. In contrast, physical exercise (Morton et al., 2018) and increased protein consumption (Calvani et al., 2018b; CoelhoJunior et al., 2018a, 2018b; Coelho-Junior et al., 2019) counteract agerelated muscle loss. Interestingly, myokine expression is induced under both anabolic and catabolic conditions, with local and systemic effects. At the time, the direct implication of insulin-growth factor 1 (IGF-1), myostatin, irisin, decorin, and myonectin on muscle mass regulation has been described (Fig. 1).

The IGF-1/Akt/mammalian target of rapamycin (mTOR) pathway is integral to the stimulation of protein synthesis (Glass, 2003; Zhang et al., 2007; Bonaldo and Sandri, 2013; Coelho Junior et al., 2016). After being secreted by contracting skeletal muscles (Musaro et al., 2001), IGF-1 binds to the tyrosine kinase IGF-1 receptor in the lipid bilayer and recruit insulin receptor substrate 1 (IRS-1) (Latres et al., 2005), which leads to the phosphorylation and activation of phosphatidylinositol 3-kinase (PI3K) (Glass, 2003; Zhang et al., 2007). Once active, PI3K triggers a number of downstream pathways, including the creation of the lipid binding site to Akt, activation of mTOR, and phosphorylation and activation of p70s6k (Stitt et al., 2004; Latres et al., 2005), eventually leading, to increased ribosomal biogenesis and protein translation (Bodine et al., 2001; Latres et al., 2005; Csibi et al., 2010; Lamas et al., 2010).

Alternatively, IRS-1 receptor, Akt and mTOR can be activated by myonectin (CTRP15), a myokine related with nutritional status and lipid metabolism (Seldin et al., 2012). This view is supported by the fact that myonectin significantly induces phosphorylation of IRS-1, Akt, and mTOR, as well as suppresses the transcription of autophagy genes (i.e., Atg7 and Atg12) in cultured hepatocytes and in the mouse liver (Seldin et al., 2013). Hence, myonectin can either act alone or

potentiate the IGF-1/PI3K/Akt/mTOR pathway. Whether these pathways are relevant to muscle physiology has yet to be proven.

Myostatin is as a negative regulator of muscle mass from embryogenesis to adult life, impairing muscle synthesis and increasing muscle catabolism (Tobin and Celeste, 2005; Carnac et al., 2006; Durieux et al., 2007). Once activated, myostatin activates activin type II receptor and consequently activin type I receptor, which phosphorylates and activates small mother against decapentaplegic (SMAD) proteins, mainly SMAD2 and SMAD3, forming a complex with SMAD4 that migrates to the nucleus and upregulates the transcription of target catabolic genes (Carnac et al., 2006; Trendelenburg et al., 2009). In addition, myostatin can induce muscle loss by stimulating and activating the ubiquitin proteasome system (UPS) and by impairing the activation of Akt, satellite cells, and myogenic factors (e.g., MyoD) (Durieux et al., 2007; Trendelenburg et al., 2009).

Decorin is a member of the small leucine-rich proteoglycan family and it is a component of the extracellular matrix (Guiraud et al., 2012). Decorin expression is significantly increased in contracting myotubes and skeletal muscle samples obtained from exercised mice (Kanzleiter et al., 2014). In humans, plasma decorin is increased after acute and chronic exercise (Kanzleiter et al., 2014). This myokine is thought to act as a counter-regulator of myostatin by binding and inactivating myostatin (Guiraud et al., 2012; El Shafey et al., 2016). This inhibits the activation of SMAD 2/3 complex possibly reducing muscle protein degradation (El Shafey et al., 2016). Indeed, intramuscular injection of decorin significantly induced muscle hypertrophy in pre-clinical models of muscle dystrophy (Guiraud et al., 2012).

Recently, Reza et al. (2017) found that irisin-treated C2C12 myotubes showed increased expression of genes associated with satellite cell regulation, skeletal muscle regeneration, muscle growth, and myogenesis. To expand their observations, researchers injected recombinant irisin in mice and observed upregulation of Akt, mTOR, and p70s6k genes, followed by noticeable muscle hypertrophy and increased muscle strength. Interestingly, the regulation of muscle mass by irisin does not seem to be restricted to muscle protein synthesis, since gene expression of Atrogin-1 and muscle RING-finger protein-1 (MuRF1), two ubiquitin ligases with important roles in ubiquitin-mediated protein degradation, were down-regulated in muscles of irisin-treated animals.

Although muscle atrophy does not completely explain age-related dynapenia, the progressive loss of muscle mass contributes to declining muscle strength/power and physical function during aging (Lauretani et al., 2003; Doherty, 2003; Goodpaster et al., 2006; Aagaard et al., 2010; Marzetti et al., 2018). Furthermore, the development of sarcopenia may influence the synthesis and release of myokines, as reflected by the fact that pre-sarcopenic and sarcopenic older women showed significantly lower serum irisin concentrations than non-sarcopenic peers (Park et al., 2019).

In this scenario, a looping back model may be proposed, in which myokines signaling is altered during sarcopenia, thereby contributing to muscle atrophy, dynapenia, and reduced physical performance. Muscle failure, in turn, may lead to reduced expression and synthesis of myokines in response to muscle stimulation, aggravating muscle wasting.

The impact of this loop on frailty appears clearer if sarcopenia is envisioned as the biological substratum of physical frailty and the pathophysiological pathway through which negative health-related outcomes of frailty occur (Landi et al., 2015). Indeed, weight loss, dynapenia, and poor mobility are convergent clinical features of the two conditions, while low physical activity levels are commonly associated with sarcopenia development (Steffl et al., 2017; Lee et al., 2018). Although myokine signaling influences and is influenced by sarcopenia, no direct evidence exists about the association between myokines and physical frailty. On the other hand, a deeper understanding of myokine signaling is worth being pursued for both frailty biomarker discovery and the identification of intervention targets.

4.2. The hypokinesia hypothesis

Although the ability to coordinate different types of physical capabilities (e.g., walk, run, climb) has been instrumental to human evolution, the comforts of current high technological world have led to the acquisition of an increasingly hypokinetic behavior.

According to the World Health Organization (WHO) (2014), physical inactivity increases with age, such that more than 30% of adults worldwide show insufficient daily physical activity levels. This scenario is particularly critical given that physical inactivity has been identified as a major risk factor for coronary heart disease, type 2 diabetes, and breast cancer colon cancer (Lee et al., 2012a, 2012b).

On the other hand, engagement in regular physical activity, any body movement that is produced by the contraction of skeletal muscles and that increases energy expenditure (Chodzko-Zajko et al., 2009), and/or physical exercise, a planned, structured, and repetitive movement to improve or maintain physical fitness (Chodzko-Zajko et al., 2009), has shown to improve quality of live, prevent and treat several medical disorders, and avoid early death (Pedersen and Saltin, 2006; Lee et al., 2012a, 2012b).

Since the discovery of myokines and the regulation of their secretion by muscle contraction, researchers have proposed that long-term benefits of physical activity and exercise may be, at least in part, mediated by myokine actions (Pedersen and Hojman, 2012; Pedersen, 2013). Indeed, systemic concentrations of many myokines, including irisin, IGF-1, brain-derived neurotrophic factor (BDNF), are increased in older adults following exercise training (Cassilhas et al., 2007; Forti et al., 2015; Tibana et al., 2017; Zhao et al., 2017).

Based on these premises, if the endocrine function of muscle is not stimulated by sufficient levels of physical activity or exercise, the synthesis and release of myokines will be limited, which may contribute to malfunction of several organs (Pedersen and Febbraio, 2008). Over time, such a biological environment may predispose to the development of frailty.

5. Myokines and frailty parameters

Currently, only a few studies have investigated the association between frailty and myokines in older adults. This lack of evidence certainly limits our discussion and the extrapolation of our models.

Results from the Women's Health and Aging Study (WHAS) indicated that both prefrail and frail older women according to Fried's criteria tend to have lower systemic IGF-1 levels than age-matched nonfrail counterparts (Cappola et al., 2009; Leng et al., 2009). Using data from the Health in Men Study (HIMS), Yeap et al. (2013) observed that community-dwelling older men with low plasma IGF-1 levels were more likely to be frail, while those without frailty but with low plasma IGF-1 levels were more likely to develop frailty over three years of follow-up.

It is possible to observe that investigations were restricted to the study of IGF-1, which was explored as a part of the growth hormone–IGF-1 axis. However, results from observational studies demonstrated a significant relationship between systemic myokines levels and some PF parameters. These findings are presented in the following sections.

5.1. Myokines and physical function

Although a clear temporal course connecting declines in physical function and the development of disability is difficult to propose, it is possible to suggest that muscle weakness, fatigue, slowness, and low levels of physical activity are closely related. Therefore, findings regarding these parameters are presented in the same section.

Findings from observational studies in older adults indicate a significant association between IGF-1 and muscle weakness (Onder et al., 2006; Taekema et al., 2011; Bucci et al., 2013; Vestergaard et al., 2014), slowness (Birnie et al., 2012; Doi et al., 2016), and disability (Cappola et al., 2003; Doi et al., 2016); myostatin and muscle weakness (Fife et al., 2018); and IL-15 and muscle weakness (Yalcin et al., 2018).

Notably, the UK-based Caerphilly Prospective Study showed that one standard deviation (SD) increase in serum IGF-1 was associated with 1.5% faster mobility over 19 years of follow-up (Birnie et al., 2012). In addition, Cappola et al. (2003) selected a random sample from the WHAS I and observed that low systemical IGF-1 levels combined with elevated pro-inflammatory markers conferred a higher risk for progressive functional decline, ADL disability, and death.

Interestingly, some studies demonstrated a significant relationship between IGF binding protein (IGFBP) and muscle weakness (Onder et al., 2006), mobility (Onder et al., 2006; Birnie et al., 2012), short physical performance battery (SPPB) scores (Onder et al., 2006), and disability (Taekema et al., 2011), which suggests that the assessment of binding proteins may be related to physical function more than IGF-1 concentrations.

5.2. Myokines and muscle wasting

Numerous investigations demonstrated an association between myostatin and muscle wasting. However, most findings derive from samples composed by participants with different chronic diseases, instead of healthy people. Indeed, myostatin is inversely correlated with total-body skeletal muscle mass in patients with chronic obstructive pulmonary disease (CPOD) (Ju and Chen, 2012). In adults with heart failure (HF), myostatin was independently associated with muscle wasting (Furihata et al., 2016), and so was in patients on hemodialysis (Delanaye et al., 2019). In addition, Delanaye et al. (2019) observed that serum levels of myostatin and IGF-1 predicted 1-year mortality in patients on hemodialysis.

Regarding older adults, in one of the few available reports on this matter, Yarasheski et al. (2002) found that serum myostatin immunoreactive protein was inversely associated with muscle mass/ height^2 and fat free mass. More recently, Peng et al. (2018) investigated a random subsample from the I-Lan Longitudinal Aging Study (ILAS) and observed that myostatin was an independent risk factor for low relative appendicular muscle mass in men, but not in women. Differences among the results are mainly related to the assessment tool used to characterize frailty, suggesting that the association between myokines and PF parameters may be assessment-dependent.

6. Challenges

In the present review, we have discussed the prospect of using myokines as biomarkers of frailty. Only a limited number of myokines have been studied in relation to frailty or frailty-related parameters.

The main concern regarding the use of myokines as biomarkers of frailty resides in the difficulty intrinsic to their assessment and interpretation. Indeed, while, basal levels of irisin, IGF-1, and myostatin, to quote a few, may reflect their synthesis rates in the skeletal muscle; systemic levels of other myokines result from their production by various tissues and cell types. In fact, IL6, for example, can be produced by almost any cell type under appropriate stimulation (Garneau and Aguer, 2019), and many investigations have studied IL6 as a pro-inflammatory cytokine with significant associations with lower muscle mass (Visser et al., 2002), muscle weakness (Visser et al., 2002; Schaap et al., 2006), and sarcopenia (Payette et al., 2003). Nevertheless, its role as a myokine has been only marginally explored. Similarly, BDNF is thought to be synthetized and released by both muscle and brain tissues (Lee and Jun, 2019), and it may be able to cross the blood-brain barrier (Pan et al., 1998). Finally, some researchers have argued that the list of myokines is much more limited than that proposed by proteomic and genomic studies. This implies that additional research is necessary to characterize these molecules as myokines, before testing their association with clinical outcomes (Di Raimondo et al., 2017; Garneau and Aguer, 2019).

Future studies aimed at investigating myokines as biomarkers of frailty should include the assessment of poorly studied biomolecules (e.g., irisin) alone or in combination with other well-established parameters (e.g., muscle strength), given that this approach may provide further interesting findings than the use of a single parameter (Cappola et al., 2003; Delanaye et al., 2019). Furthermore, since skeletal muscle contraction is likely the primary stimulus for myokine synthesis and secretion, myokine baseline levels may not reflect the muscle biosynthetic capacity. Hence, future studies should also investigate if acute changes in myokine levels after an exercise session are related with frailty. Finally, studies should use several techniques to investigate if the molecular expression of such myokines in the active muscle may represent the systemic levels.

7. Final considerations

Myokines shows potential to be used as biomarkers of frailty based on sarcopenia and sedentary models. However, the lack of empirical evidence on this issue indicates that there is still a long road ahead to understand which, how, and when myokines should be assessed to better reflect their muscle synthesis rate. Such findings could be very important in the context of biomarkers, contributing to the generation of models to predict frailty based on myokines alone or combined with other biomarkers. Declaration of competing interest None.

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ARTICLE 2

Prevalence of prefrailty and frailty in South America: a systematic review of observational studies

ABSTRACT

Aims: The present study aimed to investigate the prevalence of prefrailty and frailty in South American older adults according to the setting and region. **Methods:** We performed a literature search combining the terms "frailty", "South America" or a specific country name was performed at PubMed, EMBASE, Lilacs, and Scielo to retrieve articles published in English, Portuguese or Spanish on or before September 2019, which investigated older adults aged 60 years or older from any setting (e.g., community, hospital, nursing home). **Results:** One-hundred eighteen reports (98 performed from Brazil, seven from Chile, five from Peru, four from Colombia, two from Ecuador, one from Argentina, and one from Venezuela) were included in the present study. The mean prevalence of prefrailty in South America was 46.8% (50.7% in older in-patients, 47.6% in the community, and 29.8% in nursing-home residents). The mean prevalence of frailty in South America was 21.7% (55.8% in nursing-home residents, 39.1% in hospitalised older adults, and 23.0% in the community). **Conclusions:** Prefrailty and frailty are highly prevalent in South American older adults, with rates higher than those observed in Europe and Asia. In the community, almost one-in-two are prefrail and one-in-five are frail, while institutionalised individuals are more frequently affected. These findings indicate the need for immediate attention to avoid frailty progression toward negative health outcomes. Our findings also highlight the need for specific guidelines for frailty in South America.

Key words: Latin America, Low-income countries, Elderly, Sarcopenia, Mobility, Nursing home.

INTRODUCTION

Frailty is a potentially reversible state of increased vulnerability to stressful events[1] that occurs as a result of multisystem biological derangements[2–5] and socioeconomic inequalities[6-8]. Frailty progression increases the risk a several negative health-related outcomes, including disability, loss of independence, institutionalisation, and death[9–11]. Noticeably, frailty is associated with greater healthcare utilisation and costs[12], making this condition a top public health priority[1].

Since the operationalisation of the frailty phenotype by Fried et al.[13], considerable research has been devoted to explore its incidence[14], prevalence[15–18], associated factors[19,20], and main outcomes[21]. These efforts have allowed the generation of recommendations and guidelines for the identification and management of frailty across healthcare settings[22–24].

Yet, the majority of studies on which guidelines are based originated from high-income countries, while very few publications have been produced in South America[14–16]. Hence, epidemiological characteristics of frailty in this region are poorly described. This is especially concerning since South America, in spite of the image of a young region, is ageing at a faster pace than Europe[25]. Furthermore, risk factors for frailty development, such as socioeconomic disadvantages, chronic diseases and disabilities, are highly prevalent in South America[6].

To increase the knowledge of the epidemiology of frailty in South America, the present systematic review explored the prevalence of prefrailty and frailty in South American older adults according to settings, regions, and frailty assessment tools.

MATERIALS AND METHODS

We conducted a systematic review of observational studies to investigate the prevalence of prefrailty and frailty in South America. The study was fully performed by investigators and no librarian was part of the team. This study complies with the criteria of the Primary Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement (Appendix 1)[26]. All data are available in the Open Science Framework at DOI https://doi.org/10.17605/OSF.IO/XZ2S8.

Eligibility criteria

The following criteria were used for inclusion: (a) observational studies, including cross-sectional, cohort, case-control and longitudinal studies, which described or supplied data to calculate the prevalence of frailty in older adults from any setting (e.g., community, institutions); (b) participant age 60 years or more; (c) frailty assessment by a validated scale; and (d) published studies (English, Portuguese, and Spanish languages). There was no restriction on sample size or study population, and studies that investigated disease-specific populations were also included and analysed accordingly. Studies that did not report the prevalence of robust older adults in addition to frailty prevalence or that classified participants as frail according to reduced physical/or cognitive function only were excluded.

Search strategy and selection criteria

Studies published on or before August 2019 were retrieved from the following four electronic databases by one investigator: (1) PubMed, (2) EMBASE, (3) Lilacs, and (4) Scielo. Reference lists for reviews and retrieved articles for additional studies were checked and citation searches on key articles were performed on Google Scholar and ResearchGate for additional reports. A search strategy was designed using keywords, MeSH terms, and free text words such as frailty and South America. In addition, frailty, frail, and Frail Elderly [Mesh] were exhaustively combined with the name of South American countries. The complete search strategy used for the PubMed is shown in Appendix 2. Only eligible full-text in English, Portuguese or Spanish languages were considered for review.

Data extraction and quality assessment

Titles and abstracts of retrieved articles were screened for eligibility by two researchers. If an abstract did not provide enough information for evaluation, the full-text was retrieved. Disagreements were solved by a third reviewer. Reviewers were not blinded to authors, institutions, or manuscript journals. Data extraction was independently performed by two reviews using a standardised coding form. Disagreements were solved by a third reviewer. Coded variables included methodological quality and the characteristics of studies. If two or more studies shared the same sample, the largest sample size was considered in the analysis[15,18]. The prevalence of prefrail and frailty were calculated according to the cut-off values used in the studies (Appendix 3), so that no changes were performed when frailty identification was made using the Fried frailty phenotype[13], Tilburg frailty indicator[27], FRAIL[28], Kihon checklist[29], and SOF[30] instruments. When participants were identified

as visible vulnerable with the Edmonton frailty scale[31] and apparently vulnerable with the Clinical Frailty Scale[32] they were considered prefrail, as well as they were considered frail when were identified as Mild, Moderate, and Severe Frailty using the Edmonton frailty scale[31] and mildly, moderate, and severely frail using the Clinical Frailty Scale[32].The quality of reporting for each study was assessed by two researchers using the Newcastle Ottawa Quality Assessment Scale (NOS) for non-randomised studies[33,34]. The agreement rate between reviewers for quality assessment was κ=0.93.

RESULTS

Literature search

Of 20,229 registers recovered from electronic databases and hand search, 19,612 records were excluded based on duplicate data, title or abstract. Six-hundred seventeen records were fully reviewed and assessed for eligibility. Finally, 118 studies met inclusion criteria (Figure 1).

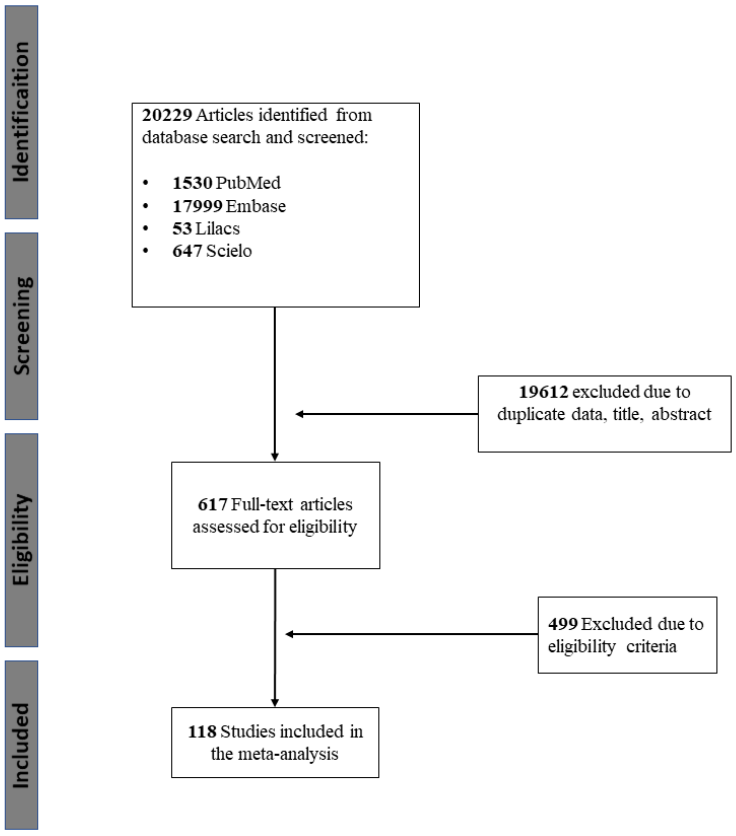

Figure 1. Flowchart of the study.

Characteristics of included studies

Table 1 provides a general description of included studies. Overall, a total of 53,134 older adults (mean age ± standard deviation [SD]= 80.1 ± 3.8 years; women= 32,006 [60.2%]) from seven countries (i.e., Argentina, Brazil, Chile, Colombia, Ecuador, Peru, and Venezuela) were studied between 2008 and 2019. Studies were based on cross-sectional, longitudinal and cohort designs. Of the 118 included studies, 98 (83.0%; n=36,786) were performed in Brazil [6,31,43–52,35,53–62,36,63–72,37,73–82,38,83–92,39,93–102,40,103–112,41,113–122,42,123–130], seven (5.9%; n=6,091) in Chile[40,131–136], five (4.2%; n=4,052) in Peru[137–141], four (3.3%; n=3,836) in Colombia[142–145], two (1.7%; n=304) in Ecuador[146,147], one (0.8%; n=100) in Argentina[148], and one (0.8%; n=1,965) in Venezuela[139].

The frailty phenotype[13] was the most commonly used tool for frailty assessment (66.6%), followed by the Edmonton frailty scale (EFS) (23.6%), Tilburg frailty indicator (TFI) (4.9%), Fatigue, Resistance, Ambulation, Illnesses, & Loss of Weight (FRAIL) scale (3.3%), Kihon checklist (KCL) (2.4%), study of osteoporotic fracture (SOF) (0.8%), and clinical frailty scale (0.8%). Most studies (n=104; 91.5%) investigated community-dwelling older adults, while nursing-home residents were investigated in nine studies, hospitalised individuals were investigated in five studies, and three studies were performed with population data. Seven studies reported the prevalence of frailty using the same sample two or more times, while three studies used more than two tools to assess frailty.

Participants were recruited in different places, including urban, rural, and areas of social vulnerability, primary and secondary healthcare centres, and community centres, to quote a few. The most common comorbidities were hypertension (33 studies), diabetes (25 studies), osteoarthritis (OA) (19 studies), cancer (17 studies), stroke (15 studies), chronic pulmonary obstructive disease (CPOD) (12 studies), chronic kidney disease (CKD) (10 studies), and heart failure (HF) (10 studies). Dyslipidaemia, obesity, coronary heart disease (CHD), myocardial infarction (MI), atrial fibrillation, cognitive impairment, and disability were reported in less than five studies each.

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Table 1. Characteristics of the included studies.

Year	Authors	Study design	Sample	Setting	Frailty criteria	Sample size	Age (mean ± SD, range)	Female, n (%)	Pre-frailty, n (%)	Frailty population, n (%)	Frailty by gender, n (%)	Comorbidities
Argentina												
2018	Costa et al.	Prospective cohort	Patients with HF	Hospitalized	Clinical Frailty Scale	100	77 ± 13.4 (60 or older)	44(44.0)	—	26 (26.0)	18 (69.2)	HTN, diabetes, dyslipidemia, obesity, CHD, CKD, stroke, atrial fibrillation, CPOD
Brazil												
2012	Alencar et al.	Cohort	Public outpatient care	Community	Fried	207	78.3 (65 or older)	159 (76.8)	112 (54.1)	48 (23.0)	38 (79.1)	Cognitive impariment, depression, disability
2018	Alves et al.	Cross-sectional	Public and private outpatient care	Community	Fried	148	69.7 ± 7.0 (60-86)	114 (77.0)	68 (45.9)	52 (35.0)	—	HTN, OA, diabetes, osteoporososis, CVD, depression
2017h	Aprahamian et al.	Cross-sectional	Public outpatient clinic	Community	Fried	124	78.6 (60 or older)	83 (66.9)	75 (60.5)	18 (15.0)	—	HTN, diabetes, cancer, CPOD, CAD, HF, asthma, stroke, OA, CKD
2017h	Aprahamian et al.	Cross-sectional	Public outpatient clinic	Community	FRAIL	124	78.6 (60 or older)	83 (66.9)	44 (35.5)	7 (6.0)	—	HTN, diabetes, cancer, CPOD, CAD, HF, asthma, stroke, OA, CKD
2017	Aprahamian et al.	Cross-sectional	Public outpatient clinic	Community	FRAIL	811	81.6 (60 or older)	591 (72.9)	394 (48.6)	305 (38.0)	231 (75.7)	HTN, diabetes, cancer, CPOD, CAD, HF, asthma, stroke, OA, CKD
2018	Aprahamian et al.	Prospective cohort	Public outpatient clinic	Community	FRAIL	701	79.5 (60 or older)	448 (63.9)	295 (42.1)	257 (37.0)	—	HTN, diabetes, HF, CAD, stroke, CKD, cancer
2017	Augusti et al.	Cross-sectional	Day care center	Community	Fried	306	72.5 ± 5.7 (65 or older)	185 (60.5)	71,5 (23.4)	66 (21.5)	54 (81.8)	HTN, diabetes, stroke, cancer, OA, CPOD, CVD
2008	Alvarado et al.	Cross-sectional	SABE	Community	Fried	2143	60 or older	1262 (58.9)	917 (42.8)	762 (36.0)	491 (64.4)	—
2018	Belisário et al.	Cross-sectional	Urban area	Community	Fried	705	60 or older	470 (66.7)	368 (52.2)	112 (15.9)	—	—

2019	Binotto et al.	Cross-sectional	Candidates to obtain a driver's license.	Community	Fried	421	60-70	127 (30.2)	189 (44.9)	8 (1.9)	—	—
2018	Bôas et al.	Cross-sectional	Public outpatient clinic	Community	EFS	150	67.7-71.5 (60 or older)	84 (56.0)	—	41 (27.3)	—	Diabetes
2019	Bolina et al.	Cross-sectional	Urban area	Community	Fried	701	60 or older	468 (66.8)	366 (52.2)	112 (16.0)	—	—
2013a	Borges et al.	Cross-sectional	Institutionalized	Institutionalized	EFS	54	60 or older	16 (29.6)	—	40 (74.1)	16 (40.0)	—
2015a	Borges et al.	Cross-sectional	Institutionalized	Institutionalized	EFS	54	60 or older	16 (29.6)	—	40 (74.1)	16 (40.0)	—
2017	Brigola et al.	Cross-sectional	Caregivers living in rural areas	Community	Fried	85	69.0±6.8 (60 or older)	65 (76.5)	45 (52.9)	8 (9.4)	6 (75.0)	—
2016	Carneiro et al.	Cross-sectional	Urban area	Community	EFS	511	74 ± 1.7 (65 or older)	327 (64.0)	—	211 (41.3)	97 (45.9)	Diabetes, HF, OA
2016b	Carneiro et al.	Cross-sectional	Urban area	Community	EFS	683	70 ±9 (60-98)	443 (64.9)	152 (22.3)	243 (35.6)	—	—
2017b	Carneiro et al.	Cross-sectional	Urban area	Community	EFS	686	70 ±9 (60-98)	445 (64.9)	63 (9.2)	46 (6.7)	33 (71.7)	—
2017b	Carneiro et al.	Cross-sectional	Urban area	Community	EFS	685	75 ± 7.6 (65-79)	281 (41.0)	—	360 (52.6)	137 (38.0)	—
2018	Carvalho et al.	Cross-sectional	Hospitalized	Community	Fried	99	74 ± 7.3 (60 or older)	41 (41.4)	53 (53.5)	38 (38.4)	—	—
2017i	Cezar et al.	Cross-sectional	Public outpatient clinic	Community	Fried	66	77.0 ± 5.6 (60 or older)	53 (80.3)	44 (66.7)	19 (28.8)	—	MCI
2017i	Cezar et al.	Cross-sectional	Public outpatient clinic	Community	EFS	66	77.0 ± 5.6 (60 or older)	53 (80.3)	34 (51.5)	4 (6.1)	—	MCI
2017	Coqueiro et al.	Cross-sectional	Urban area	Community	Fried	316	74.2 ± 9.8 (60-105)	173 (54.7)	—	76 (24.1)	—	—
2015	Cordeiro et al.	Cross-sectional	Institutionalized	Institutionalized	EFS	33	76.8 ± 9.3 (60-100)	18 (54.5)	—	6 (18.2)	—	—

2014	Corona et al.	Cross-sectional	SABE	Community	Fried	1256	70.0 (60 or older)	764 (60.8)	—	100 (8.0)	67 (67.0)	HTN, diabetes, CPOD, CVD, stroke, OA, cancer
2018	Crosseti et al.	Cross-sectional	Hospitalized	Hospitalized	EFS	395	69.7 ± 7.2 (60-94)	147 (37.2)	—	177 (44.8)	80 (45.1)	—
2017	Cruz et al.	Cross-sectional	Primary care	Community	EFS	339	74.3 ± 8.2 (60 or older)	207 (61.1)	—	117 (34.5)	79 (67.5)	—
2009	da Silva et al.	Cross-sectional	Outpatient clinic	Community	Fried	30	75.7 ± 7.6 (60 or older)	20 (66.7)	14 (46.7)	6 (22.0)	—	HTN, OA, diabetes
2018c	da Silva et al.	Cross-sectional	Primary care	Community	Fried	457	70.2 ± 8.2 (60-97)	71 (15.5)	—	101 (22.1)	71 (70.3)	—
2019c	da Silva et al.	Cross-sectional	Primary care	Community	Fried	457	70.2 ± 8.2 (60-97)	71 (15.5)	—	101 (22.1)	27 (67.5)	—
2013	de Andrade et al.	Cross-sectional	SABE	Community	Fried	1374	60 or older	818 (59.5)	561 (40.8)	116 (8.4)	11 (9.5)	—
2019	de Amorim et al.	Cross-sectional	University workers	Community	Fried	258	62.9 ± 2.47 (60 or older)	109 (42.2)	160 (62.0)	24 (9.3)	21 (87.5)	—
2014	de Melo et al.	Cross-sectional	Public outpatient clinic	Community	Fried	150	77.2 ± 6.7 (60 or older)	96 (64.0)	62 (41.3)	84 (56.0)	60 (71.4)	—
2018	de Sousa et al.	Cross-sectional	Primary care	Community	Fried	243	84.4 ± 3.8 (80-98)	161 (66.3)	155 (63.8)	36 (14.8)	—	Cardiovascular, respirOAry, digestive and metabolic diseases
2014	dos Santos et al.	Cross-sectional	Urban area	Community	Fried	1785	60 or older	1155 (64.7)	920 (51.5)	173 (9.7)	—	—
2013	Duarte et al.	Cross-sectional	Community	Community	EFS	166	73.2 (60-96)	100 (60.2)	36 (21.7)	117 (70.5)	—	—
2009	Fabrício-Wehbe et al.	Cross-sectional	Urban area	Community	EFS	137	75.3 (65-100)	102 (74.5)	28 (20.4)	43 (31.4)	36 (83.7)	—
2015	Falsarella et al.	Cross-sectional	Community	Community	Fried	235	71.76 ± 5.06 (65 or older)	—	112 (47.7)	31 (13.2)	—	—
2019	Farías-Antúnez et al.	Cross-sectional	Community	Community	EFS	1399	60 or older	884 (63.0)	233 (16.7)	192 (13.8)	147 (76.5)	HTN, HF, CKD, osteoporosis, cancer, diabetes, epilepsy, stroke
2012	Fhon et al.	Cross-sectional	Urban area	Community	EFS	240	73.5 ± 8.4 (60-94)	151 (62.9)	59 (24.6)	94 (39.2)	64 (68.0)	—

2018	Fluetti et al.	Cross-sectional	Institutionalized	Institutionalized	TFI	56	77.77 ± 9.27 (60 or older)	32 (57.1)	—	42 (75.0)	—	—
2017	Filippin et al.	Cross-sectional	Primary care	Community	Fried	322	60 – 79	195 (60.6)	74 (23.0)	63 (19.6)	48 (76.1)	—
2016	Freitas et al.	Cross-sectional	Outpatient clinic	Community	Fried	103	73.3 ± 6.4 (60 or older)	76 (73.8)	59 (57.3)	27 (26.2)	—	Visual disorders, HTN, insonia, OA
2015	Frisoli Jr et al.	Cross-sectional	Outpatient clinic	CVD	Fried	172	77.13 ± 5.86 (65 or older)	107 (62.2)	88 (51.2)	65 (37.8)	44 (67.7)	CVD
2013	Fernandes et al.	Cross-sectional	Primary health care	Community	EFS	128	68.9 ± 7.8 (60-103)	86 (67.2)	—	36 (28.1)	26 (72.2)	—
2016	Gesualdo et al.	Cross-sectional	Outpatient clinic	CKD	EFS	60	71.1 ± 6.9 (60 or older)	18 (30.0)	—	22 (36.7)	—	—
2018	Gomes et al.	Cross-sectional	Carregivers	Community	Fried	312	69.5 ± 7.1 (60-74)	240 (76.9)	176 (56.4)	65 (20.8)	—	DS
2018	Gross et al.	Cross-sectional	Primary care	Community	Fried	555	71.1 ± 8.3 (60-102)	61 (11.0)	252 (45.4)	98 (17.7)	61 (62.2)	—
2017	Grden et al.	Cross-sectional	Primary care	Community	Fried	243	80 or more	161 (66.3)	152 (62.6)	36 (14.8)	25 (69.4)	—
2012	Holanda et al.	Cross-sectional	Institutionalized	Institutionalized	Fried	69	77.5 ± 7.8 (60 or older)	43 (62.3)	31 (44.9)	32 (46.4)	—	HTN, OA, DS
2017d	Jesus et al.	Cross-sectional	Primary health care	Community	EFS	247	60 or older	197 (79.8)	—	99 (40.1)	78 (78.7)	—
2018d	Jesus et al.	Cross-sectional	Primary health care	Community	EFS	217	68.5 ± 7.3 (60-94)	176 (81.1)	46 (21.2)	82 (37.8)	—	—
2018d	Jesus et al.	Cross-sectional	Primary health care	Community	EFS	247	60 or older	197 (79.8)	—	99 (40.1)	78 (78.7)	—
2015	Lealdini et al.	Cross-sectional	Outpatient clinic	Cancer	EFS	52	72.5 (65-97)	23 (44.2)	—	30 (57.5)	—	—
2015	Lenardt et al.	Cross-sectional	Primary health care	Community	Fried	203	70.8 ± 7.4 (60-93)	104 (51.2)	115 (56.7)	39 (19.2)	29 (74.3)	—
2018	Lenardt et al.	Cross-sectional	Driving licence	Community	Fried	347	60 or older	—	163 (47.0)	4 (1.2)	—	—

2017j	Lin et al.	Cross-sectional	Public outpatient clinic	Community	FRAIL	534	79.6 ± 8.4 (60 or older)	336 (62.9)	—	198 (37.1)	—	HTN, diabetes, congestive HF, CAD, strole, CKD, cancer
2017j	Lin et al.	Cross-sectional	Public outpatient clinic	Community	Fried	534	79.6 ± 8.4 (60 or older)	336 (62.9)	—	273 (51.1)	—	HTN, diabetes, congestive HF, CAD, strole, CKD, cancer
2017j	Lin et al.	Cross-sectional	Public outpatient clinic	Community	SOF	534	79.6 ± 8.4 (60 or older)	336 (62.9)	—	203 (38.0)	—	HTN, diabetes, congestive HF, CAD, strole, CKD, cancer
2017	Llano et al.	Cross-sectional	Rural area	Community	Fried	820	60 or older	460 (56.1)	304 (37.1)	356 (43.4)	210 (59.4)	Obesity, HTN,
2013	Lustosa et al.	Cross-sectional	Community center	Community	Fried	117	70.1 ± 7.3 (60 or older)	111 (94.9)	60 (51.3)	8 (6.8)	—	—
2018	Mello et al.	Cross-sectional	Areas of social vulnerability	Community	Fried	137	70.2± 7.4 (61-97)	93 (67.9)	84 (61.3)	17 (12.4)	14 (82.3)	—
2016	Medeiros et al.	Cross-sectional	Urban area	Community	EFS	686	70.9 ± 8.08 (60-98)	445 (64.9)	—	396 (57.7)	—	HTN, OA, urinary incontinence
2018	Melo et al.	Cross-sectional	Institutionalized	Institutionalized	EFS	214	76.4 (60-104)	149 (69.6)	64 (29.9)	150 (70.1)	—	—
2016	Morais et al.	Cross-sectional	Carregivers	Community	Fried	187	68.9 (60 or older)	151 (80.7)	103 (55.1)	45 (24.1)	36 (80.0)	—
2016	Moreira et al.	Cross-sectional	Diabetic older women	Community	Fried	99	65 or older	99 (100)	61 (61.6)	26 (26.3)	—	—
2018	Nascimento et al.	Cross-sectional	Areas of social vulnerability	Community	Fried	347	70.1 ± 7.7 (65-older)	195 (56.2)	197 (56.8)	116 (33.4)	56 (48.2)	Cogntivie impairmente, DS, obesity
2013	Neri et al.	Cross-sectional	FIBRA	Community	Fried	3478	65 or older	2354 (67.7)	1770 (50.9)	308 (8.9)	224 (72.7)	—
2018	Neves et al.	Cross-sectional	Primary health care	Community	TFI	377	68.0 ± 7.4 (60 or older)	227 (60.2)	—	246 (65.3)	155 (63.0)	DS
2013	Nóbrega et al.	Cross-sectional	Institutionalized	Institutionalized	Fried	69	77.5± 7.8 (61-95)	43 (62.3)	31(44.9)	34 (49.3)	—	HTN, OA, DS, stroke, heart disease
2014	Orlandi et al.	Cross-sectional	Outpatient clinic	CKD	EFS	60	71.1± 6.8 (60-89)	18 (30.0)	16 (26.7)	23 (38.3)	—	—
2013	Oliveira et al.	Cross-sectional	Hospitalized	Hospitalized	Fried	99	74.5 ± 6.8 (65 or older)	50 (50.5)	49 (49.5)	46 (46.5)	23 (50.0)	HTN, OA, CVD, DS, diabetes, cancer, urinary incotinence

2013	Parentoni et al.	Cross-sectional	Primary health care	Community	Fried	106	73.9 ± 6.9 (65-91)	106 (100)	42 (39.6)	32 (30.2)	—	—
2017	Pavarini et al.	Cross-sectional	Carregivers	Community	Fried	343	60 or older	261 (76.1)	—	72 (21.0)	—	—
2013	Pegorari et al.	Cross-sectional	Primary health care	Community	Fried	51	73 ± 6 (65 or older)	22 (43.1)	24 (47.1)	9 (17.6)	—	—
2014	Pegorari et al.	Cross-sectional	Urban area	Community	Fried	958	73 ± 7 (60 or older)	617 (64.4)	522 (54.5)	123 (12.8)	91 (73.9)	—
2015	Ramos et al.	Cross-sectional	SABE	Community	Fried	639	70.6 ± 7.8 (60-98)	409 (64.0)	424 (66.4)	215 (33.6)	—	HTN, CVD, OA, CPOD, diabetes, osteoporosis, stroke, asthma
2014	Ricci et al.	Cross-sectional	FIBRA	Community	Fried	761	71.9 ± 5.9 (65 or older)	489 (64.3)	365 (48.0)	74 (9.7)	49 (66.2)	—
2018	Rossetti et al.	Cross-sectional	Carregivers	Community	Fried	73	70.3 ± 8.5 (60 or older)	59 (80.8)	40 (54.8)	27 (37.0)	—	—
2013	Santiago et al.	Cross-sectional	Areas of social vulnerability	Community	TFI	219	70.5 ± 7.9 (60 or older)	115 (52.5)	—	74 (33.8)	—	—
2014	Santiago et al.	Cross-sectional	Institutionalized	Institutionalized	TFI	442	75.0 ± 9.9 (60 or older)	158 (35.7)	—	230 (52.0)	88 (38.2)	—
2018	Santiago et al.	Cross-sectional	Areas of social vulnerability	Community	TFI	640	70.5 ± 8.2 (60 or older)	414 (64.7)	—	284 (44.4)	202 (71.1)	—
2019k	Santiago et al.	Cross-sectional	Areas of social vulnerability	Community	TFI	302	70.4 ± 7.6 (60 or older)	199 (65.9)	—	108 (35.8)	—	HTN, OA, HF, dyslipidemia, stroke, asthma, cancer
2019k	Santiago et al.	Cross-sectional	Areas of social vulnerability	Community	Fried	302	70.4 ± 7.6 (60 or older)	199 (65.9)	—	71 (23.5)	—	HTN, OA, HF, dyslipidemia, stroke, asthma, cancer
2017	Sampaio et al.	Cross-sectional	Community	Community	Fried	316	74.8 ± 9.8 (60 or older)	173 (54.7)	—	68 (21.5)	—	—

2015e	Santos et al.	Cross-sectional	Primary health care	Community	Fried	139	72.3 ± 8.4 (60 or older)	105 (75.5)	86 (61.9)	23 (16.5)	–	HTN, DS, diabetes
2016e	Santos et al.	Cross-sectional	Primary health care	Community	Fried	139	72.3 ± 8.4 (60 or older)	105 (75.5)	—	23 (16.5)	–	—
2015	Sewo Sampaio et al.	Cross-sectional	Community	Community	KCL	72	69.0 ± 6.41 (60 or older)	72 (100)	—	33 (45.8)	—	—
2015	Sewo Sampaio et al.	Cross-sectional	Community	Community	KCL	55	70.8 ± 8.3 (60 or older)	55 (100)	—	6 (10.9)	—	—
2016	Sewo Sampaio et al.	Cross-sectional	Community	Community	KCL	109	75.0 ± 5.8 (60 or older)	24 (100)	—	24 (22.0)	—	—
2017	Santos-Orlandi et al.	Cross-sectional	Community	Community	Fried	40	70.1 ± 8.2 (60-98)	27 (67.5)	—	23 (57.5)	—	HTN and smoke
2012	Sousa et al.	Cross-sectional	FIBRA	Community	Fried	391	74.0 ± 6.5 (65 -96)	240 (61.4)	235 (60.1)	89 (22.8)	44 (49.4)	HTN, OA, CPOD, CVD, diabetes, stoke, cancer, depression
2013	Storti et al.	Cross-sectional	Institutionalized	Institutionalized	EFS	84	73.8 ± 8.2 (60-99)	33 (39.3)	4 (4.8)	36 (42.9)	—	—
2015	Silveira et al.	Cross-sectional	Community center	Community	Fried	54	72.9 ± 6.0 (65 or older)	32 (50.3)	25 (46.3)	6 (11.1)	5 (83.3)	—
2014	Tavares et al.	Cross-sectional	Community	Community	Fried	418	60 or older	298 (71.3)	216 (51.70	116 (27.8)	84 (72.4)	—
2015	Tavares et al.	Cross-sectional	Primary health care	Community	Fried	255	68.6 ± 6.5 (60 or older)	33 (12.9)	136 (53.3)	67 (26.3)	33 (49.2)	—
2016	Tavares et al.	Cross-sectional	Hospitalized	Hospitalized	Fried	205	60 or older	81 (39.5)	106 (51.7)	54 (26.3)	15 (27.7)	HTN, obesity, dyslipedemia
2017	Tavares et al.	Cross-sectional	Community	Community	Fried	1609	60 or older	1036 (64.4)	836 (52.0)	219 (13.6)	35 (15.9)	—
2018	Tavares et al.	Cross-sectional	Community	Community	Fried	255	68.68 ± 6.56 (60 or older)	99 (39.8)	136 (53.3)	67 (26.3)	—	—
2016	Teixeira-Gasparini et al.	Cross-sectional	Community	Community	EFS	114	85.5 ± 4.3 (80-103)	79 (69.3)	29 (25.4)	51 (44.7)	38 (74.5)	—

2018	Zukeran et al.	Cross-sectional	Secondary-care outpatient clinic	Community	Fried	254	60 or older	178 (70.1)	136 (53.5)	79 (31.1)	—	—
2013	Viana et al.	Cross-sectional	Secondary-care outpatient clinic	Community	Fried	53	76.7 ± 5.8 (65 or older)	40 (75.5)	29 (54.7)	8 (15.1)	—	Cardiac and pulmonary diseases, and cancer
2013	Vieira et al.	Cross-sectional	FIBRA	Community	Fried	601	74.3 ± 6.4 (65 or older)	398 (66.2)	278 (46.3)	52 (8.7)	—	—
2017	Vieira et al.	Cross-sectional	Community	Community	Fried	83	73.9 ± 7.2 (60 or older)	56 (67.5)	59 (71.1)	6 (7.2)	3 (50.0)	—
2016	Zazzetta et al.	Cross-sectional	Areas of social vulnerability	Community	Fried	304	70.1 ± 7.6 (60 or older)	173 (56.9)	184 (60.5)	83 (27.3)	45 (54.2)	Urinary incontinence
Chile												
2017	Albala et al.	Prospective cohort	ALEXANDROS	Community	Fried	2098	68.3 ± 6.3 (60 or older)	1406 (67)	1338 (63.8)	291 (13.9)	231 (79.3)	Diabetes, HTN, MCI, depression
2018	Araya et al.	Cross-sectional	Day care center	Community	TFI	35	73.31 ± 6.11 (65-86)	29 (82.9)	—	28 (80.0)	—	—
2008	Alvarado et al.	Cross-sectional	SABE	Community	Fried	1301	60 or older	855 (65.7)	624 (48.0)	520 (40.0)	389 (74.8)	—
2019	Bustamante-Ara et al.	Cross-sectional	Rural area	Community	Fried	619	66.0 (60-74)	359 (58.0)	299 (48.3)	34 (5.5)	28 (82.3)	HF, dieabetes, HTN, OA, CKD, diabetes
2017	Díaz-Toro et al.	Cross-sectional	Patients with HF	Hospitalized	Fried	79	71.02 ± 7.99 (60 or older)	38 (48.1)	39 (49.4)	40 (50.60)	22 (55.0)	HTN, MI, CPOD, stroke, dyslipidemia, diabetes
2018	Palomo et al.	Cross-sectional	Primary care	Community	Fried	1205	73 ± 5.9 (65 or older)	816 (67.7)	469 (38.9)	296 (24.6)	221 (74.6)	—
2015	Tapia et al.	Cross-sectional	Primary health care	Community	Fried	754	73.0 ± 6.0 (65-90)	463 (61.4)	520 (69.0)	34 (4.5)	—	HTN, OA, CPOD, dyslipidemia, diabetes, cancer
Colombia												
2014	Curcio et al.	Cross-sectional	Rural	Community	Fried	1878	70.9 ± 7.4 (60 or older)	981 (52.0)	996 (53.0)	228 (12.1)	—	HTN, OA, HF, CPOD, diabetes, stroke
2013	Ocampo-Chaparro et al.	Cross-sectional	Urban area	Community	Fried	314	60 or older	202 (64.3)	79 (25.2)	28 (8.9)	20 (41.6)	CVD, HTN, OA, disabetes

2017	Ramírez et al.	Cross-sectional	Community center	Community	Fried	101	60 or older	—	46 (45.5)	8 (7.9)	—	—
2017	Ramírez et al.	Cross-sectional	Community center	Community	EFS	101	60 or older	—	13 (12.9)	9 (8.9)	—	—
2017	Samper-Ternent et al.	Cross-sectional	SABE	Community	Fried	1442	70.7 ±7.7 (60 or older)	879 (61.0)	756 (52.4)	135 (9.4)	88 (65.1)	HTN, MI, diabetes, cancer, stroke
Ecuador												
2017f	Del Brutto et al.	Cross-sectional	Native living in rural areas	Community	EFS	298	70 ±8 (60 or older)	171 (57.4)	65 (21.8)	93 (31.2)	66 (70.9)	HTN, stroke, obeisty
2016f	Del Brutto et al.	Cross-sectional	Caregivers living in rural areas	Community	EFS	304	70.0 ± 0.8 (60 or older)	174 (57.2)	74 (24.3)	92 (30.3)	65 (70.6)	—
Peru												
2015	Jotheeswaran et al.	Cohort study	Urban and rural areas	Community	Fried	1381	75.0 ± 7.4 (65 or older)	805 (58.3)	—	323 (23.4)	—	—
2010	Pinedo et al.	Cross-sectional	Community	Community	Fried	246	69.9 ± 7.6 (60 or older)	147 (59.8)	159 (64.6)	19 (7.7)	16 (984.2)	DS, MCI, Urinary incontinence, insomnia
2018	Rodriguez et al.	Cross-sectional	Urban area	Populational	Fried	1381	75.0 ± 7.4 (65 or older)	888 (64.3)	—	277 (20.1)	—	—
2018	Rodriguez et al.	Cross-sectional	Rural area	Populational	Fried	552	74.2 ± 7.3 (65 or older)	295 (53.4)	—	93 (16.8)	—	—
2014	Runzer-Colmenares et al.	Cross-sectional	Outpatient clinic	Community	Fried	311	76.1 ± 8.3 (60 or older)	126 (40.5)	147 (47.3)	86 (27.7)	38 (44.1)	CVD, CPOD, depression, cognitive impairment
2017	Runzer-Colmenares et al.	Cross-sectional	Patients raceiveing radiotheraphy	Cancer	Fried	181	78.1 ± 5.2 (60 or older)	—	—	43 (23.8)	—	—
Venezuela												
2018	Rodriguez et al.	Cross-sectional	Populational	Populational	Fried	1965	72.3 ± 6.9 (65 or older)	1252 (63.7)	—	243 (12.4)	—	—

CHD= Coronary heart disease; CKD= Chronic kidney disease; CPOD= Chronic pulmonary obstructive disease; CVD= Cardiovascular diseases; DS= Depressive symptoms; EFS= Edmonton frail scale; FIBRA= Fragilidade em idosos brasileiros; FRAIL= Fatigue, resistance, ambulation, illnesses, & loss of weight; HF= Heart failure; HTN= Hypertension; IHG= Isometric handgrip strength; KCL= Kihon checklist; MCI= Mild-cognitive impairment; MI= Myocardial infarction; OA= Osteoarthritis; SABE= Saúde, bem-estar e envelhecimento; SOF= Study of osteoporotic fracture; TFI= Tilburg frailty indicator; TUG= Timed "Up and Go" ; WS= Walking speed. a, b, c, d, e, f= These studies used the same sample; h, i, j, k= The same study reported the prevalence with different assesment tools.

2

Quality assessment

The overall score and the point-by-point analysis of quality assessment of cross-sectional and cohort studies are shown in Table 2. The overall score of cross-sectional studies ranged from 2 to 10 (maximum value: 11). All studies used a validated instrument for frailty assessment (item 4). Regarding selection criteria (item 1), 38.9% of the studies used a representative sample from a random population, 21.2% did not describe the sampling strategy, 20.3% used a selected group of participants (e.g., institutionalised older adults), and 15.3% used a somewhat representative sample selected using a non-random method. The sample size (item 2) was justified in 49.5% of the studies, while in 50.5% of studies no sample size justification was provided. Comparisons between respondents and non-respondents in the main characteristics (item 3) were only performed in 5.0% of the studies. Age was selected as the most important confounder factor (item 5) and it was controlled for in less than half of the studies (47.5%). Similarly, only 46.6% of the studies controlled for additional factors (i.e., gender or body mass index [BMI]) (item 5). Outcomes (item 6) were assessed using an independent blind method in 56.8% of the studies, self-reported scales or questionnaires in 35.2%, record linkage in 1.7%, while 1.7% did not describe the method. Finally, appropriate statistical analysis (item 7) was used in 57.8% of the studies.

Regarding cohort studies, all of them used a structured interview to assess exposure (item 3), recruited the non-exposed cohort from the same setting as the exposed cohort (item 2), demonstrated that the outcome of interest was not present at the beginning of the study (item 4), and evaluated the outcome using an independent blind method (item 6). Seventy-five percent of the studies used a truly representative sample, and 25% a somewhat representative sample (item 1). One study did not control for any main (item 5) or additional factors. The follow-up period (item 7) was not enough in one-study, a representative sample completed the follow-up period in 75% of the studies.

Table 2. Quality assessment of the included studies

	Selection					Comparability	Outcome		
Study	1	2	3	4	5		6	7	8	TOTAL*

Argentina										
Costa et al.α	b	a	a	a	a	b	d	a	NA	8
Brazil										
Alencar et al.β	a	a	a	a	—	—	a	b	b	5
Alves et al.α	c	b	c	a	a	b	c	a	NA	6
Aprahamian et al.α	a	b	c	a	—	—	c	a	NA	5
Aprahamian et al.α	b	b	c	a	a	b	a	a	NA	8
Aprahamian et al.α	b	b	c	a	a	b	a	a	NA	8
Augusti et al.α	a	a	c	a	—	—	a	b	NA	6
Alvarado et al.α	a	a	c	a	a	b	c	a	NA	8
Belisário et al.α	a	a	c	a	a	b	b	a	NA	9
Binotto et al.α	a	a	c	a	a	—	a	—	NA	7
Bôas et al.α	c	b	c	a	—	—	a	b	NA	4
Bolina et al.α	a	a	c	a	a	b	a	a	NA	9
Borges et al.α	d	b	c	a	—	—	c	b	NA	3
Borges et al.α	d	b	c	a	—	—	d	b	NA	2
Brigola et al.α	b	a	c	a	a	b	a	a	NA	9
Carneiro et al.α	a	a	c	a	a	b	a	a	NA	9
Carneiro et al.α	c	b	c	a	a	b	a	a	NA	7
Carneiro et al.α	a	a	c	a	a	b	c	a	NA	8
Carvalho et al.β	b	a	a	a	a	b	a	a	a	8
Cezar et al.α	c	b	c	a	—	b	a	a	NA	6

Coqueiro et al.α	a	a	c	a	—	—	c	b	NA	5
Cordeiro et al.α	c	b	c	a	—	—	a	b	NA	4
Corona et al.α	a	a	c	a	a	b	a	a	NA	9
Crosseti et al.α	c	a	c	a	—	b	a	b	NA	6
Cruz et al.α	a	a	c	a	a	b	a	a	NA	9
da Silva et al.α	d	b	c	a	—	—	a	b	NA	4
da Silva et al.α	a	a	c	a	a	b	a	a	NA	9
da Silva et al.α	a	a	c	a	a	b	a	a	NA	9
de Andrade et al.α	a	a	c	a	—	—	a	b	NA	6
de Amorim et al.α	a	a	c	a	a	b	c	a	NA	8
de Melo et al.α	b	b	c	a	—	—	a	b	NA	5
de Sousa et al.α	a	b	c	a	—	b	c	a	NA	6
dos Santos et al.α	a	b	c	a	—	—	c	b	NA	4
Duarte et al.α	a	a	c	a	—	—	c	b	NA	5
Fabrício-Wehbe et al.α	a	a	c	a	—	—	a	a	NA	7
Falsarella et al.α	a	a	c	a	—	b	a	b	NA	7
Farías-Antúnez et al.α	a	a	c	a	a	b	c	a	NA	8
Fhon et al.α	a	a	c	a	—	—	a	b	NA	6
Fluetti et al.α	c	b	c	a	—	—	a	b	NA	4
Filippin et al.α	a	a	c	a	a	a	a	a	NA	8
Freitas et al.α	c	b	c	a	—	—	a	b	NA	4
Frisoli Jr et al.α	d	b	c	a	a	b	a	a	NA	7
Fernandes et al.				a					NA	2

Gesualdo et al.α	d	b	c	a	a	b	a	a	NA	7
Gomes et al.α	a	a	a	a	a	b	a	a	NA	10
Gross et al.α	b	a	c	a	a	b	c	a	NA	8
Grden et al.α	a	a	c	a	a	b	c	a	NA	8
Holanda et al.α	a	b	c	a	a	b	a	a	NA	8
Jesus et al.α	c	b	c	a	—	—	a	b	NA	4
Jesus et al.α	c	a	c	a	—	—	a	b	NA	5
Lealdini et al.α	c	a	c	a	a	b	a	a	NA	8
Lenardt et al.α	c	a	c	a	a	b	c	a	NA	7
Lenardt et al.α	c	b	c	a	—	—	a	b	NA	4
Lin et al.β	b	a	b	a	a	b	a	a	NA	9
Llano et al.α	d	b	c	a	—	—	a	b	NA	4
Lustosa et al.α	a	b	c	a	—	—	a	b	NA	5
Mello et al.α	a	a	c	a	—	—	c	b	NA	5
Medeiros et al.α	a	b	c	a	a	b	a	a	NA	8
Melo et al.α	d	a	c	a	—	—	a	b	NA	5
Morais et al.α	d	b	c	a	—	—	c	b	NA	3
Moreira et al.α	d	b	c	a	a	b	a	a	NA	7
Nascimento et al.α	b	a	c	a	a	b	a	a	NA	9
Neri et al.	a	a	c	a	—	—	a	b	NA	6
Neves et al.α	b	b	c	a	—	—	a	a	NA	6
Nóbrega et al.α	d	b	c	a	a	b	a	a	NA	7
Orlandi et al.α	d	b	c	a	—	—	a	b	NA	4

Oliveira et al.α	c	b	c	a	—	—	a	b	NA	4
Parentoni et al.α	c	b	c	a	—	—	a	b	NA	4
Pavarini et al.α	b	b	c	a	—	—	a	b	NA	5
Pegorani et al.α	a	a	c	a	—	—	a	b	NA	6
Pegorani et al.α	d	a	c	a	a	b	a	a	NA	8
Ramos et al.α	a	b	c	a	—	—	c	b	NA	4
Ricci et al.α	a	a	c	a	a	b	a	a	NA	9
Rossetti et al.α	c	b	c	a	—	—	c	b	NA	3
Santiago et al.α	d	b	c	a	—	—	a	a	NA	5
Santiago et al.α	d	b	c	a	a	—	c	a	NA	5
Santiago et al.α	c	a	c	a	a	b	a	a	NA	8
Santiago et al.α	c	a	c	a	a	b	c	a	NA	7
Sampaio et al.α	d	a	a	a	a	b	a	a	NA	9
Santos et al.α	d	b	c	a	—	—	c	b	NA	3
Santos et al.α	d	b	c	a	—	—	a	a	NA	5
Sewo Sampaio et al.α	d	b	c	a	—	—	c	b	NA	3
Sewo Sampaio et al.α	d	b	c	a	—	—	c	b	NA	3
Sewo Sampaio et al.α	d	b	c	a	a	b	a	a	NA	7
Santos-Orlandi et al.α	d	b	c	a	—	—	c	b	NA	3
Sousa et al.α	a	a	c	a	a	b	c	a	NA	8
Storti et al.α	c	b	c	a	—	—	b	b	NA	4
Silveira et al.α	b	a	c	a	—	—	a	b	NA	6
Tavares et al.α	b	a	c	a	—	—	c	b	NA	5

Tavares et al.α	c	a	c	a	a	b	c	a	NA	7
Tavares et al.α	a	a	c	a	—	—	a	a	NA	7
Tavares et al.α	c	a	c	a	a	b	c	a	NA	7
Tavares et al.α	a	b	c	a	—	—	c	a	NA	5
Teixeira-Gasparini et al.α	a	a	c	a	—	—	c	b	NA	5
Zukeran et al.α	d	b	c	a	—	—	c	b	NA	3
Viana et al.α	c	b	c	a	—	b	a	a	NA	6
Vieira et al.α	a	a	c	a	a	—	c	a	NA	7
Vieira et al.α	c	a	c	a	—	—	a	b	NA	5
Zazzetta et al.α	c	b	c	a	—	—	a	a	NA	5
Chile										
Albala et al.β	a	a	a	a	b	a	a	a	a	9
Araya et al.α	d	b	c	a	—	—	a	c	NA	4
Alvarado et al.α	a	a	c	a	a	b	c	a	NA	8
Bustamante-Ara et al.α	b	a	c	a	a	b	a	a	NA	9
Díaz-Toro et al.α	b	a	c	a	a	—	c	a	NA	7
Palomo et al.α	a	b	c	a	a	—	c	a	NA	6
Tapia et al.α	a	a	c	a	—	—	c	b	NA	5
Colombia										
Curcio et al.α	b	b	c	a	a	b	c	a	NA	7
Ocampo-Chaparro et al.α	a	b	c	a	a	b	c	a	NA	7

Ramírez et al.α	d	b	c	a	—	—	a	b	NA	4
Samper-Ternent et al.α	a	a	c	a	a	b	c	a	NA	8
Ecuador										
Del Brutto et al.α	b	a	c	a	a	b	a	a	NA	9
Del Brutto et al.α	b	a	c	a	a	b	a	a	NA	9
Peru										
Jotheeswaran et al.α	a	a	a	a	a	b	a	a	NA	10
Pinedo et al.α	d	b	c	a	—	—	a	a	NA	5
Rodriguez et al.α	a	a	a	a	a	b	c	a	NA	9
Runzer-Colmenares et al.α	b	b	c	a	a	b	c	a	NA	7
Runzer-Colmenares et al.β	a	a	a	a	a	b	a	a	a	9
Venezuela										
Rodriguez et al.α	a	a	a	a	a	b	c	a	NA	9

α= Cross-sectional study; β= Cohort study; *Max= 11 points for α and 9 points for β. Cross-sectional studies: 1) Representativeness of the sample: a) Truly representative of the average in the target population, b) Somewhat representative of the average in the target population, c) Selected group of users, d) No description of the sampling strategy; 2) Sample size: a) Justified and satisfactory, b) Not justified; 3) Non-respondents: a) Comparability between respondents and non-respondents characteristics, b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory, c) No description of the response rate or the characteristics of the responders and the non-responders; 4) Ascertainment of the exposure: a) Validated measurement tool, b) Non-validated measurement tool, but the tool is available or described, c) No description of the measurement tool; 5) Comparability: a) The study controls for the most important factor, b) The study control for any additional factor; 6) Outcome: a) Independent blind assessment, b) Record linkage, c) Self report, d) No description; 7) Statistical test: a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value), b) The statistical test is not appropriate, not described or

incomplete. Cohort studies: 1) Representativeness of the exposed cohort: a) truly representative, b) somewhat representative, c) selected group of users, d) no description of the derivation of the cohort; 2) Selection of the non exposed cohort: a) drawn from the same community as the exposed cohort, b) drawn from a different source, c) no description of the derivation of the non exposed cohort; 3) Ascertainment of exposure: a) secure record (eg surgical records), b) structured interview, c) written self report, d) no description; 4) Demonstration that outcome of interest was not present at start of study: a) yes, b) no; 5) Comparability: a) study controls for age; b) study controls for any additional factor; 6) Assessment of outcome: a) independent blind assessment, b) record linkage, c) self report, d) no description; 7) Was follow-up long enough for outcomes to occur: a) yes (select an adequate follow up period for outcome of interest) b) no; 8) Adequacy of follow up of cohorts: a) complete follow up, b) subjects lost to follow up, c) no description of those lost, d) no statement.

Prevalence of prefrailty and frailty in South America

Overall, the mean prevalence of prefrailty was 46.8%, ranging from 23.0% in Ecuador to 55.9% in Peru (Figure 2). When data were analysed according to the assessment tool, the prevalence of prefrailty was 50.7%, 44.8%, and 18.4% for Fried, FRAIL scale, and EFS, respectively. The highest prevalence of prefrailty was observed in hospitalised older adults (50.7%), followed by community-dwelling persons (47.6%) and nursing-home residents (29.8%). Regarding older adults with specific conditions, CVD and CKD patients showed a prevalence of prefrailty of 51.2% and 26.7%, respectively.

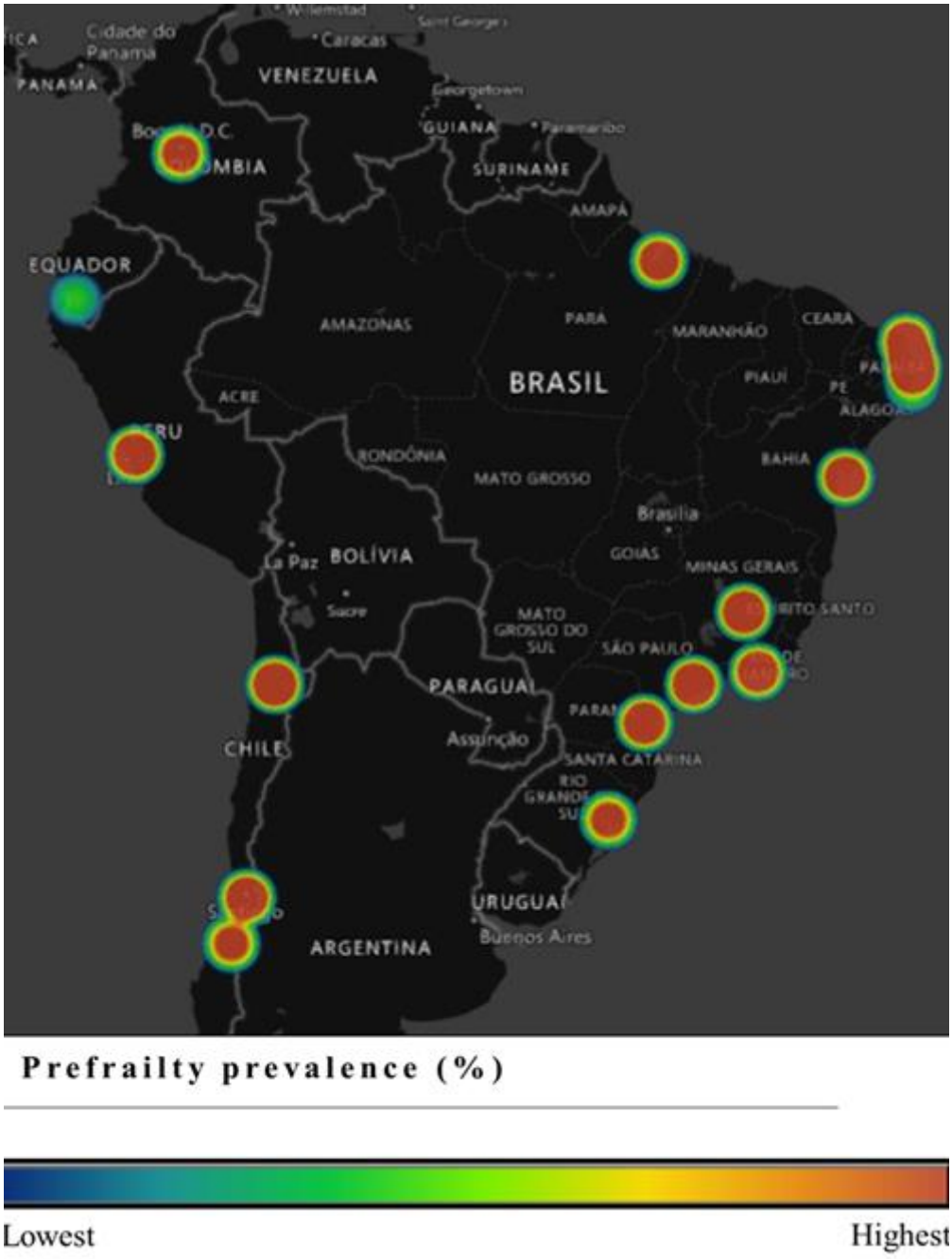

Figure 2. Mean prevalence of prefrailty according to the country in South America.

Overall, the mean prevalence of frailty was 21.7%, ranging from 10.6% in Colombia to 31.3% in Chile (Figure 3). When data were analysed according to the assessment tool, the prevalence of frailty was 48.8%, 38.0%, 34.7%, 26.9%, 26.0%, 18.4%, 18,2% according to FTI, SOF, Fried, KCL, clinical frailty scale, EFS, and FRAIL, respectively. The highest prevalence of frailty was observed in nursing-home resident persons (55.8%), followed

by hospitalised (39.1%) and community-dwelling (23.0%) older adults. Regarding older people with specific conditions, patients with cancer showed the highest prevalence (54.9%), followed by those with CVD (37.8%) and CKD (37.5%). The prevalence of frailty increased progressively with age, so that 21.4% frailty prevalence was found in those aged 60 to 69 years, 24.5% in those with a mean age between 70 and 79 years, and 30.3% in those aged ≥80 years. Most studies reported a higher prevalence of frailty in women compared with men.

Figure 3. Mean prevalence of frailty according to the country in South America.

Prevalence of prefrailty and frailty according to country Argentina

The mean prevalence of frailty in Argentina was 26.0%. Data were exclusively based on older patients with heart failure. Frailty was assessed using the clinical frailty scale.

Brazil

The mean prevalence of prefrailty in Brazil was 46.9%, ranging from 4.8% to 71.1%. When data were analysed according to the assessment tool, the prevalence of prefrailty was 49.1%, 45.6%, and 19.4% for Fried, FRAIL scale, and EFS, respectively. The highest prevalence of prefrailty was observed in hospitalised older adults (51.0%), followed by community-dwelling people (47.1%) and nursing-home residents (29.8%). Regarding older adults with specific conditions, CVD and CKD patients showed a prevalence of prefrailty of 51.2% and 26.7%, respectively.

The mean prevalence of frailty in Brazil was 26.1%, ranging from 1.9% to 75.0%. When data were analysed according to the assessment tool, the prevalence of frailty was 48.3%, 38.0%, 34.8%, 33.1%, 26.9%, and 19.3% for FTI, SOF, FRAIL, EFS, KCL, and Fried, respectively. The highest prevalence of frailty was observed in nursing-home residents (55.8%), followed by hospitalised (39.6%), and community-dwelling people (24.8%). Regarding older adults with specific conditions, patients with cancer showed the highest prevalence of frailty (57.7%), while those with CVD and CKD showed a prevalence of frailty of 37.8% and 37.5%, respectively.

Chile

The mean prevalence of prefrailty in Chile was 54.3%, ranging from 38.9% to 69.0%. The highest prevalence of prefrailty was observed in hospitalised older adults (51.0%), followed by community-dwelling people (47.1%) and nursing-home residents (29.8%).

The mean prevalence of frailty in Chile was 31.3%, ranging from to 4.5% to 80.0%. When data were analysed according to the assessment tool, Fried's criteria identified a mean of 23.2% of older adults with frailty, while 80% were identified by FTI. The highest prevalence of frailty was observed in hospitalised older adults (50.0%), followed by community-dwellers (28.1%).

Colombia

The mean prevalence of prefrailty and frailty in Colombia was 49.3% (12.9%-53.0%) and 10.6% (7.9%-12.1%), respectively. When data were analysed according to the assessment tool, Fried criteria (44.0% and 9.6%) identified a larger number of prefrail and frail older adults compared with EFS (12.9% and 8.9%).

Ecuador

The mean prevalence of prefrailty and frailty in Ecuador was 57.4% and 31.2%, respectively. Data were exclusively based on older adults from the Atahualpa region. Frailty status was assessed using the TFI.

Peru

The mean prevalence of prefrailty and frailty in Chile was of 55.9% (47.3%-64.6%) and 19.9% (7.7%-27.7%), respectively. Older patients with cancer showed a frailty prevalence of 23.8%, while 22.1% of community-dwelling older adults were frail.

Venezuela

The mean prevalence of frailty in Venezuela was 12.4%. Data were exclusively based on older adults from Caracas. Frailty status was assessed using Fried's criteria.

DISCUSSION

The present study investigated the prevalence of prefrailty and frailty in older adults from different settings in South America. Results from our systematic review show that about 46.8% of older people living in Brazil, Chile, Colombia, Ecuador, and Peru are prefrail. The highest prevalence of prefrailty was observed in hospitalised older adults (50.7%), followed by community-dwelling people (47.6%) and nursing-home residents (29.8%). The cumulative prevalence of frailty in South America was 21.7%. The prevalence of frailty across settings differed from that of prefrailty, with the highest rate observed in nursing-home residents (55.8%), followed by hospitalised (39.1%) and community-dwelling persons (23.0%). When data were analysed according to the geographic area, most countries showed a mean prevalence

of prefrailty ~50% and a mean prevalence of frailty ~20%, with the notable exceptions of Colombia (10.6%) and Chile (31.3%).

Only one systematic review investigated the prevalence of frailty (19.6%) in South America, but results were based on a limited number of search terms, South America and Caribbean countries, and only studies with representative samples of community-dwellers[15]. Our findings add to these prior results by reporting the prevalence of prefrailty and frailty in older South Americans according to setting, country, and assessment tools.

Based on the present findings, the prevalence of frailty in the community in South America (23.0%) is almost twofold higher in comparison to Europe (12.0%)[16] and more than threefold higher than in Japan (7.4%)[18]. Similarly, a higher prevalence of frailty was observed in South American nursing-home residents (55.8%) when compared with European peers (45.0%)[16]. These findings are consistent with previous investigations that showed a higher prevalence of prefrailty and frailty in low- and middle-income countries compared with high-income regions[14,15,149]. A possible explanation for this phenomenon may reside in the fact that disadvantaged socioeconomic conditions are frequently associated with inequalities in healthcare access, lower dietary quality, physical inactivity, multimorbidity and disability[150,151], all of which contribute to the development and progression of frailty[6–8,20].

Divergent prevalence rates of prefrailty and frailty were observed across settings, which may reflect different patterns of healthcare utilisation in South America depending on the frailty status. As people progress from robustness to prefrailty, they show increased prevalence of multimorbidity[152,153], disability[154], and risk of adverse health-related events[153], leading to higher healthcare utilisation[153] and potentially hospitalisation[155]. In addition, muscle strength, gait speed, and balance[155,156] are reduced in prefrail persons compared with robust older adults, which may account for increased incidence of falls[152,154] and fractures[154] and related hospitalisation in these individuals[155].

On the other hand, frail older people show worse overall health status compared with their prefrail counterparts[152], which make them need more time to recover from stressful events, increasing the need of critical care services[157] and frequent hospital readmission[158]. Mortality is a frequent outcome in hospitalised frail older adults[158], and

nursing-home allocation is a common discharge disposition for survivors[158]. Indeed, frailty is highly prevalent in nursing-homes[11,159], possibly reflecting the increased need of medical attention[157], cognitive decline[155,159], and disabilities of residents[160].

According to Ofori-Asenso et al.[14], the 3-year frailty incidence rate among prefrail individuals worldwide is 62.7 cases per 1000 person-years, which might suggest that more than 1 million new cases of frailty may be expected in South America each year. This figure has relevant public health implications and calls for immediate actions against frailty in South America. Indeed, early detection of prefrailty and frailty may reduce the risk for negative health-related outcomes and healthcare utilisation through the design and implementation of person-tailored interventions[161].

Our study is not free of limitations. First, although our findings are based on the majority of the Latin American countries, limited evidence was available for most countries, except for Brazil. In fact, there were no studies investigating the prevalence of prefrailty and frailty in Bolivia, Paraguay, Uruguay, Guyana and Suriname, and only few reports were available for Argentina, Venezuela and Ecuador. Second, although unlikely, it is possible that more studies could be available in other databases than those used in the present study. However, selected databases have wide coverage without losing the quality of journals. Third, the cross-sectional design of included studies limits extrapolation and interpretation of findings.

CONCLUSION

Prefrailty and frailty are highly prevalent in South American older adults, with rates higher than in Europe and Asia. Among community-dwellers, almost one in two is prefrail and one in five is frail, while institutionalised individuals are more often affected. These findings call for immediate actions to ensure sustainability of healthcare systems. In this scenario, our report may provide basic information for healthcare authorities and policy makers to devise novel models of care responsive to emerging medical needs of older South Americans.

COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of potential conflicts of interest: The authors declare that they have no conflict of interest.

Research involving Human Participants and/or Animals: This article does not contain any studies with human participants or animals performed by any of the authors.

Ethical approval: Ethical approval was not required for this review because only published data were included.

Informed consent: For this review, informed consent forms were not required

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Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5-6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	—

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	—

Supplementary Material 1

Frailty AND South America;

Frailty AND Latin America;

Frailty AND Brazil;

Frailty AND Argentina;

Frailty AND Bolivia;

Frailty AND Chile;

Frailty AND Colombia;

Frailty AND Ecuador;

Frailty AND Guyana;

Frailty AND Paraguay;

Frailty AND Peru;

Frailty AND Suriname

Frailty AND Uruguay;

Frailty AND Venezuela;

Frail AND South America;

Frail AND Latin America;

Frail AND Brazil;

Frail AND Argentina;

Frail AND Bolivia;

Frail AND Chile;

Frail AND Colombia;

Frail AND Ecuador;

Frail AND Guyana;

Frail AND Paraguay;

Frail AND Peru;

Frail AND Suriname

Frail AND Uruguay;

Frail AND Venezuela;

Frail Elderly [Mesh] AND South America;

Frail Elderly [Mesh] AND Latin America;

Frail Elderly [Mesh] AND Brazil;

Frail Elderly [Mesh] AND Argentina;

Frail Elderly [Mesh] AND Bolivia;

Frail Elderly [Mesh] AND Ecuador;

Frail Elderly [Mesh] AND Guyana;

Frail Elderly [Mesh] AND Paraguay;

Frail Elderly [Mesh] AND Peru;

Frail Elderly [Mesh] AND Suriname

Frail Elderly [Mesh] AND Uruguay;

Supplementary Material 2

Cutoffs values for frailty instruments

	Cutoff values (points)						
Instruments	Robust		Prefrail		Frail		
Fried frailty phenotype[1]	0		0		≥3		
Tilburg frailty indicator[2,3]	0		0		≥5		
FRAIL[4]	0		0		3-5		
Kihon checklist*[5]	0		—		25		
SOF[6]	0		0		2-3		
	No frailty		Visible Vulnerable Frailty		Mild, Moderate, and Severe Frailty		
Edmonton frailty scale[7,8]	0-4		5-6		≥7		
	Very fit	Well	Well, with threated comorbid disease	Apparently vulnerable	Mildly frail	Moderately frail	Severely frail
Clinical Frailty Scale[9]	1	2	3	4	5	6	7

*There is no stabilized cutoff for the Kihon checklist

ARTICLE 3

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Sarcopenia-related parameters in adults with Down syndrome: A crosssectional exploratory study

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ABSTRACT

Background: People with Down syndrome (DS) experience premature aging. Whether this accelerated aging also involves early declines in muscle mass, strength and physical performance is presently unclear. The present study investigated the prevalence of sarcopenia parameters in adults with DS. In addition, the relationship between well-established muscle mass indexes and a set of body composition, functional, biological, and clinical parameters was explored.

Methods: One hundred-five adults with DS participated in the study. Demographic, clinical, anthropometric, and functional parameters were assessed. Lean body mass (LBM) was estimated using bioelectrical impedance analysis. Bone mineral density (BMD) of the hip and the spine was measured through dual X-ray absorptiometry. For the analysis, participants were categorized into two subgroups (i.e., low and high) for each LBM-related measurement (i.e., crude LBM, LBM to body mass index ratio, and skeletal muscle index) according to their median values.

Results: The mean age of participants was 38.4 ± 12.1 years, with 43 men (41%). Muscle mass, handgrip strength, and gait speed were lower than established cutoffs for sarcopenia. All muscle mass indexes were negatively correlated with age. However, only crude LBM and the skeletal muscle index were correlated with a set of anthropometric parameters and BMD.

Conclusion: Findings from this exploratory study indicate that adults with DS show muscle mass indexes and physical performance levels similar to or lower than older adults with sarcopenia. The assessment of muscle mass and functional status should therefore be included in the routine evaluation of this population starting at young age.

Abbreviations: AD, Alzheimer's disease; ADL, activities of daily living; BIA, bioimpedance analysis; BMD, bone mineral density; BMI, body mass index; CTX, carboxyterminal collagen crosslink; DHEA, dehydroepiandrosterone; DS, Down syndrome; DXA, dual X-ray absorptiometry; FTI, free testosterone index; HC, hip circumference; IGF-1, insulin-like growth factor 1; LBM, lean body mass; MAC, mid-arm circumference; TUG, timed "up-and-go"; SHBG, sex hormone binding globulin; SMI, skeletal muscle index; TSH, thyroid-stimulating hormone; WC, waist circumference; WH, waist-to-hip ratio

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Introduction

People with Down syndrome (DS) show an accelerated aging phenotype, including early skin wrinkling, graying and loss of hair, visual impairments, early menopause, and high prevalence of Alzheimer's disease (AD) (Esbensen, 2010). Such a premature aging is thought to occur in response to a set of biological processes involving DNA methylation, abnormal brain Aβ deposition, and immunosenescence (Horvath et al., 2015; Kusters et al., 2011).

Among the clinical features of DS, special attention has been paid to cognitive deficits due to their impact on quality of life and prognosis (Lott and Dierssen, 2010; Bayen et al., 2018). However, musculoskeletal abnormalities (e.g., hypotonia, ligament laxity) are also typical features of DS, that contribute to the development of physical dysfunction (Foley and Killeen, 2018). Whether precocious muscle atrophy also plays a role in physical function impairment in DS individuals is

not established. In this context, reduced myofiber area has been described in young adult animals with DS, suggesting that muscle atrophy may be part of the myriad of features induced by the trisomy of human chromosome 21 (Cisterna et al., 2013).

Muscle atrophy is one defining criterion of sarcopenia, an age-related condition characterized by loss of muscle mass and function with a risk of adverse events (Cruz-Jentoft et al., 2010). The condition is highly prevalent in older adults across different settings, including community, hospitals, and long-term care institutions (Tarantino et al., 2016; Diz et al., 2017; Marzetti et al., 2018a; Xu et al., 2018). Furthermore, muscle loss often associates with other detrimental changes in body composition, including increased adiposity (Buch et al., 2016) and reduced bone mineral density (BMD) (Cheng et al., 2014; Borges Pereira et al., 2015; Edwards et al., 2015). Notably, obesity and osteoporosis are frequently observed in DS people (Luke et al., 1996; Melville et al., 2005; Bell and Bhate, 2008; Carfì et al., 2014, 2017). Nevertheless, to the best of our knowledge, no study has yet investigated the prevalence of sarcopenia-related parameters, as well as the relationship between indexes of muscle mass, physical function, and bone mineral density in persons with DS.

Clinically, whole-body lean body mass (LBM) assessed trough bioelectrical impedance analysis (BIA) is a well-accepted parameter for the diagnosis of sarcopenia (Chen et al., 2014; Tosato et al., 2017; CruzJentoft et al., 2019). However, it has been proposed that LBM adjusted for either height or body mass index (BMI) should be used instead of crude LBM, since muscle mass is correlated with body size (Chen et al., 2014; Cruz-Jentoft et al., 2019).

Based on these premises, the present study aimed at investigating the prevalence of sarcopenia parameters in adults with DS. In addition, the relationship between well-established muscle mass indexes and a set of body composition, functional, biological, and clinical parameters was explored to obtain preliminary indications on the more meaningful muscle index in DS adults.

Materials and methods

This was a cross-sectional study that was approved by the Ethics Committee of the Università Cattolica del Sacro Cuore (Rome, Italy), under the protocol number 7437/14. The study was conducted in compliance with the Declaration of Helsinki and the Resolution 196/96 of the National Health Council.

Study participants

Study participants were recruited from the outpatient clinic of the Department of Geriatrics, Fondazione Policlinico Universitario "Agostino Gemelli" IRCCS at the Università Cattolica del Sacro Cuore (Rome). Volunteers were recruited by convenience and asked verbally by the researchers about their willingness to take part in the study. Prior to inclusion, written informed consent was obtained from each participant or surrogate legal representatives as needed. To minimize the risk of selection bias, no specific inclusion criterion was required. Candidates were considered to be eligible to participate if they had a diagnosis of DS, were ≥18 years, and possessed sufficient physical and cognitive abilities to perform all the measurements required by the protocol.

Clinical characteristics

Information on comorbid conditions and pharmacological treatment was collected by the attending physician through a careful review of medical records. Biological parameters, including carboxy-terminal collagen crosslinks (CTX), dehydroepiandrosterone (DHEA), free testosterone index (FTI), insulin-like growth factor 1 (IGF-1), osteocalcin, sex hormone binding globulin (SHBG), thyroid-stimulating hormone (TSH) and 25-hydroxycholecalciferol, were assessed by the hospital laboratory.

Assessment of anthropometry, body composition, and bone mineral density

A medical graded weight scale with a stadiometer was used to measure body mass and height. BMI was calculated as the ratio between body mass (kg) and the square of height

(m^2). An anthropometric tape (flexible and inextensible) was used to measure waist circumference (WC), hip circumference (HC), and mid-arm circumference (MAC). The waist-to-hip ratio (WH) was subsequently calculated. For these measurements, participants were requested to wear light clothes and to stay in a standing position, head held erect, eyes forward, with the arms relaxed at the sides of the body, and feet kept together. WC was taken at the mid-point between the last floating rib and the highest point of the iliac crest. HC was measured at the highest point of the buttocks. MAC was taken at the mid-point between the elbow and the deltoid muscle (Landi et al., 2010; World Health Organization, 2011). Body composition was estimated by BIA using a Quantum/S Bioelectrical Body Composition Analyzer (Akern Srl, Florence, Italy) with an operating frequency of 50 kHz at 800 μA, after an overnight fast. Measurements were taken under standard conditions, with the participant lying supine and surface electrodes placed on the right wrist and ankle (Marzetti et al., 2014). Muscle mass was estimated using the equation developed by Janssen et al. (2000). The skeletal muscle index [SMI (kg/m^2)] was obtained by dividing absolute muscle mass by squared height.

BMD was measured at the neck of the right femur and at the lumbar spine by dual X-ray absorptiometry (DXA) using a Hologic® Discovery A (Hologic, Inc., Bedford, MA). Hip BMD was based on measurements at the femoral neck, while total spine BMD was evaluated on measurements of three lumbar vertebrae (L2–L4) (Carfì et al., 2017).

Assessment of muscle strength, physical function, and disability

- Isometric handgrip strength

Isometric handgrip strength was measured using a Jamar handheld hydraulic dynamometer (Patterson Medical Products, Inc., Cincinnati, OH). For the test, the participant seated on a standard chair with the shoulder abducted, the elbow near the trunk and flexed at 90°, and the wrist in a neutral position (thumb up). The contralateral arm remained relaxed under the thigh. To determine handgrip strength, participants performed one familiarization trial and one measurement trial with the dominant hand (Landi et al., 2017b). The maximal contraction was measured during 4 s under encouragement.

- Usual walking speed

Usual walking speed was measured over 4 m. In the test, volunteers were required to walk 4 m at their usual pace. Before the evaluation, both feet were to remain before the starting line. The stopwatch was started when a foot reached the starting line and was stopped when a foot reached the 4-m line (Coelho-Junior et al., 2018). The faster of two trials (m/s) was used for the analysis.

- Disability status

Functional status was further assessed using the Katz activities of daily living (ADL) scale (Katz et al., 1963).

Statistical analysis

Normality of data was ascertained using the Kolmogorov-Smirnov test. For the analysis, participants were categorized into two subgroups (i.e., low and high) for each LBM-related measurement (i.e., crude LBM, LBM/BMI, and SMI) according to their median values. This approach was chosen because there is no cutoff for any muscle mass indexes that is specific for people with DS. Median values were 43.44 kg, 1.69, and 8.38 kg/m^2 for crude LBM, LBM/BMI, and SMI respectively.

Differences in continuous and categorical variables between groups (low vs. high) were assessed by independent t-test and chi-square (χ^2) statistics, respectively. Pearson's tests were run to explore correlations between continuous variables and muscle mass indexes. For all tests, the level of significance was set at 5% ($p < 0.05$). All analyses were performed using the IBM SPSS Statistics, version 23.0, software (IBM Corp., Armonk, NY).

Results

The study sample included 105 adults diagnosed with DS. Table 1 shows the main characteristics of participants according to muscle mass indexes. Individuals allocated into the high crude LBM subgroup (≥43.44 kg) showed lower prevalence of autoimmune diseases and higher WC, MAC, FTI, and consumption of antipsychotic drugs in comparison with the low LBM category. The high LBM/BMI subgroup (≥1.69) showed higher FTI and lower BMI, WC, and HC values relative to low LBM/BMI participants. Finally, BMI, WC, and HC were greater in the high SMI subgroup (≥8.38 kg/m^2) compared with the low SMI subgroup (≥8.38 kg/m^2). In addition, higher serum CTX levels, a marker of bone resorption (Rosen et al., 2000), were observed in the high SMI subgroups in comparison to participants with low SMI.

Table 1. Main characteristics of participants according to muscle mass indexes.

Total (n = 105)						
		Lean body mass		Lean body mass/BMI		SMI
	Total sample	Low (< 43.44 kg)	High (≥43.44 kg)	Low (< 1.69 kg/(kg/m²))	High (≥1.69 kg/(kg/m²))	Low (< 8.38 kg/m²)
Demographics						
Age (years), mean ± SD	38.4 ± 12.1	39.7 ± 13.2	35.8 ± 10.6	37.8 ± 12.3	37.7 ± 12.1	42.0 ± 13.1
Gender (male), %	41.0	52.2	34.8	45.7	41.3	53.2
Comorbidities and medications (%)						
Cardiovascular disease	57.4	52.2	47.8	43.5	56.5	59.6
Autoimmune diseases	81.9	73.9	71.7**	69.6	76.1	72.3
Malnutrition	4.3	6.5	0.0	0.0	6.5	6.4
Antipsychotics	22.3	25.0	26.7*	100	100	32.4
Benzodiazepines	4.3	10.0	0	0	11.8	8.8
Antidepressants	14.9	20.0	13.3	22.2	11.8	11.8
Polypharmacy (≥ 4 drugs)	9.6	7.5	13.3	8.3	11.8	11.8
ADL impairment (%)						
1	35.1	42.9	51.7	42.4	51.6	40.6
2	52.1	71.4	65.5	66.7	71.0	65.6
≥3	63.8	85.7	82.8	87.9	80.6	81.3
Anthropometric characteristics (mean ± SD)						
BMI (kg/m²)	27.9 ± 6.5	25.6 ± 5.3	29.1 ± 6.2	31.0 ± 5.9	23.7 ± 3.3*	24.9 ± 4.0
WC (cm)	86.4 ± 12.8	79.9 ± 9.7	92.5 ± 12.9*	91.0 ± 14.1	81.4 ± 9.8*	83.0 ± 9.1
HC (cm)	102.1 ± 12.1	98.5 ± 9.6	105.0 ± 13.7	107.8 ± 9.5	95.7 ± 6.7*	96.7 ± 7.8
WH	0.85 ± 0.7	0.81 ± 0.6	0.88 ± 0.6	0.84 ± 0.8	0.85 ± 0.7	0.86 ± 0.0
MAC (cm)	28.8 ± 3.5	27.4 ± 2.4	30.1 ± 4.0*	30.0 ± 3.8	27.5 ± 2.8	27.5 ± 2.8
Fat mass (kg)	17.4 ± 11.4	13.7 ± 8.8	20.9 ± 12.6	23.7 ± 11.4	10.9 ± 6.8	13.9 ± 8.8
Lean body mass (kg)	44.2 ± 5.9	39.4 ± 2.8	48.9 ± 4.2*	42.8 ± 5.8	45.6 ± 5.7	42.1 ± 5.0
Lean body mass/BMI	1.7 ± 0.31	1.5 ± 0.31	1.7 ± 0.32	1.4 ± 0.18	1.9 ± 0.18	1.7 ± 0.30
SMI (kg/m²)	8.4 ± 1.3	8.0 ± 1.3	8.7 ± 1.2	8.6 ± 1.4	8.1 ± 1.2	7.3 ± 0.94
Bone parameters						
Femoral BMD (g/m²)	0.68 ± 0.12	0.66 ± 11	0.72 ± 12	0.68 ± 0.11	0.69 ± 0.12	0.61 ± 0.11
Spine BMD (g/m²)	0.90 ± 0.13	−1.5 ± 1.2	−1.6 ± 1.1	0.91 ± 0.11	0.89 ± 0.14	0.87 ± 0.14
Physical function tests						
Handgrip strength (kg)	12.6 ± 6.0	10.8 ± 6.3	13.6 ± 5.7	12.3 ± 5.5	12.7 ± 6.6	14.2 ± 4.9
Usual walking speed (m/s)	0.8 ± 0.2	0.7 ± 0.3	0.9 ± 0.4	0.8 ± 0.4	0.9 ± 0.2	0.8 ± 0.5
Laboratory parameters						
25-hydroxycholecalciferol (nmol/L)	19.2 ± 10.0	18.7 ± 11.2	19.7 ± 8.8	18.4 ± 10.2	19.9 ± 10.2	19.7 ± 10.8
CTX (ng/mL)	0.53 ± 0.24	0.43 ± 0.17	0.64 ± 0.25	0.49 ± 0.24	0.59 ± 0.23	0.55 ± 0.31
DHEA (mg/mL)	2300 ± 1341	1864 ± 1167	2966 ± 1312	2281 ± 1134	2602 ± 1567	2270 ± 1320
FTI (pmol/L)	24.7 ± 33.1	7.9 ± 14.2	43.2 ± 38.8*	12.7 ± 20.1	43.6 ± 40.9*	25.0 ± 33.8

IGF-1 (nmol/L)	198.4 ± 73.4	185.1 ± 58.3	213.5 ± 83.0	176.6 ± 55.8	224.8 ± 81.4	185.2 ± 62.8
Osteocalcin (ng/mL)	29.7 ± 10.2	30.1 ± 10.4	31.8 ± 9.7	26.8 ± 9.4	35.5 ± 9.7	32.6 ± 10.5
SBGH (nmol/L)	56.6 ± 39.1	74.0 ± 41.3	34.9 ± 15.7	63.0 ± 45.8	43.7 ± 18.5	66.8 ± 44.2
TSH (U/mL)	3.2 ± 3.1	3.5 ± 4.2	2.7 ± 1.5	3.6 ± 4.1	2.6 ± 2.1	3.2 ± 4.0

Abbreviations: BMD = bone mass density; BMI = body mass index; CTX = carboxy-terminal collagen crosslinks; DHEA = dehydroepiandrosterone; FTI = free testosterone index; HC = hip circumference; IGF-1 = insulin-like growth factor 1; MAC = mid-arm circumference; SD = standard deviation; SHBG = sex hormone binding globulin; SMI = skeletal muscle index; TSH = thyroid-stimulating hormone; WC = Waist circumference; WH = waist-to-hip ratio. * $p < 0.05$ vs. low subgroup.

Pearson's correlations were performed to investigate which variables were significantly associated with the different muscle mass indexes (Table 2). Low crude LBM (−0.35), low LBM/BMI (−0.30), and low SMI (−0.52) were negatively correlated with age. Furthermore, low crude LBM was correlated with HC (0.29). On the other hand, low LBM/BMI (−0.63) was negatively correlated with all anthropometric measures (WC: −0.40, HC: −0.63, MAC: −0.31, fat mass: −0.49), except for WH. MAC (−0.33) and fat mass (−0.28) were also negatively correlated with high LBM/BMI. Similarly, high SMI was positively correlated with WC (0.49), HC (0.45), MAC (0.32), and fat mass (0.41). Low and high crude LBM as well as low SMI were correlated with femoral BMD (0.38, 0.49, 0.38). Additional correlations were observed between spine BMD and low crude LBM (0.33). Finally, serum 25-hydroxycholecalciferol levels were positively correlated with low SMI (0.51).

Table 2. Pearson's correlations between muscle mass indexes and continuous variables.

	Lean body mass		Lean body mass/BMI		SMI
	Low (< 43.44 kg)	High (≥43.44 kg)	Low (< 1.69 kg/(kg/m^2))	High (≥1.69 kg/(kg/m^2))	Low (< 8.38 kg/m^2)
Age (years)	−0.35*	−0.12	−0.30*	0.25	−0.52**
Anthropometric characteristics					
WC (cm)	0.22	0.22	−0.40**	−0.21	0.20
HC (cm)	0.29*	0.13	−0.63**	−0.14	0.22
WH	−0.02	0.18	0.17	−0.16	0.06
MAC (cm)	0.21	0.23	−0.31*	−0.33*	0.23
Fat mass (kg)	0.19	0.12	−0.49**	−0.58**	0.09
Bone parameters					
Femoral BMD (g/m^2)	0.38*	0.49**	0.03	−0.10	0.38*
Spine BMD (g/m^2)	0.33*	0.17	−0.18	0.08	0.28
Physical function tests					
Handgrip strength (kg)	−0.45	0.04	0.15	0.25	0.55
Usual walking speed (m/s)	0.00	0.01	−0.48	0.09	0.12
Hormonal profile					
25-hydroxycholecalciferol (nmol/L)	0.19	0.02	0.16	0.08	0.51**

TSH (U/mL)	0.04	0.25	−0.00	0.02	0.18
IGF-1 (nmol/L)	0.29	0.19	0.22	−0.10	0.08
SBGH (nmol/L)	−0.38	−0.20	0.17	0.11	−0.05
DHEA (mg/mL)	0.07	−0.11	0.01	−0.10	−0.00
FTI (pmol/L)	0.44	0.35	0.34	0.20	0.22
CTX (ng/mL)	−0.06	−0.00	−0.05	−0.25	0.27
Osteocalcin (ng/mL)	0.31	0.07	0.13	−0.11	0.12

Abbreviations: BMD = bone mass density; BMI = body mass index; CTX = carboxy-terminal collagen crosslinks; DHEA = dehydroepiandrosterone; FTI = free testosterone index; HC = hip circumference; IGF-1 = insulin-like growth factor 1; MAC = mid-arm circumference; SHBG = sex hormone binding globulin; SMI = skeletal muscle index; TSH = thyroid-stimulating hormone; WC = waist circumference. * $p < 0.05$. ** $p < 0.001$.

Discussion

The present study was undertaken to investigate (a) sarcopenia-related parameters and (b) functional, body composition and biological measures associated with muscle mass indexes in adults with DS. Our findings indicate that LBM is negatively correlated with age in DS, regardless of the muscle mass index considered. While the relationship between aging and muscle loss is well-established in the general population (Marzetti et al., 2017), our study is the first describing a similar phenomenon in persons with DS.

Results of the present study lend support to the hypothesis that the trisomy of human chromosome 21 can impact skeletal muscle tissue development (Cisterna et al., 2013), since the mean muscle mass (44.1 kg) and SMI values (8.3 kg/m^2) of adults with DS who participated in the present study was slight higher (Baumgartner et al., 1998) or even lower (Chien et al., 2008; Bianchi et al., 2015; Martone et al., 2017) than the proposed cutoffs for sarcopenia in older adults (Fig. 1). Specifically, the mean SMI of the low SMI subgroup (7.3 kg/m^2) was markedly lower than in non-sarcopenic older adults aged ≥75 years (−15%) (Bianchi et al., 2015) and older patients admitted to acute care wards (−18%) (Martone et al., 2017).

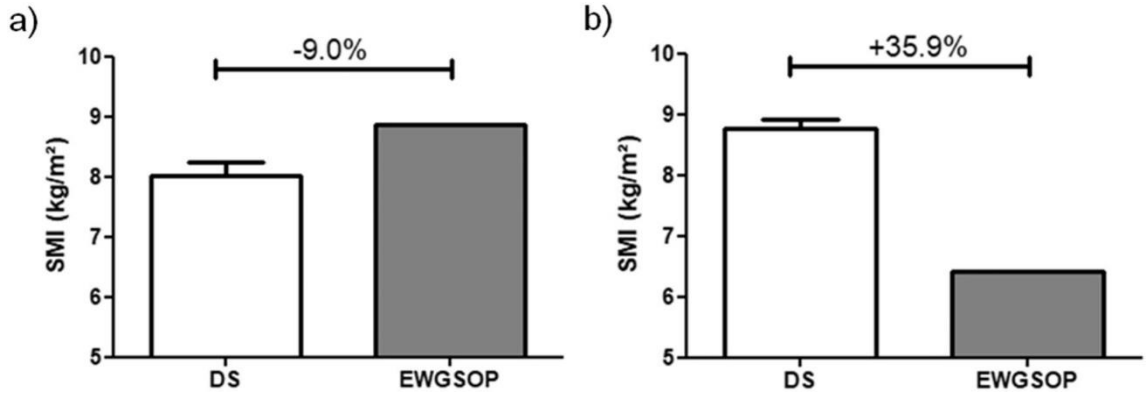

Fig. 1. Comparison between mean values of skeletal muscle index in men (a) and (b) women with Down syndrome and the cutoffs for low muscle mass by the European Working Group on Sarcopenia in Older People (Cruz-Jentoft et al., 2010). DS = Down syndrome; EWGSOP = European Working Group on Sarcopenia in Older People; SMI = Skeletal muscle index.

Although not linearly, muscle mass is linked to muscle strength and muscle power (Lauretani et al., 2003). Consequently, muscle atrophy has been associated with reduced physical function and other negative outcomes, such as disability, hospitalization, and mortality (Bianchi et al., 2015). Interestingly, low muscle mass indexes were not associated with reduced handgrip strength or walking speed relative to the high subgroups, probably indicating that muscle atrophy is not the main factor driving muscle weakness in DS individuals. This hypothesis is supported by findings by Bala et al. (2018), who demonstrated that Ts1Cje mice, a well-established animal model of DS, displayed lower muscle strength without changes in muscle cross sectional area. Nevertheless, similar to muscle mass indexes, mean handgrip strength and gait speed values in our sample of DS adults were markedly lower than the cutoff levels for sarcopenia (Cruz-Jentoft et al., 2019) (Fig. 2). Noticeably, the handgrip performance of adults with DS (12.5 kg) was lower than that observed in Italian community-dwellers aged 80 years or older (Landi et al., 2017a).

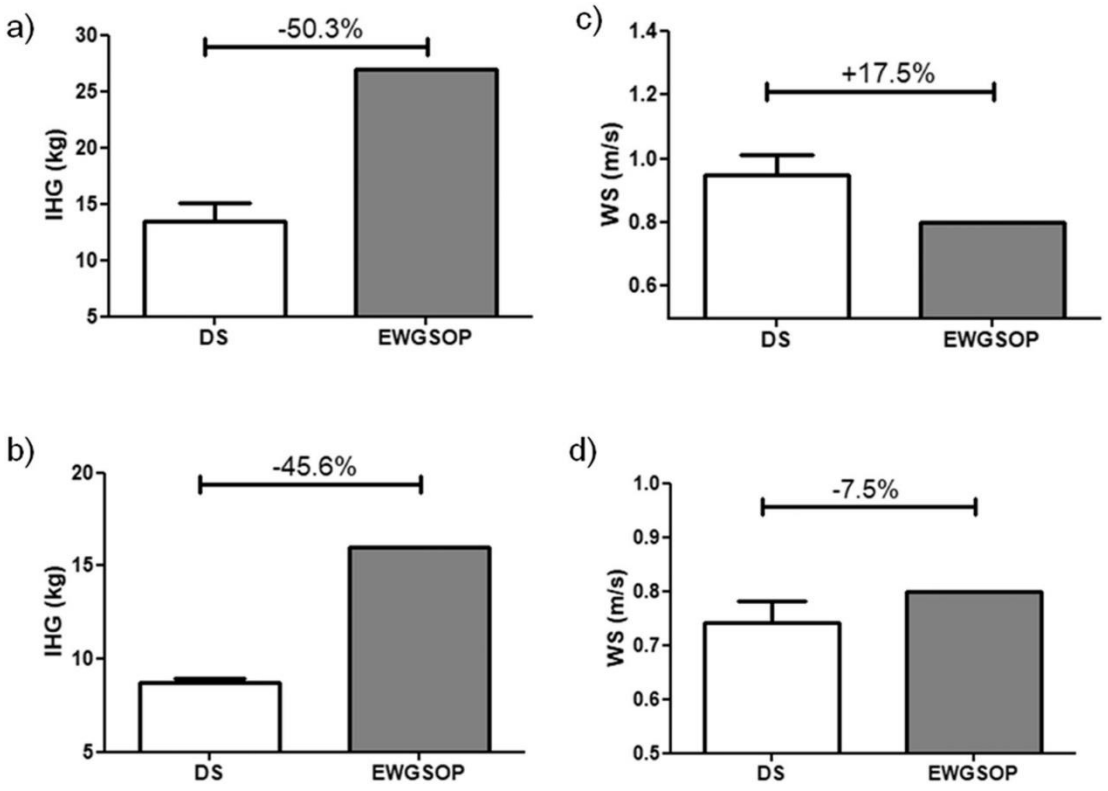

Fig. 2. Comparisons between handgrip strength and walking speed in DS and proposed cutoffs for sarcopenia by EWGSOP (Cruz-Jentoft et al., 2019), according to gender (a and c, men; b and d, women). DS = Down syndrome; EWGSOP = European Working Group on Sarcopenia in Older People; IHG = isometric handgrip strength; WS = walking speed.

A distinct pattern of correlations was observed between anthropometric characteristics and muscle mass indexes. Low LBM was correlated with HC, which may suggest an association with fat mass and muscle quality. However, other anthropometric parameters (i.e., MAC and WC) and fat mass did not show significant correlations. In turn, both low and high LBM/BMI were negatively correlated with MAC and fat mass. An interesting positive correlation was also observed between high SMI and all anthropometric measures, except for WH. These findings were unexpected as fat mass has been strongly associated with muscle wasting in older adults (Buch et al., 2016; Marzetti et al., 2018b). It should be stressed that obesity has long been recognized as a high prevalent clinical feature in DS individuals (Luke et al., 1996; Melville et al., 2005; Bell and Bhate, 2008), and evidence suggests that these individuals show reduced caloric intake in comparison with individuals with traditional development (Luke et al., 1996). A possible explanation for these results could be that participants in the high SMI subgroup might have been practicing physical exercise with or without nutritional supervision. However, physical activity and exercise levels as well as diet were not controlled in the present study.

In the low SMI subgroup, muscle mass and serum 25-hydroxycholecalciferol levels were significantly correlated. Previous studies have shown that vitamin D deficiency is associated with sarcopenia and may intervene in the pathogenesis of muscle atrophy (Calvani et al., 2013). Indeed, vitamin D modulates several pathways involved in muscle growth and homeostasis, including protein turnover, myogenesis, and myoblast differentiation (Gunton and Girgis, 2018). The possibility that low circulating vitamin D levels might contribute to muscle loss also in DS persons warrants further investigation.

Regarding bone parameters, LBM and SMI were significantly correlated with spine and femoral BMD. These findings are supported by numerous investigations proposing that sarcopenia is associated with osteopenia and osteoporosis in older adults (Cheng et al., 2014; Borges Pereira et al., 2015; Edwards et al., 2015). Furthermore, disruption of bone-muscle crosstalk is proposed to play a role in the pathogenesis of both sarcopenia and osteoporosis (Picca et al., 2017; Tarantino and Scimeca, 2018). Nevertheless, our findings do not support a clear-cut pattern between muscle mass indexes and bone parameters in DS. Indeed, in the low, but not the high subgroup, SMI was associated with femoral BMD. These results may be, at least partly, explained by the cross-sectional design of the present study.

Although this study presents novel findings, some aspects need to be discussed. The main limitations include the relatively low number of participants and the lack of a deeper analysis of body composition and physical function, as well as the analysis of the metabolic status and physical activity levels. Regarding the latter, muscle strength and physical function were assessed by handgrip strength and walking speed, respectively, since these tests are endorsed by the European (Cruz-Jentoft et al., 2019) and Asian (Chen et al., 2014) working groups on sarcopenia in older people. However, according to the recently revised European consensus (Cruz-Jentoft et al., 2019), other physical performance tests, such as the timed “up-and-go” (TUG) and the 5-repetition chair-stand tests, might be included in the evaluation. In addition, because participants of the present study were relatively young (mean age: 38 years), findings may not be extrapolated to older people with DS. Future research should address the aforementioned limitations and expand these highly novel initial findings.

Conclusion

Taken as a whole, findings from the present study indicate that adults with DS show muscle mass indexes and physical performance levels similar to or lower than older adults with sarcopenia. Furthermore, LBM and SMI were correlated with a set of anthropometric and bone parameters. Since DS persons seem to suffer from premature sarcopenia, the assessment of

muscle mass and functional status should be included in the routine evaluation of this population starting at young age. Future studies are warranted to confirm these initial findings and investigate whether the sarcopenic status of DS people may be improved by established interventions, such as exercise and optimized nutrition.

Declaration of interest statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Authors' contributions

All authors participated in the development of the research project, analysis, and interpretation of the data, and preparation of the manuscript.

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ARTICLE 4

nutrients

MDPI

Review

Relative Protein Intake and Physical Function in Older Adults: A Systematic Review and Meta-Analysis of Observational Studies

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Abstract: (1) Background: The present work aims to conduct a systematic review and meta-analysis of observational studies, in order to investigate the association of relative protein intake and physical function in older adults; (2) Methods: Observational studies, that investigated the association between protein intake and physical function in older adults, were retrieved from MEDLINE, SCOPUS, CINAHL, AgeLine, EMBASE, and Cochrane-CENTRAL. Two independent researchers conducted study selection and data extraction; (3) Results: Very high protein intake (≥1.2 g/kg/day) and high protein intake (≥1.0 g/kg/day) groups showed better lower limb physical functioning and walking speed (WS) performance, respectively, in comparison to individuals who present relative low protein (<0.80 g/kg/day) intake. On the other hand, relative high protein intake does not seem to propitiate a better performance on isometric handgrip (IHG) and chair rise in comparison to relative low protein intake. In addition, there were no significant differences in the physical functioning of high and middle protein intake groups; (4) Conclusions: In conclusion, findings of the present study indicate that a very high (≥1.2 g/kg/day) and high protein intake (≥1.0 g/kg/day) are associated with better lower-limb physical performance, when compared to low protein (<0.80 g/kg/day) intake, in community-dwelling older adults. These findings act as additional evidence regarding the potential need to increase protein guidelines to above the current recommendations. However, large randomized clinical trials are needed to confirm the addictive effects of high-protein diets (≥1.0 g/kg/day) in comparison to the current recommendations on physical functioning. All data are available in the Open ScienceFramework.

Keywords: sarcopenia; protein intake; physical function

Introduction

Sarcopenia is a geriatric condition characterized by progressive muscle atrophy accompanied by loss of muscle strength and/or function [1]. The incidence of sarcopenia rises with aging and its prevalence is markedly increased in older subjects [2]. In the absence of targeted interventions, the clinical course of sarcopenia is marked by higher odds of mobility disability, loss of independence, and mortality [3–6]. In this sense, adequate protein intake and physical exercise have been suggested as the two main strategies to counteract sarcopenia, and prevent its deleterious effects [7,8].

Although protein supplementation may be advisable in the management of sarcopenia, the optimal protein requirement for older adults is presently unclear. Indeed, the established guidelines recommended for a number of agencies, such as the Dietary Allowance (RDA), RDI (recommended daily intake) [9], and the RNI (reference nutrient intake) [10] have been questioned, and researchers have discussed if the recommended protein intake is enough to maintain the functional status or even prevent its decline and muscle atrophy in older adults [11,12]. Most critical are regarding the RDA, so that the main concern is that the amount of protein recommended is based on nitrogen balance studies, which may be associated with a methodological bias [11,13].

Opinion articles and consensus statements have argued that older people should be encouraged to consume greater quantities of protein than the RDA (1.0–1.5 g/kg) [11–14]. Findings from observational studies are in line with these inferences, since higher protein consumption is associated with lower risk of frailty, loss of lean body mass, slow walking speed, dynapenia, and poor balance [15–18]. Nevertheless, there is a lack of direct evidence testing the proposed cut-off points for protein consumption. The few available studies have reported incongruent results regarding the association of protein intake and physical function [17,19–21]. However, to the best of our knowledge, meta-analyses have not been performed to determine the pool of results.

Therefore, the present work aimed at conducting a systematic review and meta-analysis of observational studies to investigate the association of relative protein intake and physical function in older adults.

Materials and Methods

We conducted a systematic review and meta-analysis of observational studies to assess the association between relative protein intake and physical function in older adults. The study was fully performed by investigators and no librarians were part of the team. This study

complies with the criteria proposed by the Primary Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement [22], and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [23]. All data are available in the Open Science Framework at https://doi.org/10.17605/ OSF.IO/JP5SB.

Eligibility Criteria

The inclusion criteria consisted of: (a) Observational studies, including cross-sectional and case-control studies, which investigated as primary or secondary outcome the association of relative protein intake and physical function in older adults. Longitudinal cohort studies were also included if crude baseline data were available; (b) participant age of 60 years or older; (c) direct assessment of at least one physical function domain (studies provided self-reported physical function were excluded); (d) provided the comparison of at least two groups with different relative protein intakes; (e) mean values and a measure of dispersion (standard deviation or confidence interval) were provided; (f) published studies (English language). We excluded randomized-clinical trials (RCTs), quasi-experimental, cross-over studies and any kind of investigation that examined the effects of a nutritional intervention associated or not with other interventions (e.g., physical exercise) on physical function. Studies that enrolled institutionalized participants or non-institutionalized participants with cognitive impairment and/or disorder, gastrointestinal and/or renal diseases, anorexia, cancer or any kind of condition that may directly impair protein metabolism (e.g., maple syrup urine disease, tyrosinemia) were also excluded. Sarcopenic and frailty older people were included.

Search Strategy and Selection Criteria

Studies published on or before August 2018 were retrieved from the following three electronic databases by one investigator (H.J.C.J): (1) MEDLINE (PubMed interface); (2) the Cochrane Library (Wiley interface); (3) SCOPUS (Elsevier interface); (4) CINAHL (EBSCO interface); (5) AgeLine (EBSCO interface); and (6) EMBASE (EBSCO interface). Reference lists for reviews and retrieved articles for additional studies were checked and citation searches on key articles were performed in Google Scholar and ResearchGate for additional reports. Initially, a search strategy was designed using keywords, MeSH terms, and free text words, such as protein consumption, physical function, older adults. Additionally, keywords and subject headings were exhaustively combined using Boolean operators. The complete search strategy used for the PubMed is shown in List S1. Only eligible full texts in English language were considered for review. Authors were contacted if necessary.

Data Extraction and Quality Assessment

Titles and abstracts of retrieved articles were screened for eligibility by two researchers (H.J.C.-J. and B.R.). If an abstract did not provide enough information for evaluation, the full-text was retrieved. Disagreements were solved by a third reviewer (M.U.). Reviewers were not blinded to authors, institutions, or manuscript journals. Studies that provided data for more than two groups—for example, low, middle, high, and very high relative protein intake were also added—since the volunteers were not shared among the groups. Data extraction were independently performed by two reviewers (H.J.C.-J. and L.M.-T) using a standardized coding form. Disagreements were solved by a third reviewer (M.U.).

Coded variables included methodological quality and the characteristics of the studies, including: Year, authors, country, study design, setting, sample size (*n*), age, prevalence of female, body mass index (BMI), lean mass, appendicular muscle mass, dietary intake assessment method, total protein intake, relative protein intake.

Afterwards, studies were allocated into four different groups (*low* (<0.8 g/kg/day), *middle* (0.8–0.99 g/kg/day), *high* (≥1.0 g/kg/day), and *very high* (≥1.2 g/kg/day) protein intake). These cutoffs were selected according to previous research. Indeed, longitudinal [24,25] and review [11–14] studies have arguing that older adults should consume at least 1.0 g/kg/day of protein (i.e., *high*) to maintain muscle mass and optimal physical functioning, so that values below the RDA (<0.8 g/kg/day) may be considered *low*, while values higher than the RDA, but lower than the recommended for these aforementioned studies may be considered *middle*. In addition, some evidence has proposed that a minimum of 1.2 g/kg/day of protein should be consumed by older adults in attempt to avoid poor health-related outcomes and maintain functional performance, regardless the presence of chronic diseases [26,27]. In this sense, investigations that showed a mean protein intake of at least 1.2 g/kg/day were allocated in the *very high* group.

The quality of reporting for each study was performed by two researchers (H.J.C.-J. and L.M.-T) using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) instrument [28]. The agreement rate between reviewers was $\kappa = 0.96$ for quality assessment.

Statistical Analysis

Meta-analyses were conducted using Revman V.5. Effect size (ES) were measured using standard mean difference (SMD) and mean difference and are reported with 95%

confidence intervals (95% CI). SMD was used in the comparisons between *High protein intake* and *Very high protein intake* versus

Low protein intake in relation to *Mobility* and *Lower limb physical functioning*, respectively, since the investigations assessed the same outcome, but using different tools. However, the mean difference was used in the remaining comparisons, since all the other studies used the same outcome. If the required outcome metric was not reported in the study, values were calculated using available data. Due to the different characteristics of the included studies, a random-effect model was used to calculate the pooled ES. Heterogeneity across studies was tested using Q-statistics and I^2 index was used to assess inconsistency [29]. The I^2 index was classified as not important (0–40%), moderate (30–60%), substantial (50–90%), and considerable (75–100%).

Results

Characteristics and Quality of Included Studies

Table 1 provides a general description of the included studies. Of the 4392 registers recovered from electronic databases and hand search, 4253 records were excluded based on duplicate data, title or abstract. One hundred thirty-nine studies were fully reviewed and assessed for eligibility. Finally, seven studies met the inclusion criteria (Figure 1).

Included studies were published between 2014 and 2018, the majority had a prospective longitudinal cohort design [17,30–32], while two had a cross-sectional design [20,33] and one study was a case-control [21]. Overall, a total of 8754 community-dwelling older adults from six different countries were included. Volunteers were characterized as healthy in three studies [17,31,34], post-menopausal in two studies [20,31], sarcopenic in one study [21], and diabetic in one study [32]. Mean age of the subjects ranged from 67.8 to 83.0 years, and the percentage of women among total subject population of various study groups varied from 10% to 100%. Mean BMI ranged from 23.7 kg/m^2 to 29.5 kg/m^2, so that one study investigated volunteers with normal BMI [34], while the other six studies investigated overweight individuals [17,20,21,31–33]. Limited information was available regarding the clinical characteristics of study participants. Nevertheless, osteoporosis, diabetes, hypertension, depression, rheumatoid arthritis, and heart diseases were diagnosed among the included individuals. Lean mass and appendicular skeletal muscle represented 55.8% and 24.4%, respectively, of the total weight. Twenty-nine percent of the volunteers reported an episode of fall in the 12 months before the investigations. Physical and functional evaluations included

isometric handgrip strength (IHG), knee extensor strength, one-leg stance, usual walking speed (WS), chair rise, tandem walk speed, narrow

walk speed, short physical performance battery (SPPB), and timed 8-foot walk. However, only IHG, WS, knee extensor strength, SPPB, and chair rise were included in the final analysis, due to availability of data. According to protein intake per kg of body weight, volunteers could be divided into four major groups: *Low* (<0.8 g/kg/day), *middle* (0.8–0.99 g/kg/day), *high* (≥1.0 g/kg/day), and *very high* (≥1.2 g/kg/day). Methods to evaluate dietary intake included 24-h dietary recall (28.5%), 3-day dietary intake record (28.5%), 4-day dietary intake record (14.3%), food frequency questionnaire (14.3%), and the Semi Quantitative-Food Frequency Questionnaire (SQFFQ) (14.3%).

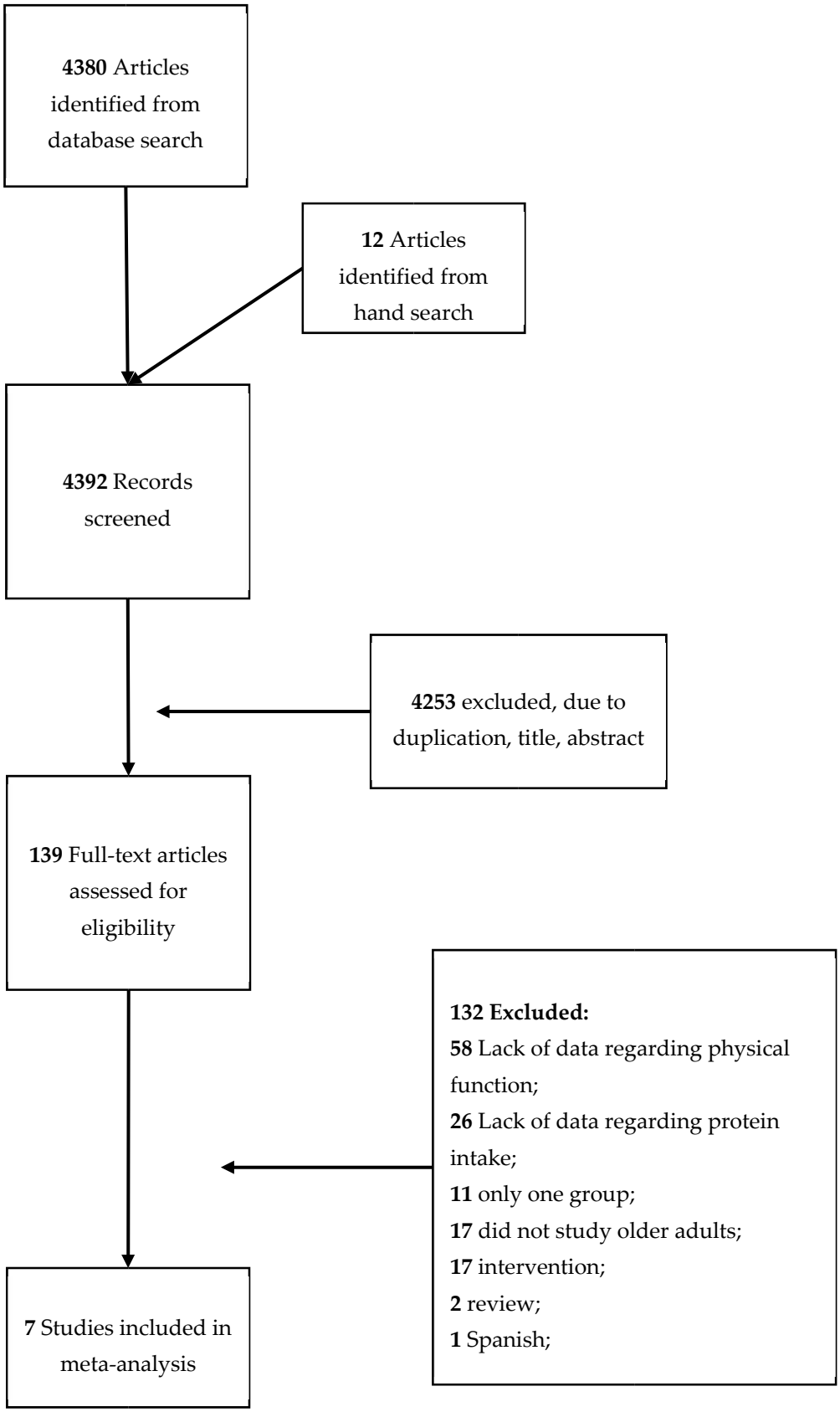

Figure 1. Flowchart of the present study.

Table 1. General description of the included studies.

Year	Authors	Country	Study Design	Population	Setting	Sample Size	Age	Female (%)	BMI	Lean Mass	Appendicular Muscle Mass	Dietary Intake Assessment Method	Total Protein Intake (g/Day)	STROBE Score
2018	ten Haaf et al.	Netherland	Cross-sectional	Healthy	Community-dwelling	HP: 80; LP: 60	83.0	10	26.1	—	—	24-h dietary recall	HP: 89.5; LP: 64.7	19
2016	Isanejad et al.	Finland	Longitudinal	Healthy	Community-dwelling	HP = 112; MP = 269; LP = 171	67.8	100	26.6	HP: 41.3, 16.4, 6.5; MP:40.1, 15.9, 6.7; LP: 39.1, 15.6, 6.6	—	3-day dietary intake record	HP: 83.4; MP:65.0; LP: 51.4	20
2016	Rahi et al.	Canada	Longitudinal	Diabetic	Community-dwelling	HP: 73; LP: 99	75.0	62	29.5	—	—	24-h dietary recall	HP: 91; LP: 64.3	20
2015	Larocque et al.	United States	Longitudinal	Post-menopausal women	Community-dwelling	LP = 1756; HP = 2889	80.1	100	26.8	—	—	Food frequency questionnaire	LP = 42.6; HP = 71.6	17
2015	Verlaan et al.	United Kingdom	Case-control	Sarcopenic and non-sarcopenic	Community-dwelling	Sarcopenic: 66; Non-sarcopenic: 66	71.1	39	26.1	—	Sarcopenic:19.0; Non-sarcopenic: 20.4	3-day dietary intake record	Sarcopenic: 72.5; Non-sarcopenic: 75.3	19
2014	Chan et al.	China	Longitudinal	Healthy	Community-dwelling	LP = 617; MP =677; HP = 705; HP2 = 727	71.6	49.8	23.7	—	—	Semi Quantitative-Food Frequency Questionnaire (SQFFQ)	—	19
2014	Gregorio et al.	United States	Cross-sectional	Post-menopausal women	Community-dwelling	LP = 97; HP = 290	73.0	100	27.4	LP = 40.7; HP = 38.2	LP = 17.0; HP = 15.9	4-day dietary intake record	LP = 49.7; HP = 79.7	20

BMI = body mass index; HP = high protein; MP = middle protein; LP = low protein.

Table 2 provides the general characteristics of the volunteers according to their relative protein intake. All groups presented similar mean age (~73 years). The lowest sample size was observed in the middle protein intake group, followed by the very high protein intake group, low protein intake group and high protein intake group. The groups presented a similar mean lean mass and mean appendicular mass. However, it is important to observe that High protein intake and Very high protein intake groups showed a higher percentage of lean mass when compared to Low protein intake and Middle protein intake groups. In addition, a greater performance in knee extensor strength and SPPB was observed in High protein intake and Very high protein intake groups when compared to Low protein intake group. Protein, carbohydrate and fat intake increased according to relative protein intake. It should be stressed that these parameters were not reported by all the investigations.

Table 2. Characteristics of the volunteers according to relative protein intake *.

	Low Protein Intake (0.67)	***Middle Protein Intake (0.88)***	***High Protein Intake (1.3)***	***Very High Protein Intake (1.5)***
Variables	***n* = 2641**	***n* = 395**	***n* = 5619**	***n* = 1145**
Anthropometric characteristics				
Age (years)	73.8	74.0	74.6	73.5
BMI (kg/m^2)	29.1	26.7	27	27.1
Lean Mass (kg) (% in relation to weight)	41.0 (53)	40.1 (56.1)	38.7 (58.7)	38.2 (58.1)
Appendicular Muscle Mass (kg) (% in relation to weight)	—	19.0 (25.5)	20.4 (24.7)	15.9 (24.2)
Physical functional tests				
IHG (kg)	20.4	27.5	24.3	19.1
Knee Extensor Strength (lb)	54.5	44.5	52.1	57.5
One-Leg Stand (s)	13.5	19.3	18.4	15.3
Chair Rises (s)	11.4	10.6	11.8	13.5
Tandem Walk Speed for 6 m (m/s)	0.30	0.34	0.33	—
Usual Walking Speed (m/s)	1.1	1.2	1.2	1.07
SPPB (points)	9.9	9.0	11.0	10.6
Timed 8-Foot Walk (m/s)	1	—	1.1	1.1
Dietary factors				
Protein (g/day)	58.8	67.4	85.4	87.2
Carbohydrate (g/day)	162.6	199.8	215.9	220.6
Fat (g/day)	43.6	58.6	64.4	—

BMI = body mass index; IHG = Isometric handgrip; SPPB = Short physical performance battery (i.e., combination of results in gait speed, chair stand e balance tests; The final score ranged from 0 (worst performance) to 12 (best performance). * Information was not available by all the included investigations.

Study quality results are shown in Table S1, while the point by point analysis is shown in Table S2. The overall score ranged from 17 to 20. All studies reported the items required by the STROBE criteria in relation to the abstract (items 1 and 2), clarity of the outcomes (items 7 and 15), methods of assessment (item 8), handle of quantitative variables (item 11), statistical methods and analysis (items 12, 16), discussion (items 18–21), and funding (item 22). However, 14.2% of the studies failed to clearly state specific objectives, including any prespecified hypotheses (item 3), the main aim of the investigation (item 4), describe the setting, locations and relevant dates of recruitment and data collection (item 5) [25], give the characteristics of study participants (item 14); and report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses (item 17). In turn, 28.5% did not properly report the eligibility criteria, and the sources and methods of selection of participants (item 6), 71.4% did not describe any efforts to address potential sources of bias (item 9), 57.1% explained how the study size was arrived at (item 10) and reported numbers of individuals at each stage of study (item 13).

High Protein Intake verses Low Protein Intake

A total of four studies provided information to investigate the association of high and low protein intake with physical function (Figure 2). It should be stressed, that Rahi et al. [32] provided their data according to gender, and the results are presented accordingly. *Upper-limb muscle strength*—Upper-limb muscle strength was measured by IHG in all studies. Three studies were added in the meta-analysis [17,20,31]. Results did not demonstrate significant differences in IHG between the groups, and a small non-significant ES was observed (ES = −0.36; 95% CI = −1.15 to 0.44, $p = 0.38$). Moderate heterogeneity was found across studies ($\chi^2 = 4.16$, df = 2, $p = 0.12$, $I^2 = 52\%$) (Figure 2a). *Lower-limb muscle strength*—Lower-limb muscle strength was evaluated by chair-rise and knee extensor strength. A meta-analysis of three studies—but evaluating four subgroups—observed a small non-significant difference between groups (ES = −0.09; 95% CI = −0.26 to 0.08, $p = 0.30$). A not important heterogeneity was found across studies ($\chi^2 = 3.75$, df = 3, $p = 0.29$, $I^2 = 20\%$) (Figure 2b).

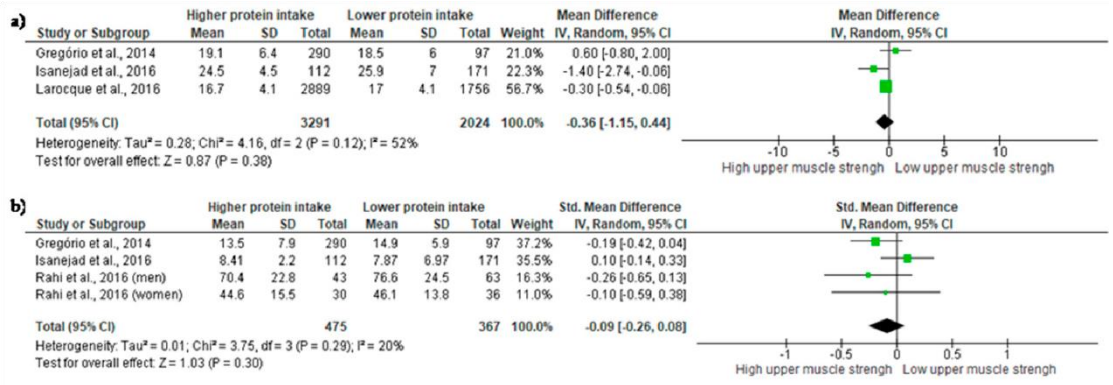

Figure 2. Mean difference in (**a**) *Upper-limb muscle strength* and Standardized mean difference in (**b**) *Lower-limb muscle strength* according to protein intake. Squares represent study-specific estimates; diamonds represent pooled estimates of random-effects meta-analyses.

Mobility

Mobility was evaluated by 10-m WS [17] and 6-m WS [34]. In the study of Chan et al. [34], three out of four groups showed a high protein intake (≥1.0 g/kg/day). In this sense, groups will be mentioned as Chan et al., 2014, 2014b, and 2014c, according to relative protein intake. In addition, the groups were evaluated alone and grouped. A small ES were observed when the analysis was performed with Chan et al. [34] (1.0 g/kg/day) and Isanejad et al. [17] (ES = 0.10; 95% CI= −0.06 to 0.27, $p = 0.23$, $\chi^2 = 20.66$, df = 1, $p < 0.00001$, $I^2 = 95\%$) (Figure 3a), as well as with Chan et al. (2014b) (1.4 g/kg/day) and Isanejad et al. [15] (ES = 0.11; 95% CI = −0.05 to 0.26, $p = 0.18$, $\chi^2 = 18.41$, df = 1, $p < 0.00001$, $I^2 = 95\%$) (Figure 3b). The combination of the groups—Chan et al. (2014 and 2014b)—changed the results, so that a small and significant ES was observed (ES = 0.07; 95% CI = 0.01 to 0.12, $p = 0.02$, $\chi^2 = 20.84$, df = 2, $p < 0.00001$, $I^2 = 90\%$) (Figure 3c). Significant results were also observed when Chan et al. (2014c) was evaluated alone (ES = 0.13; 95% CI = 0.01 to 0.24, $p = 0.04$, $\chi^2 = 10.29$, df = 1, $p = 0.01$, $I^2 = 90\%$) (Figure 3d) and with the other groups (ES = 0.06; 95% CI = 0.02 to 0.11, $p = 0.003$, $\chi^2 = 27.52$, df = 3, $p < 0.00001$, $I^2 = 89\%$) (Figure 3e).

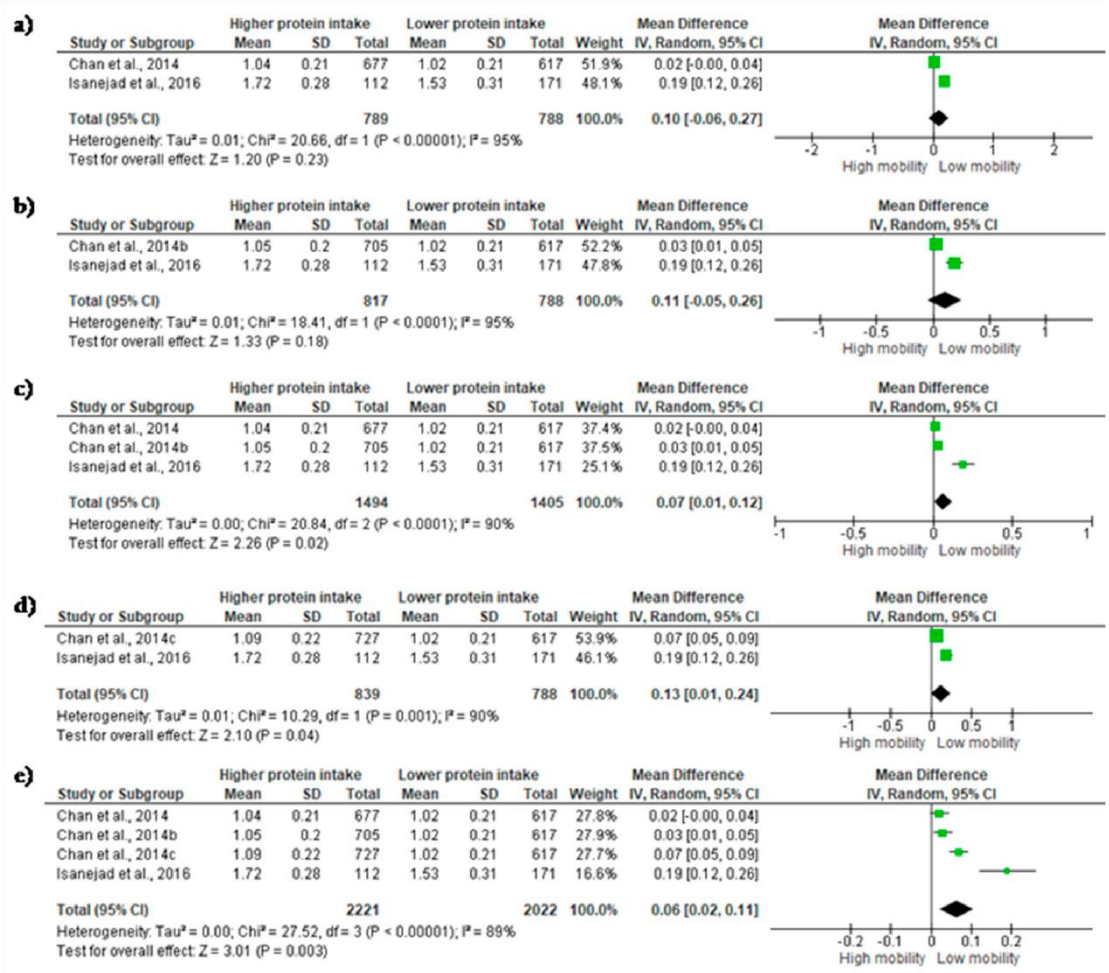

Figure 3. Mean differences in *Mobility* according to protein intake. (**a**) Chan et al., 2014, and Isanejad et al., 2016; (**b**) Chan et al., 2014b, and Isanejad et al., 2016; (**c**) Chan et al., 2014ab, and Isanejad et al., 2016; (**d**) Chan et al., 2014c, and Isanejad et al., 2016; (**e**) Chan et al., 2014abc, and Isanejad et al., 2016. Squares represent study-specific estimates; diamonds represent pooled estimates of random-effects meta-analyses.

Middle Protein Intake verses High Protein Intake

A total of four studies provided information to investigate the association of high and middle protein intake with physical function (Figure 4). *Upper-limb muscle strength*—Upper-limb muscle strength was measured by IHG in all studies. Three studies were added in the meta-analysis [17,21,33]. Results did not demonstrate significant differences in IHG between groups, and a large non-significant ES was observed (ES = 1.09; 95% CI = −3.78 to 5.96, $p = 0.66$). A considerable heterogeneity was found across studies ($\chi^2 = 25.07$, df = 2, $p = < 0.00001$, $I^2 = 92\%$) (Figure 4a). *Mobility*—Mobility was evaluated in three studies. Pooling of results indicated a small and non-significant ES (ES = 0.17; 95% CI= −0.12 to 0.46, $p = 0.26$). A considerable heterogeneity was found across studies ($\chi^2 = 56.46$, df = 2, $p = < 0.0001$, $I^2 = 96\%$) (Figure 4b). *Lower-limb muscle strength*—Lower-limb muscle strength was evaluated by chair-rise in all studies. A meta-analysis of two studies observe a moderate non-

significant difference between the groups (ES = 0.49; 95% CI= −0.01 to 0.99, p = 0.05). An insignificant heterogeneity was found across studies (χ^2 = 0.72, df = 1, p = 0.40, I^2 = 0%) (Figure 4c).

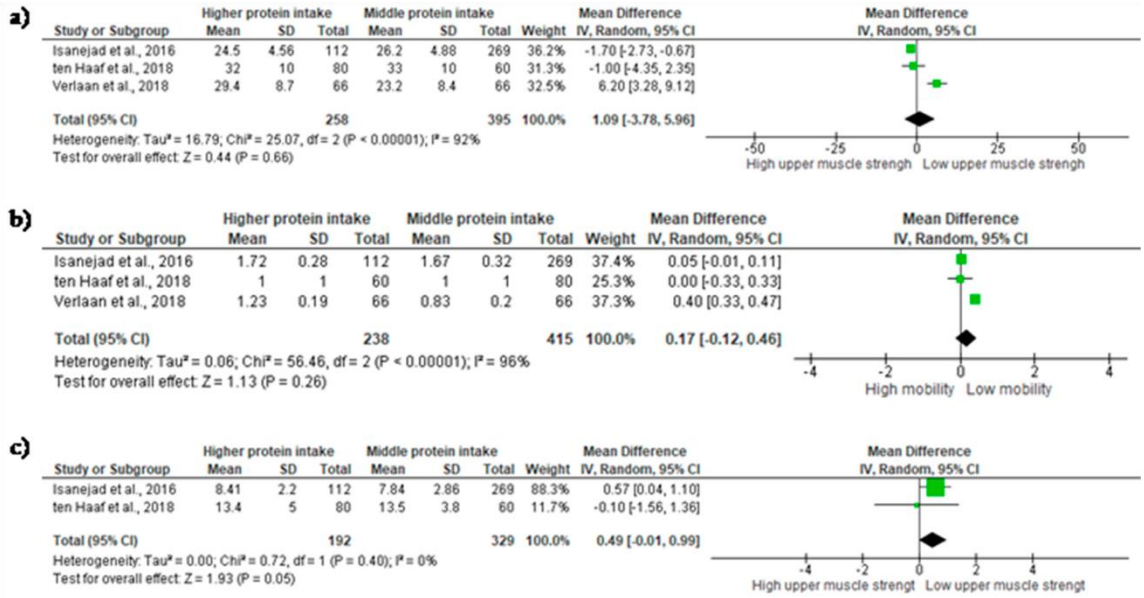

Figure 4. Mean difference in (**a**) *Upper-limb muscle strength*; (**b**) *Mobility*; and (**c**) *Lower-limb muscle strength* according to protein intake. Squares represent study-specific estimates; diamonds represent pooled estimates of random-effects meta-analyses.

Very High Protein Intake verses Low Protein Intake

A total of five investigations provided information to investigate the association of *very high protein intake* and *low protein intake* with physical function (Figure 5). Due to the lack of available evidence, we did not divide the evaluation according to the type of physical assessment, as was performed above, and studies should assess at least one lower limb physical function to be included. The evaluations included knee extensor strength [32], SPPB [20], and walking speed [34]. Pooling of results indicated a small and significant ES (ES = 0.18; 95% CI = 0.01 to 0.35, p = 0.04). A considerable heterogeneity was found across studies (χ^2 = 15.56, df = 4, p = 0.004, I^2 = 74%).

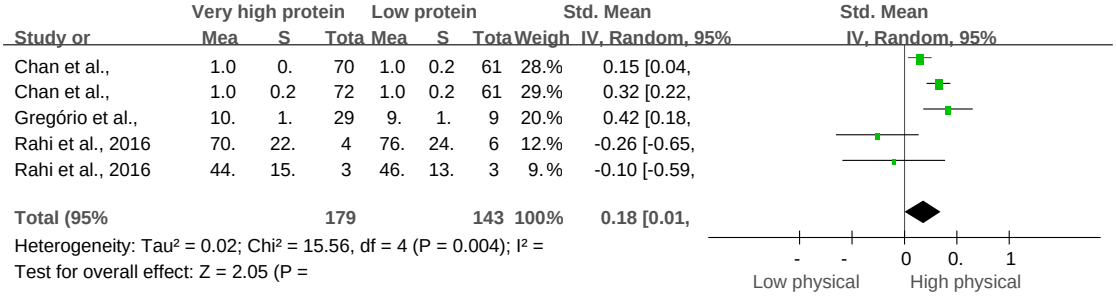

Figure 5. Standardized mean difference in *Lower-limb muscle functioning* according to protein intake. Squares represent study-specific estimates; diamonds represent pooled estimates of random-effects meta-analyses.

Discussion

The present study was designed to investigate the available evidence regarding the association of relative protein intake and physical function in older adults. Findings of this investigation indicate that individuals with relatively very high (≥1.2 g/kg/day) and high (≥1.0 g/kg/day) protein intakes show higher mobility and lower limb physical functioning, respectively, in comparison to those with relative low protein (<0.80 g/kg/day) intake.

The assessment of study quality demonstrated that reports were of very good quality and scored between 17 and 20. The main bias associated with the studies was the lack of adequate description about the efforts to address potential sources of bias (item 9), the design of the study size (item 10), and the report regarding the number of participants in all the phases of the study (item 13).

Although in recent years several study groups have strongly recommended that older adults consume greater levels of protein intake than the RDA, there is a lack of direct evidence testing this hypothesis [11,13]. Several observational studies have demonstrated incongruent results, so that it is possible to observe null [19,33,34] and positive [17,20,21] associations between protein intake and physical function in older adults.

To the best of our knowledge, this is the first study that directly compared the physical function of older adults with different relative protein intakes. Our findings support at least partially the need to increase protein guidelines to above the current RDA in older adults, since the very high and high protein intake groups showed better muscular health when compared to the low protein intake group. The plausibility behind these findings is based on the anabolic resistance hypothesis, according to which the muscular anabolic response to appropriate stimulation would be blunted in advanced age (to review, see Calvani et al. [14]; Landi et al. [35]). This idea is supported by the observation that the aging muscle presents diminished muscle protein synthesis in response to small amount of essential amino acids (EAAs) [36], the key nutrient for the stimulation of protein synthesis. This would eventually lead to muscle catabolism, loss on lean body mass, dynapenia, and impairment on muscle function [35]. Higher availability of EAAs, mainly leucine, seems to be necessary to reverse overcome the anabolic resistance of muscle [37]. Therefore, the greater physical performance observed in the groups with higher protein intake levels (i.e., very high and high) might be ascribed to a larger EAAs availability.

Although our findings demonstrated that very high and high protein intakes were associated with greater physical functioning in comparison to low protein intake, there were no differences between high and middle protein intake groups. These results are interesting and deserve concern because the *middle* group represented the level of protein intake recommended by the RDA.

The main motivation for considering changes from a minimum of 0.8 g/kg/day to 1.0 g/kg/day has been the findings of longitudinal studies that demonstrated preserved muscle mass [24] and lower risk of frailty [25] in older adults who had a protein intake ≥1.0 g/kg/day, as well as the evidence that showed a significant reduction on muscle mass of older adults who consumed the current RDA of protein for a long period [38]. However, no previous studies had directly comparing these proposed protein cutoffs, and the lack of significant differences between *high* and *middle* groups may occur, because the values of protein intake are similar, according to ten Haaf et al. [33].

Nonetheless, some researchers may argue that *very high* protein intake could be sufficient to elicit significant differences, since the studies of Vellas et al. [26] and Mustafa et al. [27] demonstrated that a very high protein intake was associated with a lower risk to poor health-related outcomes and physical disability. However, there was no available evidence to compare *very high* and *middle* protein intake groups. Taken together, these data suggest that a protein intake higher than 1.0 g/kg/day causes beneficial effects when compared to protein intake levels lower than 0.8 g/kg/day, but more studies are still necessary to precisely define the different effects of *very high* and *high* protein intakes in comparison to *middle* protein intake.

Conversely, from a practical point of view, the consumption of high protein intake by older adults has been the subject of intense scientific debate and a frequent concern of health professionals. Nowadays, has been accepted that older adults without a previous history of kidney disease show a lower risk of poor-health outcomes in response to high-protein diets [13,39]. However, although higher glomerular filtration rate seems to be a normal mechanism in response to the elevated amount of protein in the physiological system of patients with normal kidney function, an increased protein intake may collaborate to decline in the renal function of patients with a pre-existing renal disease [39]. Therefore, findings of the present study should be carefully extrapolated for other populations than healthy older adults.

On the other hand, data of the present study demonstrated that high protein intake was not associated with better performance on the IHG and chair rise when compared to low

protein intake group. These findings support the inferences that a higher protein intake may be associated with better scores on some, but not all physical tests [19].

One possible explanation for these results is that a greater intake of protein might promote better functioning of systems other than the neuromuscular system. It should be stressed that the performance on the IHG and chair-rise seems to be mainly dictated by the neuromuscular system. On the other hand, walking ability needs a larger integration among the body systems in comparison with sit and stand up or tightening an object. Indeed, walking is a complex activity involving a variety of neural process (e.g., sensory, cortical cognitive, temporal) [40,41], cerebral and peripheral vascular beds [42,43], as well as lung [44], cardiac and muscular functions [45], to list a few. Consequently, walking ability represents the functioning of multiple organ systems instead of just one system [46], and marked disturbances in gait pattern may occur in response to cardiovascular, neurological and neuromuscular pathologies [40,41].

Regarding the relationship between protein intake and neural functioning, for example, evidence has demonstrated that an insufficient protein intake may impair spatial learning and memory and cause brain atrophy [47], while high protein intake decreases markers of oxidative stress (lipid peroxidation) in the brain of rats [48], and is associated with low levels of insoluble amyloid-β protein (Aβ) in older adults [49]. In addition, a systematic review showed that protein intake was positively associated with cognitive function in older adults [50]. Furthermore, increased protein intake may cause changes in the vessel wall structure and in cardiovascular control exerted by the central nervous system, consequently mediating the negative association between protein intake and blood pressure [51,52].

Physical activity levels [33], vitamin intake [31], inflammation [15], mood disorders [53], and the prevalence of chronic conditions (e.g., sarcopenia) [17] may also affect the relationship between protein intake and physical function. In the study by Isanejad et al. [17], for example, higher protein intake and physical function were significantly associated in non-sarcopenic, but not in sarcopenic older women. These inferences are in keeping with the hypothesis that individuals suffering from illness, physical stress, sarcopenia and/or frailty may require higher protein levels (1.2–1.5 g/kg) than healthy older adults [11,12,14]. In the present investigation, a considerable heterogeneity (I^2)

was observed in most of the studies. Although we tried to explore heterogeneity among the studies performing the analysis with random effects, the investigations did not offer sufficient details about the samples, as indicated in the quality assessment and food intake

limiting the analysis of subgroups and meta-regression (see Table 2). Therefore, our results should be taken with caution and should be confirmed with further studies.

In this context, future studies aimed at investigating the association of protein intake and physical function should collect a number of data allowing better inferences and an inclusion in future systematic reviews and meta-analysis, including total and appendicular muscle mass, the prevalence of morbidities, frailty and sarcopenia assessment, physical activity levels, and an extensive report on food consumption (e.g., amino acid content, protein source) and not just the consumption of macronutrients. Other limitations of the present study include the lack of comparison between low and middle protein intake, as well as very high and middle protein intake (due to the lack of available data), and the use of the mean protein intake to identify the groups.

In relation to the latter, we allocated the groups mentioned in the studies into low, middle, high, and very high according to the mean protein intake reported. Nevertheless, it is possible that some individuals showed higher or lower protein intake levels. One possible way to solve this problem

would be that future studies designed the groups based on proposed cut-offs for older adults [11,12,14], instead of separatrix measures (e.g., quartiles), since a low quartile does not necessarily represent a low protein intake.

Conclusions

In conclusion, findings of the present study indicate that a very high (≥1.2 g/kg/day) and high protein intake (≥1.0 g/kg/day) are associated with better lower-limb physical performance when compared to low protein (<0.80 g/kg/day) intake in community-dwelling older adults. These findings add evidence regarding the potential need to increase protein guidelines to above the current recommendations. However, large randomized clinical trials are needed to confirm the addictive effects of high-protein diets (≥1.0 g/kg/day) in comparison to the current recommendations on physical functioning.

Supplementary Materials: The following are available online at http://www.mdpi.com/2072-6643/10/9/1330/ s1, List S1: The complete search strategy used for the PubMed. Table S1: Quality assessment analysis, Table S2: Individual quality assessment analysis of each included study.

Author Contributions: Conceptualization, H.J.C.-J., B.R., E.M. and M.U.; Methodology, H.J.C.-J., M.U., B.R. and L.M.-T; Analysis, H.J.C.-J.; Writing-Original Draft Preparation, H.J.C.-J., L.M.-T., B.R., R.B., E.M. and M.U.; Writing-Review & Editing, H.J.C.-J., L.M.-T., B.R., R.B., E.M. and M.U.; Supervision, M.U.; Project Administration, H.J.C.-J.

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ARTICLE 5

nutrients

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Review

Low Protein Intake Is Associated with Frailty in Older Adults: A Systematic Review and Meta-Analysis of Observational Studies

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Abstract: (1) Background: Several factors have been suggested to be associated with the physiopathology of frailty in older adults, and nutrition (especially protein intake) has been attributed fundamental importance in this context. The objective of this study was to conduct a systematic review and meta-analysis to investigate the relationship between protein intake and frailty status in older adults. (2) Methods: A search of scientific studies was conducted in the main databases (Medline, Scopus, Cochrane library), and in the reference lists of selected articles. The search terms included synonyms and Medical Subject Headings and involved the use of Boolean operators which allowed the combination of words and search terms. Observational studies—cross-sectional and longitudinal—that met the eligibility criteria were included in the review. Article selection and data extraction were performed by two independent reviewers. Meta-analyses with random effects were performed. Publication bias was measured using the Strengthening the Reporting of Observational Studies in Epidemiology instrument. (3) Results: In the final sample, 10 articles, seven cross-sectional and three longitudinal, were included in the present study. Overall, studies investigated a total of 50,284 older adults from three different continents between 2006 and 2018. Four cross-sectional studies were included in the meta-analyses. The results demonstrated that a high protein intake was negatively associated with frailty status in older adults (odds ratio: 0.67, confidence interval = 0.56 to 0.82, $p = 0.0001$). (4) Conclusions: Our findings suggest that a high consumption of dietary protein is inversely associated with frailty in older adults.

Keywords: frailty; protein intake; older adults

Introduction

The aging process is a continuous phenomenon characterized by alterations in major physiological systems, accompanied by the development of chronic diseases and geriatric

syndromes, such as frailty. Frailty may be conceptualized as a multidimensional geriatric clinical state that involves multiple signs and symptoms leading to extreme vulnerability to stressors and resulting in increased risk of negative health-related outcomes (e.g., functional decline, disability, falls, hospitalization, institutionalization, death) [1,2].

Nutrition is acknowledged as a major factor in the context of frailty. In fact, malnutrition is considered one of the pillars for the development of this condition [3], since it can influence all diagnostic criteria for frailty (i.e., unintentional weight loss, low muscle strength, exhaustion, reduced physical activity levels, and slow walking speed) [4]. Three previous systematic reviews have been

conducted on the association between nutrition and frailty. Authors observed that several factors might be responsible for this close relationship between frail and nutrition, including oral health, nutritional status, dietary patterns, diet quality, the antioxidant capacity of the diet, micronutrients and macronutrients intake [3,5]. Nevertheless, protein intake might be the main factor behind this relationship, through its actions on muscle mass and strength.

Indeed, human skeletal muscle protein turnover comprises the process of muscle protein synthesis and muscle protein breakdown [6–8]. On one hand, muscle hypertrophy occurs when the rates of protein synthesis exceed protein breakdown, which may be elicited by hyper amino acidemia induced by dietary protein intake; on the other hand, an inadequate protein intake leads to lower protein synthesis rate, resulting in net protein breakdown and muscle catabolism [6–8]. During aging, numerous process collaborate to a reduced protein intake, such as lack of hunger, impaired oral health, and loss of acuity in taste, smell and sight, to quote a few [9]; consequently, collaborating to muscle catabolism [9]. In addition, evidence has demonstrated that the anabolic response to hyper aminoacidemia may be blunted in older adults [10,11], which indicate that this population should consume larger amounts of protein in comparison to young adults in an attempt to maintain muscle protein synthesis. Nevertheless, over time, the lack of adequate protein intake leads to a state called as sarcopenia [9,12,13], which is characterized by marked muscle atrophy, dynapenia, and reduced physical function, all variables encompassed on frailty definition [14]. If there is no immediate intervention to reduce sarcopenia and frailty progression, as well as improve protein intake, the patients will develop a severe physical disability and consequently exhaustion and sedentary behavior [1,15].

It should be stressed that other pathways besides sarcopenia may be also responsible for the association between protein intake and frailty, since evidence has demonstrated that protein intake is associated with dementia, global cognitive scores, visuospatial skill, nonverbal memory, and logical memory in older adults [16–18]; all aspects linked with frailty [1].

However, investigations on the association between protein intake and frailty have shown positive, negative and even null results. In addition, to the best of our knowledge, there is a lack of systematic reviews and meta-analysis dedicated to investigating the relationship between protein intake and frailty in older adults.

Therefore, the present study was conducted to perform a systematic review to identify and compare studies reporting the relationship between frailty status and protein intake in older adults. Additionally, data were combined to calculate the pooled overall relationship between frailty status and protein intake.

Materials and Methods

We conducted a systematic review and meta-analysis of observational studies to investigate and quantify the association between protein intake and frailty in older adults. The study was fully performed by investigators and no librarian was part of the team. This study complies with the criteria of the Primary Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement [19] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [20].

Eligibility Criteria

The inclusion criteria of the present study consisted of: (a) observational studies, including cross-sectional, case-control and longitudinal studies, which investigated as primary or secondary outcome the association of protein intake and frailty in older adults; (b) study sample 60 years or older; (c) frailty defined by a validated scale; (d) reported information on the proportion of frailty among those with high and low levels of protein intake; (e) published studies (English language). To be included in the meta-analysis, in addition to the aforementioned inclusion criteria, the investigations had to provide: (f) at least two groups divided according to protein intake (e.g., high and low), (g) the prevalence of frailty in each group, (h) and the total sample size in each group. We excluded randomized-clinical trials (RCTs), quasi-experimental, cross-over studies and any kind of investigation which examined the effects of a nutritional intervention associated or not with other interventions (e.g., physical exercise) on frailty. Studies that classified the volunteers as frail according to reduced physical/or cognitive function were also excluded.

Search Strategy and Selection Criteria

Studies published on or before July 2018 were retrieved from the following three electronic databases by one investigator: (1) PubMed, (2) the Cochrane Library, and (3) SCOPUS. Reference lists for reviews and retrieved articles for additional studies were checked and citation searches on key articles were performed on Google Scholar and ResearchGate for additional reports. Initially, a search strategy was designed using keywords, MeSH terms, and free text words such as protein intake, frailty, older adults. Additionally, keywords and subject headings were exhaustively combined using Boolean operators. The complete search strategy used for the PubMed can be shown in List S1. Only eligible full texts in English language were considered for review. Authors were contacted if necessary.

Data Extraction and Quality Assessment

Titles and abstracts of retrieved articles were screened for eligibility by two researchers. If an abstract did not provide enough information for evaluation, the full-text was retrieved. Disagreements were solved by a third reviewer. Reviewers were not blinded to authors, institutions, or manuscript journals. Data extraction was independently performed by two reviews using a standardized coding form. Disagreements were solved by a third reviewer. Coded variables included methodological quality and the characteristics of the studies. The quality of reporting for each study was performed by two researchers using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) instrument [21]. The agreement rate between reviewers was $\kappa = 0.98$ for quality assessment.

Statistical Analysis

The meta-analysis was conducted using Revman V.5. Effect sizes (ESs) were measured using odds ratio (OR) and 95% confidence intervals (CIs). The OR indicates the risk for frailty according to protein intake, high in relation to low. A significant OR is required to have a 95% confidence interval (CI 95%) that did not include the value of 1 and a *p* value for the test of significance of the total overall effect (Z) lower than 0.05. An inverse variance random-effect model was used to calculate the pooled ES since the studies demonstrated different characteristics regarding the main aspects associated with frailty (e.g., modified frailty criteria), protein intake (e.g., different cut-offs for high and low protein intake definition), and covariates (e.g., energy intake). Funnel plots and Egger's regression analysis were used to evaluate the publication bias. Heterogeneity across studies was tested using the Q-statistics and I^2 index was used to assess inconsistency [22]. Additionally, I^2 index was classified as might

not be important (0–40%), may represent moderate heterogeneity (30–60%), may represent substantial heterogeneity (50–90%), and considerable heterogeneity (75–100%) [22]. Forest plots were used to illustrate summary statistics and the variation (heterogeneity) across studies.

Results

Literature Search

Of the 2555 registers recovered from electronic databases and hand search, 2523 records were excluded based on duplicate data, title or abstract. Thirty-two studies were fully reviewed and assessed for eligibility. Finally, 10 studies met the inclusion criteria (Figure 1).

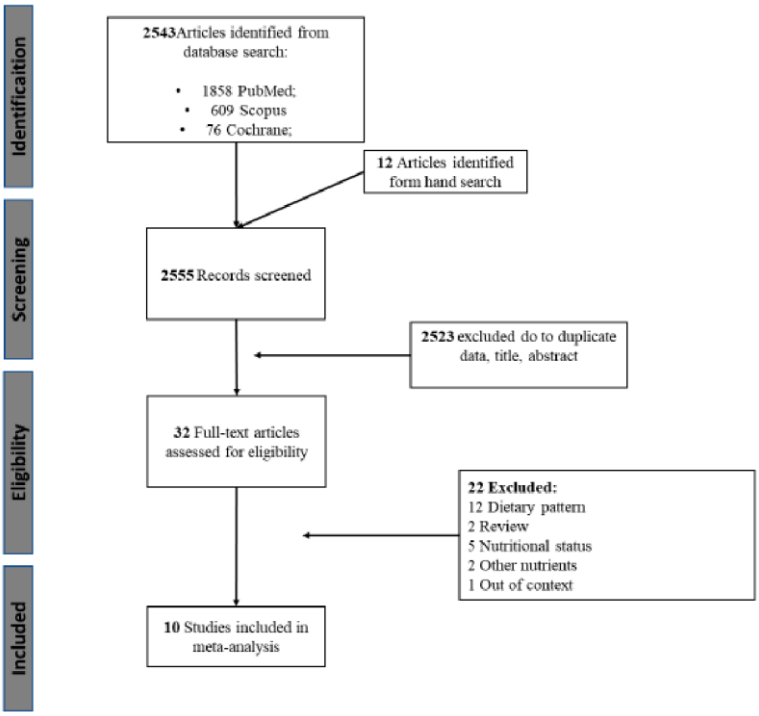

Figure 1. Flow chart of the present study.

Characteristics of the Included Studies

Table 1 provides a general description of the included studies. Overall, a total of 18,120 community-dwelling older adults from five different countries (France, Germany, Italy, Japan, and the United States of America) were investigated between 2006 and 2018 in the cross-sectional studies. Frailty assessment was performed with two tools. The frailty phenotype proposed by Fried et al. (2001) was used in six of the seven studies [23–28], while one study used the Kihon checklist (KCL) [29]. However, it is important to mention that the frailty phenotype [14] was modified in 5 of the 6 studies. Indeed, weight loss criterion was modified in the studies of Rahi et al. [28] and Shikany et al. [27], while Bartali et al. [23] removed this

variable. In turn, in the investigations performed by Kobayashi et al. [24,25], slowness and weakness were indirectly measured based on a questionnaire. Slowness assessment was also modified in the study of Rahi et al. [28]. Dietary intake was primarily assessed by population-specific food-frequency questionnaires (FFQ) (57.1%) [23,26,27], followed by self-administered diet history questionnaires (28.6%) [24,25], and the 24 h dietary recall (14.3%) [28]. High and low protein intake was differently defined in the investigations. Measures of centrality (e.g., tertiles, quartiles, quintiles) were used in 6 of the 7 studies [23–27], while Rahi et al. [28] performed the analysis based on a pre-established cut-off (i.e., protein intake levels ≥ 1 g/kg of body weight). Regarding longitudinal studies, 32,164 community-dwelling older adults were investigated between 2010 and 2016. The studies were conducted in North America (United States of America) and Europe (Spain). The mean duration of follow-up was 3.7 years (3.0–4.6 years). The frailty phenotype was used in all studies for frailty assessment. However, as was observed in cross-sectional studies, the frailty phenotype was modified in 2 of the 3 longitudinal studies. Shikany et al. [27] considered the loss of appendicular lean mass as a measurement of weight loss. In turn, Beasley et al. [30] used a modified version of frailty phenotype as they measured muscle weakness and slowness using the Rand-36 Physical function scale. FFQ (66.6%) and computerized face-to-face diet history (33.3%) were used for a dietary intake assessment. In longitudinal studies, all investigations used measures of centrality (i.e., quartile and quintile) to determine the levels of protein intake.

Table 1. General description of the included studies.

Year	Authors	Country	Study Design	Setting	*n*	Mean Age (age range; min–max)	Sex Ratio of Participants (female/male) by frail vs. non-frail	Frailty Assessment Method	Dietary Intake Assessment Method	Protein Intake (g/day)	Protein Intake Level Definition	Outcomes	Covariates Included in Models	Quality Analysis Score
Cross-sectional														
2006	Bartali et al. [23]	Italy	Crosssectional	Communitydwelling	802	74.1	1.2	CHS frailty index (a)	Food-frequency questionnaire	-	Dichotomous	Low protein intake is associated with frailty	Results were adjusted for age, sex, education, economic status, household composition, smoking status, number of diseases, cognitive function, body mass index, and "happiness."	22
2013	Kobayashi et al. [24]	Japan	Crosssectional	Communitydwelling	2108	74.7	-	CHS frailty index (b)	Self-administered diet history questionnaire	74.0	Quintile (≤62.9 g/day, 6369.8 g/day, 69.8–76.1 g/day, 76.1–84.3 g/day, ≥84.3 g/day)	Protein intake was inversely associated with frailty	Results were energy-adjusted and for age, BMI, residential block, size of residential area, living alone, current smoking, alcohol drinking, dietary supplement use, history of chronic disease, depression symptoms, and energy intake.	20
2013	Bollwein et al. [26]	Germany	Crosssectional	Communitydwelling	194	83.0 (75–96)	6.5 vs. 1.3	CHS frailty index	Food-frequency questionnaire	76.6	Quartiles (≤0.90, 0.91–1.07, 1.08, ≥1.27)	Protein intake was not associated with frailty	Results were adjusted for age and sex, instrumental activities of the daily living score, number of medications, and chewing difficulties	19
2014	Shikany et al. [27]	United States of America	Crosssectional	Commnitydwelling	5925	75.0	-	CHS frailty index (c)	Food-frequency questionnaire	-	Quintile (≤6.0–13.7%, 13.8–15.2%, 15.3–16.5%, 16.6%–18.3%, 18.4–29.3%)	Protein intake was not associated with frailty	Results were adjusted for age, race, center, education, marital status, smoking, health status, medical conditions, body mass index, and energy intake	20
2016	Rahi et al. [28]	France	Crosssectional	Communitydwelling	1345	75.6	4.0 vs. 1.46	CHS frailty index (d)	24 h dietary recall	70.4	Dicothomous <1g/kg body weight/day and ≥1g/kg body weight	Protein intake was associated with frailty	The model 1 was adjusted for age, sex, and educational level; and the model 2 was additionally adjusted for BMI, diabetes, cardiovascular history, depression, cognitive performance, number of drugs, and total energy intake.	20
2017	Kobayashi et al. [25]	Japan	Crosssectional	Communitydwelling	2108	74.0	-	CHS frailty index (b)	Self-administered diet history questionnaire	73.1	Tertile (≤67.6 g/day, 67.6–78.3 g/day, ≥78.3 g/day)	Protein intake was inversely associated with frailty	Dietary total antioxidant capacity	20

2018	Nanri et al. [29]	Japan	Crosssectional	Communitydwelling	5638	73.2	0.88 vs. 1.05 *	KCL	Food-frequency questionnaire	-	Men = quartiles (≤48.8 g/day, 48.8–56.1 g/day, 56.1–65.4 g/day, >65.4 g/day); Women = quartiles (<43.8 g/day, 43.8–51.1 g/day, 51.1–59.5 g/day, >59.5 g/day)	Protein intake was inversely associated with frailty	For men, the model 1 was adjusted forage, body mass index, total energy intake, alcohol status, smoking status and history of disease and the model 2 was adjusted for family structure, educational attainment, population density, and self-related health.	20

Table 1. *Cont.*

Year	Authors	Country	Study Design	Setting	*n*	Mean Age (age range; min–max)	Sex Ratio of Participants (female/male) by frail vs. non-frail	Frailty Assessment Method	Dietary Intake Assessment Method	Protein Intake (g/day)	Protein Intake Level Definition	Outcomes	Covariates Included in Models	Quality Analysis Score
Longitudinal														
2010	Beasley et al. [30]	United States of America	Longitudinal (3.0 years follow-up)	Communitydwelling	24,417	65–79	-	CHS frailty index (e)	Food-frequency questionnaire	72.8	Quintiles of protein intake (% kilocalories)	Protein intake was significantly associated with the odds of becoming frail	Results were adjusted for age, ethnicity, BMI, income, education, having a current health care provider, smoking, alcohol, general health status, history of comorbid conditions, history of hormone therapy use, number of falls, whether participant lives alone, disabled defined by at least 1 activity of daily living affected, depressive symptoms, log-transformed calibrated energy intake	20
2014	Shikany et al. [27]	United States of America	Longitudinal (4.6 years follow-up)	Communitydwelling	5925	75.0	-	CHS frailty index (c)	Food-frequency questionnaire	-	Quintile (≤6.0–13.7%, 13.8–15.2%, 15.3–16.5%, 16.6%–18.3%, 18.4–29.3%)	Protein intake was not associated with the odds of becoming frail	Results were adjusted for age, race, center, education, marital status, smoking, health status, medical conditions, body mass index, and energy intake	20
2016	Sandoval-Insausti et al. [31]	Spain	Longitudinal (3.5 years follow-up)	Communitydwelling	1822	68.7	0.9 vs. 2.4	CHS frailty index	Computerized face-to-face diet history	76.6	Quartiles of protein intake	Protein intake was associated with the odds of becoming frail	Results were adjusted for age, energy intake, ethanol, lipids, animal or vegetal protein, level of education, marital status, tobacco consumption, BMI, abdominal obesity, and dietary fiber, diseases.	20

CHS = Cardiovascular Health Study; KCL = Kihon checklist; bw/d = body weight/day; BMI= Body mass index; (a) Bartali et al. used a modified version of the CHS frailty index, since weight loss was removed; (b) Kobayashi et al. used the CHS frailty index version modified by Woods et al as they did not have direct measures of gait speed and strength; (c) Shikany et al., used a modified version of the CHS frailty index as they measured weight loss criterion based on loss of appendicular lean mass; (d) Rahi et al., used a modified version of the CHS frailty index as a loss of 3 kg and a reduced BMI (<21 kg/m^2) were both accepted as measures of weight loss criterion, slowness was determined based on the Rosow-Breslau test, and weakness was identified using the chair standing method (e) Beasley et al., used a modified version of the CHS frailty index as they measured muscle weakness and slow walking speed using the Rand-36 Physical function scale; * frail vs non-frail.

Quality Assessment

The overall score of the quality assessment of cross-sectional and longitudinal studies is shown in Table 1 and the analysis of each variable is detailed in Tables S1 and S2, respectively. The point by point analysis is shown in Table S3. The overall score of cross-sectional studies ranged from 19 to 22. All studies reported the items required by the STROBE criteria in relation to the abstract (items 1 and 2), objectives and hypothesis (items 3 and 4), described the settings, locations, relevant dates, eligibility criteria and the source and methods of selection of participants (items 5 and 6), clarity of the outcomes (items 7), methods of assessment (item 8), handle of the quantitative variables (item 11), give the characteristics of study participants (item 14), reported the number of outcome events (item 15), statistical methods and analysis (items 12, 16, 17), and discussion (items 18–21). However, 57.1% of the studies failed to clearly report the efforts performed to address potential sources of bias (item 9) [24,26–28], 42.9% did not properly explain how the study size arrived at (item 10) [26–28], and 14.3% did not show the number of individuals at each stage of study (item 13) [26].

Similar results were seen in longitudinal studies, in which all investigations received a STROBE score of 20. None of the studies adequately presented a description of how the study was arrived at (item 10), while 66.6% failed to describe any efforts to address potential sources of bias (item 9) [27,31], and 33.3% did not show the number of individuals at each stage of study (item 13) [30].

Association between Protein Intake and Frailty

-Protein Intake and Frailty Prevalence (i.e., Cross-Sectional Studies)

A total of four studies provided information regarding different intakes of protein in at least two groups, the prevalence of frailty in each group, and the total sample size in each group; therefore, they were added in the meta-analysis (Figure 2). Two aspects should be mentioned before the presentation of data. First of all, Nanri et al. [29] provided the data according to gender, and the results are presented accordingly. In turn, the investigations performed by Kobayashi et al. [24, 25] used the same database (i.e., Three-generation Study of Women on Diets and Health), so that the studies were not analyzed in combination. The overall meta-analysis results showed a 0.67 OR (Figure 2a) and a 0.66 OR (Figure 2b) for frailty (95% CI = 0.56 to 0.82, p = 0.0001; 95% CI = 0.54 to 0.80, p = 0.0001) in older adults with high protein intake compared with low protein intake according to the inclusion of Kobayashi et al. [24] or Kobayashi et al. [25], respectively. When the study of Kobayashi et al. [25] was not in the analysis, it was possible to observe an I^2 lower than 40% accompanied by a p = 0.18,

indicating that this heterogeneity might not be important [22]. However, when the study of Kobayashi et al. [24] was removed, the I^2 increased to 49% and p value was of 0.12, which can indicate a moderate heterogeneity [22].

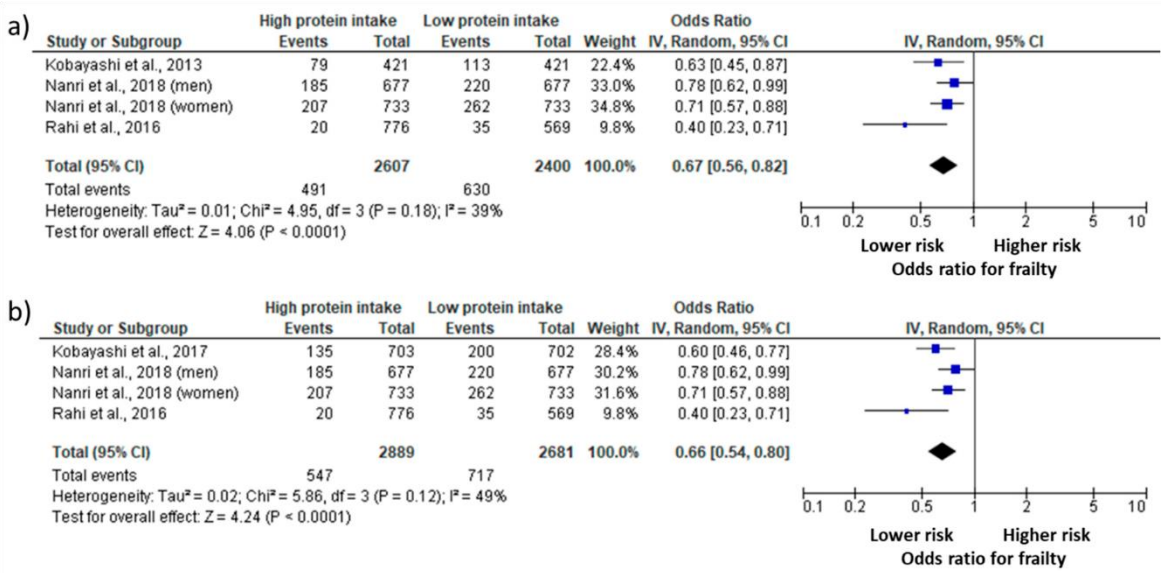

Figure 2. Odds ratio (OR) of the prevalence of frailty in older adults with high and low protein intake. Squares represent study-specific estimates; diamonds represent pooled estimates of random-effects meta-analyses. (**a**) The analysis was performed included Kobayashi et al. 2013; (**b**) The analysis was performed included Kobayashi et al. 2017.

Figure 3 shows the funnel plots (a) and (b) based on the primary outcome according to the inclusion of Kobayashi et al. [24] or Kobayashi et al. [25], respectively. The figures are asymmetrical indicating that potential publication bias might influence the results of this review. Egger's linear regression test indicated possible publication bias for the association when the study of Kobayashi et al. [24] was included (p = 0.02), but not Kobayashi et al. [25] (p = 0.09).

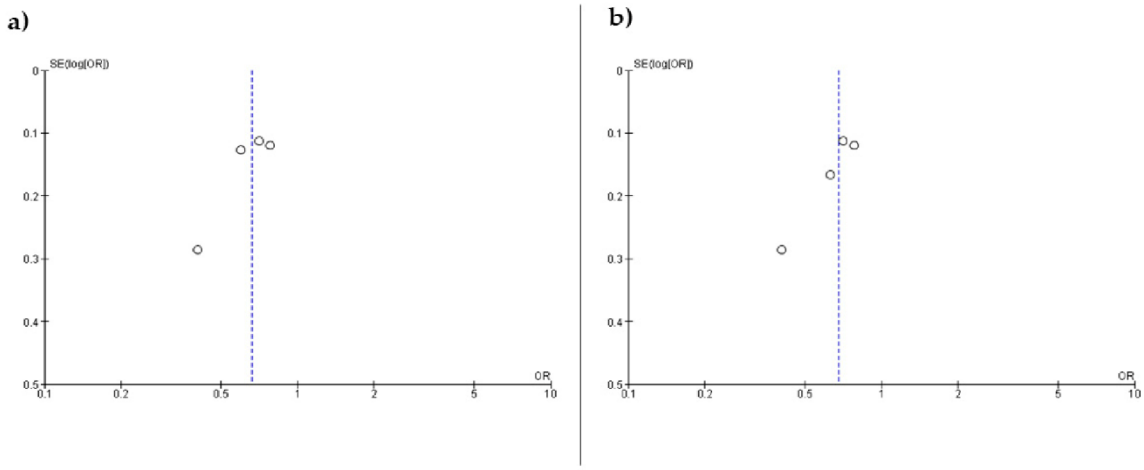

Figure 3. Funnel plots including (**a**) Kobayashi et al. 2013 and (**b**) Kobayashi et al. 2017 OR.

-Protein Intake and Frailty Risk (i.e., Longitudinal Studies)

We found three studies that evaluated the longitudinal relationship between protein intake and frailty risk. The findings demonstrate that two of the three studies observed that higher protein intake was negatively associated with frailty risk.

Discussion

Frailty is a multifactorial condition associated with poor prognosis. Low protein intake has been proposed among the factors possibly involved in the pathogenesis of frailty. We, therefore, performed a systematic review and meta-analysis to investigate the relationship between protein intake and frailty in older adults. The main findings of the present study indicate that low protein intake is associated with frailty prevalence in older adults.

Study quality assessment demonstrated that reports were of very good quality, such that cross-sectional studies scored between 19 and 22 and all longitudinal studies scored 20. Interestingly, cross-sectional and longitudinal studies did not provide the same items, including efforts to address potential sources of bias (item 9), the design of the study size (item 10), and the report regarding the number of participants in all the phases of the study (item 13).

Some recent systematic and descriptive reviews have investigated the relationship between nutrition and frailty [3,4,32,33]. However, none of these studies was specifically designed to investigate the role of protein intake in this phenomenon and the findings were not quantitatively assessed. Thus, to the best of our knowledge, this is the first systematic review and meta-analysis designed to investigate the relationship between protein intake and frailty in older adults.

The results of the present study may be at least partially explained by the theoretical overlap between sarcopenia and physical frailty [34,35]. Indeed, physical frailty, as measured by the Fried's criteria [14,36], encompasses features as slowness, weakness, exhaustion, and sedentary behavior, which are strongly associated with the sarcopenia condition [34,35]. Slowness (i.e., slow walking speed) and weakness (i.e., low upper-limb muscle strength), for example, are proposed as diagnostic criteria for sarcopenia by the European Working Group on Sarcopenia in Older Persons (EWGSOP) [15], while exhaustion and sedentary behavior are common consequences of sarcopenia progression [37]. Indeed, Landi et al. [35] suggested that sarcopenia may be envisioned as a central mechanism for the development of physical frailty. In another word, physical frailty may be the final pathway of sarcopenia progression [35]. This idea is further supported by the higher prevalence of sarcopenia in pre-frail and frail older adults when compared to non-frail peers [38,39].

Sufficient protein consumption may cause a shifting on net balance in favor of muscle protein synthesis [7,40]. Protein supplementation *per se* has been shown to prevent the progression of physical decline in frail older adults [30,41]. In addition, protein intake has a key role in the physiological adaptations elicited by the resistance training on the neuromuscular apparatus since a greater muscle protein synthesis is expected when both non-pharmacological therapies are offered in combination [6,7]. Taken together, these findings suggest that sufficient protein intake may reverse or at least prevent functional decline in frail older adults.

However, this kind of inference deserves caution since not all evidence has demonstrated the positive effects of protein supplementation on the sarcopenia aspects associated with frailty, such as muscle mass, muscle strength and physical function [42,43]. Finally, it should be noted that the changes observed after protein supplementation may be different from those observed in response to dietary protein intake.

It is worth mentioning, that our main findings are based on cross-sectional studies and causal extrapolations should be performed carefully. Unfortunately, there were no available data from longitudinal studies to perform a meta-analysis. Overall, findings are still controversial. Shikany et al. [27] observed that protein intake was inversely associated with the risk of transitioning from robust to pre-frail status in a range of 4.6 years, while there were no significant associations between protein and frailty status. However, Sandoval-Insausti et al. [31] reported that total protein and animal protein intake were inversely associated with frailty and its components (i.e., slowness) over a mean follow-up of 3.5 years. Similarly, Beasley et al. [30] concluded that higher protein intake

was associated with reduced risk of frailty in community-dwelling older women.

Interestingly, the main variables investigated in the present study were differently defined across the investigations. Regarding frailty, although this variable was assessed using the frailty phenotype in most investigations, adaptations of some of the criteria were observed in 5 of the 6 cross-sectional studies, as well as in 2 of the 3 longitudinal studies. In fact, weight loss criterion was modified in the trial of Rahi et al. [28], in which researchers included volunteers with self-reported unintentional loss > 3 kg or as a body mass index < 21 kg/m^2, while Shikany et al. [27] included subjects who lost appendicular muscle mass. In turn, Bartali et al. [23] removed the weight loss criterion of their investigation. Slowness and weakness were also modified. In this case, Kobayashi et al. [24,25], Beasley et al. [30], and Rahi et al. [28] (only slowness) used self-reported questionnaires instead of direct evaluations. It is also possible to observe that different cutoffs to define high a low protein intake (i.e., tertiles, quartiles, quintiles and pre-established values) were used in the investigations.

These modifications have direct implications in the findings of the present study. Although scales and questionnaires may offer more information in a shorter period when compared to performance-based measurements, evidence has demonstrated the limited capacity of these tools to reflect different measures of physical status [44,45]. This probably occurs because the results of patient-reported questionnaires may be biased due to mood, motivation, fatigue, health status, fluctuations in memory, and the specific knowledge and familiarity with the questionnaires and scales [44,45]. In this sense, different results than those observed in the present study could occur if the investigations were performance based on direct measures, as proposed by Fried et al. [14]. Furthermore, the use of different cut-offs to define protein intake levels leads to disagreements and restrict the proposal of public health recommendations to older adults due to the range of approaches used by the studies.

Taken together, these differences may also explain the heterogeneity of results observed among the longitudinal studies. Nevertheless, different settings, eligibility criteria, gender, sarcopenia status, dietary assessment methods, and follow-up periods of the various studies may also explain this variability. In this sense, more well-controlled cross-sectional and longitudinal studies are still necessary to improve the actual knowledge about frailty and protein intake in older adults, as well as to confirm our findings.

We should state the absence of subgroup analyses as the major limitation of the present study. Indeed, the use of crude OR limits interpretation of our meta-analysis, since the influence of important covariates (e.g., age, type of protein [animal, vegetal], sarcopenia) were not taken into consideration in the results, and we recommend that readers interpret our results carefully. The main aspect that prevented us to perform the analysis was the lack of available data in the included studies. Regarding dietary assessment, it is worth mentioning that total protein intake, which was used in all studies for comparisons, is probably not the best parameter to represent adequate protein consumption, since investigations in the context of physical function and sarcopenia have used relative protein intake (g/kg/day) [46–48]. In addition, recent evidence has demonstrated that a spread distribution of protein intake during the main meals is better associated with gait speed than relative protein intake [49]. Providing support to the importance of the distribution of protein intake, Loenneke et al. [50] observed that a frequent consumption of meals containing at least 30 g of protein was associated with greater lean mass and lower-limb muscle strength in middle-aged and older adults. The role of animal and plant-based protein sources on variables associated with frailty has also been the object of discussion among researchers [51,52]. Therefore, although future investigations are still necessary to confirm our findings, the present study may serve as a guide for future studies in this field; so

that investigation should include more information regarding the factors that may interfere in the relationship between protein intake and frailty, taking into account the variables that have been investigated by other studies.

In addition, funnel plots and Egger's linear regression test indicated that biases from publications and other factors may have had a significant influence on the results of our meta-analysis mainly

when the study of Kobayashi et al. [24] was included. Possible explanations for this publication bias included the small number of studies investigated, multiple publication bias, and heterogeneity [22].

Finally, another aspect of the present study that deserves concerns is the use of STROBE instrument as a tool to quality assessment. As discussed by da Costa et al. [53], STROBE was primarily developed to improve the reporting of observational studies. Thus, some may argue that another tool should have been used in the present study. However, it should be stressed that there is no gold standard tool to assess the risk of bias in non-randomized studies, as well as some of the STROBE questions may represent an evaluation of risk of bias; consequently, making it a tool commonly used in systematic reviews and meta-analysis [53].

In conclusion, our findings support the need for increased protein intake in older adults in an attempt to avoid frailty development.

Supplementary Materials: The following are available online at http://www.mdpi.com/2072-6643/10/9/1334/ s1, List S1. The complete search strategy used for the PubMed, Table S1. Quality assessment of cross-sectional studies, Table S2. Quality assessment of longitudinal studies, Table S3 Point by point analysis.

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ARTICLE 6

Protein-related dietary parameters and frailty status in older adults: A comparison among 4 frailty instruments

Abstract

Aims: The present study investigated the associations of frailty status using 4 different frailty instruments and a) daily protein consumption, b) daily body weight-adjusted protein consumption, c) branched chain amino acids (BCAA) consumption, d) evenness of protein distribution across the three main meals, e) number of daily meals providing at least 0.30 g of protein per meal, and f) number of daily meals providing at least 0.4 g of protein/kg of body weight in community-dwelling older adults. **Methods:** Two-hundred older women (mean age: 68.7 years) were recruited to take part of the present study. Frailty were identified using Fried frailty phenotype, FRAIL, SOF, and Gérontopôle Frailty Screening Tool (GFST). Dietary assessment was assessed using a 24-h recall diary. **Results:** We observed that the relationship between protein-related dietary parameters and frailty status is tool-dependent, given that protein consumption was only associated with frailty status when participants were identified using Fried frailty phenotype and GFST. In addition, a higher consumption of protein and BCAA was observed in robust and prefrail individuals, while both were poor consumed in frail participants. **Conclusions:** Our findings suggest that the relationship between diet characteristics and frailty status is tool-dependent. In addition, a lower consumption of protein and BCAA is observed in frail older adults.

Keywords: Elderly; Diet; Physical function; Disability; Sarcopenia

Introduction

Frailty is a highly prevalent condition among older adults, and is defined as a state of increased vulnerability to negative health-related outcomes [1], which occurs as a result of multisystem physiological derangements and poor social support that impact the individual's ability to maintain homeostasis after a stressor event [2–4]. Frailty progress increase the risk for many negative events, such as fractures, disability, hospitalization, nursing home placement, and death [5,6]. As such, frailty represents a major public health problem [1] and researchers have been looking for therapies to counteracting this condition.

Good diet habits are suggested as a key factor for the preservation of independence during aging [7,8]. In this context, prior investigations found that high protein intake is associated with better physical performance [9,10] and low prevalence of frailty [11–15], leading to the recommendation that adequate protein consumption might avoid the genesis and progression of frailty in older adults [15,16].

Nevertheless, positive effects of protein intake on frailty seems to occur in the light of the metabolism of branched chain amino acids (BCAA) in skeletal muscle [17]. In fact, adequate amounts of BCAA, and mainly leucine are essential to stimulate muscle protein synthesis by being a building block for protein synthesis [17], and also stimulates intracellular anabolic signaling involved in the initiation of protein synthesis [17,18].

Although much importance has been given to the role of protein quantity on frailty-related parameters, evidence has supporting the hypothesis that the distribution of protein intake across meals might be more important than simply the total amount of macro and micronutrients consumed [19–21]. Recent evidence observed that older adults who showed a spread-feeding pattern in which considerable amounts of protein are distributed over the main meals had higher gait speed than those who had a pulse-feeding pattern (i.e., high protein intake in a unique meal) [21].

It is worth mentioning, that Loenekke et al. [19] found that adults who consumed ≥ 30 g of protein in at least one meal had greater lower-limb muscle strength and leg lean mass in comparison with those who consumed <30 g, leading to the assumption that a minimum of 30g of protein per meal seem to be necessary to avoid negative health related outcomes. However, contrarious to the hypothesis of absolute doses of protein per meal, Moore et al. [22] found a plateau in muscle protein synthesis stimulation at 0.4 g of protein/kg of body weight in older men.

Based on these premises, the present study investigated the associations of frailty status using 4 different frailty instruments and a) daily protein consumption, b) daily body

weight-adjusted protein consumption, c) BCAA consumption, d) evenness of protein distribution across the three main meals (i.e., breakfast, lunch, dinner), e) number of daily meals providing at least 0.30 g of protein per meal, and f) number of daily meals providing at least 0.4 g of protein/kg of body weight in community-dwelling older adults.

Materials and Methods

The study approved by the Research Ethics Committee of the University of Campinas. All study procedures were conducted in compliance with the Declaration of Helsinki and the Resolution 196/96 of the National Health Council. All participants were thoroughly informed about the study procedures before providing written consent.

Participants

Participants were recruited by convenience in a community senior center located in Poá, Brazil. Poá is a city located in the southern area of São Paulo with a population of approximately 100 thousand people, being ~3460 older (60 year or over) [23]. The community senior center offers daily sessions of flexibility, aquatic and multicomponent physical exercises, dance classes, adapted sports, nursing and medical care, and cognitive stimulation therapy. Candidate participants were considered eligible if they were 60 or older, were community-dwellers, and possessed sufficient physical and cognitive abilities to perform all of the measurements required by the protocol.

Anthropometric measurements

A weight scale with a stadiometer was used to measure body mass and height. The body mass index (BMI) was subsequently calculated as following:
a) body mass (kg)/ height (m^2).

Frailty assessment

-Frailty phenotype

The frailty phenotype was first described by Fried et al. [24]. The instrument incorporates measures of multiple physical domains, including weight loss, exhaustion, weakness, slowness, and sedentary behavior [25,26]. People are respectively identified as robust, prefrail and frail according to the presence of none, 1-2, and ≥3 of the following criteria: (1) unintentional weight loss of ≥5 kg in the prior year; (2) self-reported fatigue; (3) weakness, grip strength lower than 0.8 kg; (4) slowness, defined by Timed “Up-and-Go” (TUG)

performance [27] equal or higher than 4.4 s; and (5) low physical activity levels according to the short form of the International Physical Activity Questionnaire (IPAQ) [28]. Gender- and BMI-specific cutoff points were used for grip strength and height-specific cutoff points were used for TUG based in the median values of our sample. Gender-specific cutoffs were used for physic activity levels [26].

-*FRAIL index*

FRAIL scale consists of 5 simple questions require a yes or no answer, with 1 point given to any affirmative response [29]. Instrument scores range from 0 to 5 points, and people are identified as robust (0 points), prefrail (1-2 points), and frail (≥3 points) according to the following criteria: (1) self-reported fatigue; (2) poor resistance, based on the inability to climb a flight of stairs; (3) limited ambulation, based on the inability to walk 1 block; (4) illnesses, presence of ≥ 5 illnesses; and (5) unintentional weight loss of ≥5% in the past 6 months.

-*SOF index*

SOF is derived from the Study of Osteoporotic Fractures [30]. The instrument is based on 3 criteria: (1) unintentional weight loss of ≥4.5 kg in the prior year; (2) self-reported exhaustion; (3) inability to rise from a chair 5 times without using arms. SOF scores range from 0 to 3, and people are identified as robust, prefrail, and frail according to the presence of 0, 1, and 2-3 criteria.

Gérontopôle Frailty Screening Tool

The Gérontopôle Frailty Screening Tool (GFST) is an 8-item questionnaire assessing individual's social, physical, functional and cognitive situation. In the present study, only the first six self-reported questions were used to analysis given that the last two questions are dependent of general practitioner's personal view. The GFST is based on the following criteria: (1) living alone; (2) unintentional weight loss in the prior 3 months; (3) self-reported fatigue in the last 3 months; (4) self-reported mobility difficulties in the last 3 months; (5) complains of memory problems; and (6) slowness, defined by a Timed "Up-and-Go" (TUG) performance equal or higher than 4.4 s. Once there is no clear cut-off point to classify the patient as frail or not [31], we proposed the following cutoffs for robust, prefrail and frail individuals, respectively, 0, 1-2, ≥3 components.

Dietary assessment

Food intake was assessed using a 24-h recall diary. This method uses an open-ended questionnaire to provides a quantitative and subjective estimation of actual food consumption. In the present protocol, trained researchers asked the participants to detailly recall all foods they consumed on a meal-by-meal basis, including snacks, during the previous 24-h period. Interviews occurred on Tuesdays, Wednesdays, Thursdays, and Fridays to avoid bias associated with the weekend. Participants were requested to detailly describe cooking methods (e.g., fried, grilled, roasted), amounts in portions, product brands, sauces, spices, and condiments consumed, and the use of dietary supplements. The amounts of beverages consumed were also recorded, and participants should describe if and how beverages were sweetened. Two-dimensional aids (e.g., photographs), household utensils (e.g., standard measuring cups and spoons), and food models were used as memory aids to assess portion sizes. Diet composition was estimated using the NutWin software, version 1.5 (Federal University of São Paulo, Brazil)[9].

Statistical Analysis

Continuous and categorical variables were compared among the three groups (i.e., robust, prefrail, and frail) via one-way analysis of variance (ANOVA) and chi-square (χ^2) statistics, respectively. Bonferroni posthoc analyses were performed to determine whether there were significant differences between groups. χ^2 and Z-score were further used to explore the association between diet characteristics and frailty status across frailty instruments. Median values were chosen as the cutoff values for isoleucine (4.4 g), leucine (7.1 g), and valine (4.7g). Cutoff values for body weight-adjusted protein consumption [15,32], body weight-adjusted protein consumption per meal [22], and protein consumption per meal [19] were chosen based on prior reports. Protein intake distribution across the main meals (i.e., breakfast, lunch, and dinner) was calculated for each participant as a coefficient of variance (CV)[20], as following: b) CV= Standard deviation of grams of protein intake per main meals/ mean average total amount of proteins (grams) of the main meals.

Participants were further divided into tertiles according to CV values (<0.8 g/kg, 0.8-1,2 g/kg, and >1.2 g/kg). A low CV represents less difference in protein intake between the meals and therefore a more spread distribution, whereas a high CV represents a pulse-feeding distribution of protein intake [21]. For all tests, alpha was set at 5% ($p < 0.05$) and Z-score was set at 1.96. All analyses were conducted using the IBM SPSS Statistics, version 20.0, software (IBM Corp., Armonk, NY, USA).

Results

Clinical Characteristics

Two-hundred fifty-four people accepted to be evaluated for inclusion. Of these, forty-six were middle-aged adults, 6 had missing data for frailty status, and 2 had missing data for diet characteristics, leaving a total of 200 participants. Table 1 shows clinical, sociodemographic, and diet characteristics of study participants according to frailty status and instruments. Frailty frequency was 26.0% using FRAIL index, 23.0% using SOF, 15.5% using Fried frailty phenotype, and 12.5% using GFST. There were no differences on clinical, sociodemographic and diet characteristics among frailty status when participants were identified using FRAIL and SOF indexes. On the other hand, significant differences in clinical parameters and diet characteristics were observed using Fried and GFST. When participants were identified according to Fried criteria, prefrail individuals had higher body weight (P=0.34) in comparison to robust counterparts. Frail individuals showed a lower intake of total protein (P=0.005), valine (P=0.005), leucine (P=0.004), and isoleucine (P=0.004) when compared to prefrail and robust individuals, while body weight-adjusted protein (P=0.020) consumption was only lower when compared to non-frail participants. Frail individuals according to GFST index were older (P<0.001) and had higher body weight (P=0.036) than both prefrail and robust. Frail individuals had lower consumption of body weight-adjusted protein (P=0.008), valine (P=0.004), leucine (P=0.001), isoleucine (P=0.003), and total protein lunch (P=0.010) when compared to prefrail participants, while total protein consumption (P=0.001) was only significantly lower in comparison to robust participants. A lower consumption of body weight-adjusted protein dinner (P= 0.004) was observed in frail when compared to prefrail and robust. Finally, prefrail individuals had higher intake of body weight-adjusted protein dinner (P= 0.036) in comparison to robust individuals.

Table 1. Characteristics of the participants according to frailty status.

	FRAIL			Fried			GFST			SOF		
Variables	Robust (n=22)	Prefrail (n=126)	Frail (n=52)	Robust (n=15)	Prefrail (n=154)	Frail (n=31)	Robust (n=38)	Prefrail (n=137)	Frail (n=25)	Robust (n=27)	Prefrail (n=127)	Frail (n=46)
Characteristics												
Age, years	66.0 ± 4.5	68.8 ± 7.3	67.6 ± 6.4	65.1 ± 7.5	67.8 ± 6.1	71.2 ± 9.1	**65.2 ± 3.8**	**67.8 ± 6.3**	**75.1 ± 9.0ab**	68.6 ± 8.0	68.2 ± 6.9	68.0 ± 6.1
Body weight, kg	66.5 ± 11.7	69.6 ± 12.7	68.2 ± 10.4	**63.5 ± 9.2**	**69.9 ± 12.1[a]**	**66.4 ± 12.4**	**71.3 ± 11.1**	**68.9 ± 11.7**	**65.3 ± 14.5ab**	68.8 ± 12.2	69.7 ± 12.0	66.7 ± 12.0
BMI, kg/m²	28.1 ± 4.4	28.9 ± 5.3	28.5 ± 4.3	27.7 ± 3.6	28.9 ± 5.0	28.4 ± 5.5	28.6 ± 4.6	29.0 ± 4.9	27.5 ± 4.8	29.4 ± 5.2	29.0 ± 4.8	27.5 ± 5.1
Sex, f (%)	18 (81.8)	103 (81.7)	45 (86.5)	13 (92.9)	125 (81.2)	27 (87.1)	31 (81.6)	115 (83.9)	20 (80.0)	22 (81.5)	106 (83.5)	38 (82.6)
Tabagism, n (%)	0 (0.0)	3 (2.4)	3 (5.8)	1 (7.1)	4 (2.6)	1 (3.2)	1 (2.6)	3 (2.2)	2 (8.0)	0 (0.0)	3 (2.4)	3 (6.5)
Diseases, n (≥ 5)	0 (0.0)	7 (5.6)	7 (13.5)	2 (14.3)	6 (3.9)	6 (19.4)	1 (2.6)	6 (4.4)	7 (28.0)	4 (14.8)	9 (7.1)	1 (2.2)
Race, n (%)												
Asian	0 (0.0)	8 (6.3)	3 (5.8)	0 (0.0)	9 (5.8)	2 (6.5)	1 (2.6)	7 (5.1)	3 (12.0)	0 (0.0)	7 (5.5)	4 (8.7)
Black	3 (13.6)	22 (17.5)	12 (23.1)	2 (14.3)	28 (18.2)	7 (22.6)	9 (23.7)	23 (16.8)	5 (20.0)	6 (22.2)	22 (17.3)	9 (19.6)
Caucasian	19 (86.4)	96 (76.2)	37 (71.2)	12 (85.7)	117 (76.0)	22 (71.0)	28 (73.7)	107 (78.1)	17 (68.0)	21 (77.8)	98 (77.2)	33 (71.7)
Diet												
Protein, g	112.6 ± 47.3	105.4 ± 40.8	104.9 ± 38.7	**122.2 ± 37.3**	**108.2 ± 41.4**	**89.7 ± 36.4ab**	**101.1 ± 42.1**	**111.7 ± 41.6**	**81.9 ± 23.0a**	106.4 ± 43.8	107.4 ± 41.4	102.4 ± 38.3
Protein, g/kg	1.7 ± 0.8	1.5 ± 0.6	1.5 ± 0.5	**1.9 ± 0.6**	**1.5 ± 0.6**	**1.3 ± 0.4[a]**	**1.4 ± 0.6**	**1.6 ± 0.6**	**1.3 ± 0.5b**	1.6 ± 0.7	1.5 ± 0.6	1.5 ± 0.5
Valine, g	5.5 ± 2.3	5.2 ± 2.1	5.3 ± 2.1	**6.1 ± 1.9**	**5.4 ± 2.1**	**4.4 ± 1.9ab**	**5.1 ± 2.1**	**5.5 ± 2.1**	**4.0 ± 1.1b**	5.2 ± 2.1	5.3 ± 2.1	5.0 ± 2.0
Isoleucine, g	4.6 ± 2.9	4.7 ± 2.3	4.7 ± 2.0	**5.3 ± 2.2**	**4.8 ± 2.3**	**3.9 ± 1.9ab**	**4.2 ± 2.7**	**5.0 ± 2.2**	**3.6 ± 1.1b**	4.4 ± 2.7	4.8 ± 2.3	4.6 ± 1.9
Leucine, g	8.4 ± 3.5	7.9 ± 3.2	7.9 ± 3.0	**9.3 ± 2.9**	**8.2 ± 3.2**	**6.7 ± 2.9ab**	**7.7 ± 3.2**	**8.4 ± 3.2**	**6.1 ± 1.7b**	7.9 ± 3.2	8.1 ± 3.2	7.7 ± 3.0
Protein breakfast, g	11.4 ± 5.2	13.3 ± 7.1	12.9 ± 7.4	12.8 ± 5.2	12.9 ± 7.7	12.6 ± 7.1	13.6 ± 8.3	12.9 ± 7.4	11.4 ± 5.9	11.7 ± 4.7	13.1 ± 7.1	12.8 ± 9.4
Protein lunch, g	59.5 ± 33.6	54.8 ± 26.4	58.5 ± 28.4	70.2 ± 28.4	56.2 ± 28.5	50.8 ± 22.0	**49.2 ± 32.2**	**59.8 ± 27.5**	**47.7 ± 16.6b**	56.4 ± 30.8	56.3 ± 28.1	56.3 ± 27.7

Protein dinner, g	31.0 ± 29.7	23.9 ± 27.2	21.7 ± 25.7	28.3 ± 30.9	25.8 ± 27.7	14.9 ± 21.0	26.5 ± 25.0	26.2 ± 28.6	9.8 ± 16.4	25.4 ± 29.3	24.8 ± 27.6	21.6 ± 24.8
Protein breakfast, g/kg	0.17 ± 0.09	0.19 ± 0.10	0.17 ± 0.12	0.20 ± 0.09	0.18 ± 0.11	0.18 ± 0.10	0.19 ± 0.12	0.18 ± 0.10	0.19 ± 0.12	0.17 ± 0.81	0.19 ± 0.11	0.18 ± 0.11
Protein lunch, g/kg	0.90 ± 0.55	0.81 ± 0.41	0.86 ± 0.41	1.1 ± 0.46	0.82 ± 0.44	0.76 ± 0.30	**0.71 ± 0.51**	**0.88 ± 0.41[a]**	**0.75 ± 0.34**	0.82 ± 0.50	0.83 ± 0.43	0.85 ± 0.3.
Protein dinner, g/kg	0.49 ± 0.49	0.35 ± 0.40	0.30 ± 0.37	0.46 ± 0.51	0.38 ± 0.41	0.20 ± 0.29	**0.38 ± 0.37**	**0.39 ± 0.43**	**0.13 ± 0.25ab**	0.40 ± 0.48	0.36 ± 0.41	0.30 ± 0.37

BMI = body mass index; GFST= Gérontopôle Frailty Screening Tool; SOF= Study of Osteoporotic Fractures; aP<0.05 vs Robust; bP<0.05 vs Prefrail.

The association between diet characteristics and frailty status across the different frailty indexes are shown in Table 2. No significant associations were observed when individuals were identified using FRAIL and SOF instruments. On the other hand, a significant association between the consumption of isoleucine, leucine, and valine ($P< 0.001$ for all) and frailty status were observed in Fried and GFST indexes. Z-score indicated that a higher frequency of prefrail individuals identified by both frailty indexes consumed more than the median values for all BCAA, while an inverse phenomenon was observed in frailty participants, so that a lower frequency of frail individuals consumed more than the median values for leucine (Z-score= 4.2 and 3.7), isoleucine (Z-score= 4.2 and 3.7), and valine (Z-score= 4.1 and 3.6). In addition, a higher prevalence of robust and prefrail individuals identified by the GFST index showed a body weight-adjusted protein consumption ≥1.2 g/kg ($P= 0.008$, Z-score= 2.2 and 3.1).

Table 2. Frequency (%) of the distribution of older adults according to diet characteristics and frailty status.

Variables	FRAIL			Frailty phenotype			GFST			SOF		
	Robust (n=22)	Prefrail (n=126)	Frail (n=52)	Robust (n=15)	Prefrail (n=154)	Frail (n=31)	Robust (n=38)	Prefrail (n=137)	Frail (n=25)	Robust (n=27)	Prefrail (n=127)	Frail (n=46)
Protein, g/kg												
<0.8	0 (0.0)	8 (4.0)	3 (1.5)	0 (0.0)	10 (5.0)	1 (5.0)	4 (2.0)	5 (2.5)	2 (1.0)	0 (0.0)	7 (3.5)	4 (2.0)
≥0.8	22 (11.0)	118 (59.0)	49 (24.5)	14 (7.0)	144 (72.4)	30 (15.1)	34 (19.0)	137 (68.5)	25 (12.5)	27 (13.5)	120 (60.0)	42 (21.0)
Protein, g/kg												
<1.0	2 (1.0)	27 (13.5)	10 (5.0)	0 (0.0)	30 (15.1)	9 (4.5)	10 (5.0)	21 (10.5)	8 (4.0)	4 (2.0)	26 (13.0)	9 (4.5)
≥1.0	20 (10.0)	99 (49.5)	42 (21.0)	14 (7.0)	124 (62.3)	22 (11.1)	28 (14.0)	116 (8.5)	17 (8.5)	23 (11.5)	101 (50.5)	37 (18.5)
Protein, g/kg												
<1.2	10 (5.0)	39 (19.5)	16 (8.0)	2 (1.0)	50 (25.1)	12 (6.0)	**18 (9.0)**	**35 (17.5)**	**12 (6.0)**	12 (6.0)	38 (19.0)	15 (7.5)
≥1.2	12 (6.0)	87 (43.5)	36 (18.0)	12 (6.0)	104 (52.3)	19 (9.5)	**20 (10.0)***	**102 (51.0)***	**13 (6.5)**	15 (7.5)	89 (44.5)	31 (15.5)
Protein, g/kg												
<1.5	12 (6.0)	66 (33.0)	25 (12.5)	4 (2.0)	78 (39.2)	20 (10.1)	22 (11.0)	64 (32.0)	17 (8.5)	17 (8.5)	65 (32.5)	21 (10.5)
≥1.5	10 (5.0)	60 (30.0)	27 (13.5)	10 (5.0)	76 (38.2)	11 (5.5)	16 (8.0)	73 (36.5)	8 (4.0)	10 (5.0)	62 (31.0)	25 (12.5)
Isoleucine, g												
<4.4	12 (6.0)	62 (31.0)	25 (12.5)	**5 (2.5)**	**67 (33.7)**	**26 (13.1)**	**22 (11.0)**	**56 (28.0)**	**21 (10.5)**	17 (8.5)	56 (28.0)	26 (13.0)
≥4.4	10 (5.0)	64 (32.0)	27 (13.5)	**9 (4.5)**	**87 (43.7)***	**5 (2.5)***	**16 (8.0)**	**81 (40.5)***	**4 (2.0)***	10 (5.0)	71 (35.5)	20 (10.0)
Leucine, g												
<7.1	11 (5.5)	62 (31.0)	26 (13.0)	**5 (2.5)**	**67 (33.7)**	**26 (13.1)**	**22 (11.0)**	**56 (28.0)**	**21 (10.5)**	16 (8.0)	56 (28.0)	27 (13.5)
≥7.1	11 (5.5)	64 (32.0)	26 (13.0)	**9 (4.5)**	**87 (43.7)***	**5 (2.5)***	**16 (8.0)**	**81 (40.5)***	**4 (2.0)***	11 (5.5)	71 (35.5)	19 (9.5)
Valine, g												

<4.7	12 (6.0)	62 (31.0)	26 (13.0)	**5 (2.5)**	**68 (34.2)**	**26 (13.1)**	**22 (11.0)**	**57 (28.5)**	**21 (10.5)**	17 (8.5)	57 (28.5)	26 (13.0)
≥4.7	10 (5.0)	64 (32.0)	26 (13.0)	**9 (4.5)**	**86 (43.2)***	**5 (2.5)***	**16 (8.0)**	**80 (40.0)***	**4 (2.0)***	10 (5.0)	70 (35.0)	20 (10.0)
CV, g/kg												
<0.8	6 (3.0)	52 (26.0)	18 (9.0)	6 (3.0)	57 (28.6)	13 (6.5)	14 (7.0)	55 (27.5)	7 (3.5)	6 (3.0)	53 (26.5)	17 (8.5)
0.8-1,2	16 (8.0)	71 (35.5)	32 (16.0)	8 (4.0)	94 (47.2)	16 (8.0)	23 (11.5)	79 (39.5)	17 (8.5)	21 (10.5)	71 (35.5)	27 (13.5)
>1.2	0 (0.0)	3 (1.5)	2 (1.0)	0 (0.0)	3 (1.5)	2 (1.0)	1 (5.0)	3 (1.5)	1 (5.0)	0 (0.0)	3 (1.5)	2 (1.0)
≥0.4g protein/kg/meal												
0	1 (5.0)	15 (7.5)	8 (4.0)	1 (5.0)	19 (9.5)	4 (2.0)	6 (3.0)	13 (6.5)	5 (2.5)	1 (5.0)	16 (8.0)	7 (3.5)
1	14 (7.0)	74 (37.0)	28 (14.0)	9 (4.5)	84 (42.2)	22 (11.1)	21 (10.5)	78 (39.0)	17 (8.5)	19 (9.5)	72 (36.0	25 (12.5)
≥2	7 (3.5)	37 (18.5)	16 (8.0)	4 (2.0)	51 (25.6)	5 (2.5)	11 (5.5)	46 (23.0)	3 (1.5)	7 (3.5)	39 (19.5)	14 (7.0)
≥0.30g protein/meal												
0	1 (5.0)	15 (7.5)	8 (4.0)	1 (5.0)	19 (9.5)	4 (2.0)	6 (3.0)	13 (6.5)	5 (2.5)	1 (5.0)	16 (8.0)	7 (3.5)
1	14 (7.0)	74 (37.0)	28 (14.0)	9 (4.5)	84 (42.2)	22 (11.1)	21 (10.5)	78 (39.0)	17 (8.5)	19 (9.5)	72 (36.0	25 (12.5)
≥2	7 (3.5)	37 (18.5)	16 (8.0)	4 (2.0)	51 (25.6)	5 (2.5)	11 (5.5)	46 (23.0)	3 (1.5)	7 (3.5)	39 (19.5)	14 (7.0)

CV= coefficient of variation; GFST= Gérontopôle Frailty Screening Tool; SOF= Study of Osteoporotic Fractures; *P<0.05

Discussion

The main findings of the present study indicate that the relationship between diet characteristics and frailty status are tool-dependent. Indeed, a significant association between frailty status and protein consumption were only observed when participants were identified using Fried frailty phenotype and GFST, while no significant associations were observed with FRAIL and SOF. In addition, a poor consumption of protein and BCAA was observed in frail participants.

Prior studies have compared the association between different frailty instruments and cognitive function, falls, disability, fractures, hospitalization, and all-cause mortality [33–35]. Most studies have found significant associations among the frailty indexes, even when participants were identified using different frailty concepts (e.g., Fried frailty phenotype and frailty index) [34]. However, Mori et al. [26] observed differences to predict disability and hospitalization among frailty indexes in prefrail older adults, suggesting that the pathogenic bases associated with frailty progress might be tool-dependent.

In the present study, protein intake-related parameters were significantly associated with frailty status using Fried frailty phenotype and GFST, but not FRAIL and SOF. One potential explanation for these differences may be the type of physical assessment used in each instrument, given that protein intake has a key role in muscle protein synthesis and consequently in the preservation of muscle mass and physical function with aging [18,36]. Indeed, if on one hand, objective measures of physical function and self-reported exhaustion are part of the frailty criteria proposed by both Fried frailty phenotype [24] and GFST [31]; on the other hand, the analysis of the physical component of FRAIL [29] and SOF [30] instruments are exclusively dependent of the patient's perception, which does not necessarily reflect current physical performance status [37,38].

We observed an inverse relationship between body-adjusted protein (only for GFST) and BCAA consumptions and frailty status, so that most robust and prefrail older adults consumed more leucine, isoleucine, and valine than the median, while only a lower frequency of frail participants showed this diet pattern. Findings of the present study are supported by prior investigations which observed a negative association between frailty and essential AA [12,39].

Beasley et al. [12] found that higher intake of essential AA was significantly associated with a lower risk to develop frailty over three years in a subset of older women of the Women's Health Initiative Observational Study (WHI-OS). Similarly, Kobayashi et al. [40] observed that higher consumption of selected AA, including BCAA, were associated with lower prevalence of frailty in 2108 Japanese older women.

Our findings add to the current knowledge on the relationship between AA intake and frailty and suggest that this phenomenon may be highly influenced by BCAA intake. According to the anabolic resistance hypothesis [41,42], muscular anabolic response to appropriate stimulation is blunted in advanced age, collaborating to muscle catabolism, loss of lean body mass, dynapenia, and impairment on physical function [42,43].

In this context, a higher availability of AA, mainly leucine, would be necessary to reverse this state and stimulates muscle protein synthesis [18]. These premises have been confirmed by observational studies which observed that reduced systemic concentration of BCAA were significantly associated with sarcopenia markers in older adults [44,45].

Notably, an exclusive association between body weight-adjusted protein consumption ≥ 1.2 g/kg/day and frailty status were observed when participants were identified using GFST. These differences may be explained by the fact that only GFST contains a cognitive component based on memory complains [31], and an increasing number of evidences suggested that protein consumption may collaborated with cognitive function in older adults [46]. However, future studies are still necessary to investigate if protein consumption is differently associated across different frailty definitions (e.g., physical frailty, cognitive frailty, accumulative deficit frailty).

The present study has some limitations that should be acknowledged. The study population was relatively small and composed exclusively by community-dwellers, limiting inferences to older adults from other settings (i.e., nursing homes) and deeper statistical analysis. Second, both Fried frailty phenotype and GFST were adapted given that walking speed test was replaced by TUG. In addition, the cross-sectional design of the study does not allow inference to be drawn on the time course of changes of the variables considered and on cause-effect relationships.

Conclusions

Our findings suggest that the relationship between diet characteristics and frailty status is tool-dependent, so that a significant association between frailty status and protein consumption were only observed when participants were identified using Fried frailty phenotype and GFST. In addition, a poor consumption of protein and BCAA was observed in frail participants.

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ARTICLE 7

Association Between Diet Habits and Physical Function in Brazilian and Italian Older Women: A cross-sectional study

ABSTRACT

Aims: The present study was undertaken to determine the differences in protein consumption and physical function between Brazilian and Italian older women. In addition, we investigated if physical function could be differently associated with different diet patterns among the samples. **Methods:** Seventy-five Brazilian older women (mean age: 75.2 years) were recruited in a community senior center located in the southern area of São Paulo. Fifty-three Italian older women (mean age: 77.6 years) matched on age and body mass index (BMI) were randomly selected from the Italian survey ("Longevity Check-up"), conducted during Milan EXPO 2015. In both studies, physical performance was evaluated by isometric handgrip strength (IHG) and sit-to-stand tests. Dietary assessment was assessed using a 24-h recall diary. **Results:** A different intake of specific protein sources was observed among the groups, given that Italian older women consumed more animal-based protein, while a higher intake of plant-based protein was found in Brazilian older women. The binary logistic regression analysis indicated that body weight-adjusted protein consumption was positively associated with IHG/BMI and negatively associated with sit-to-stand in Brazilian. In the Italian sample, valine, isoleucine, and leucine were significantly associated with sit-to-stand performance. C**onclusions:** Our findings indicate that Brazilian and Italian community-dwellers older women show different patterns of protein consumption, given that a higher consumption of plant-based protein was observed in the Brazilian sample, while Italians consumed more animal-based protein. These diet pattern likely influenced the relationship between physical function and protein intake found in these samples.

INTRODUCTION

Physical function refers to the ability to integrate and convert many physiological stimuli, but mainly those arising from the neuromuscular system, into an action (e.g., walk, jump) that allow the interaction between the subject and the world. Notably, substantial changes occur in physical function over the course of life, so that infancy is characterized by a dramatic increase of motor abilities[1], while an age-related decline in physical performance has been

widely described among people from different countries after ~30 years of age[2,3]. Regarding gender, such reductions seem to be more pronounced in women due to the effects of menopause[4].

The biggest concern regarding the deterioration of physical function with aging is its close association with a wide range of poor outcomes, such as cognitive impairment, falls, disability, institutionalization, and mortality[5–9], as well as its impact on the development of geriatric syndromes (e.g., frailty)[10,11] and neuromuscular diseases (e.g., sarcopenia)[12,13]. These premises lead the World Health Organization (WHO) to indicate the maintaining of physical function as a central component for the preservation of functionality, autonomy and independence in older adults[14].

In this context, diet habits have been identified as a strategy to counteract age-related decline in physical performance[15,16]. Protein intake, for example, has a key role in muscle protein synthesis and consequently in the preservation of muscle mass and physical function[17,18]. In the last years, many studies have investigated the association between protein-related diet parameters (e.g., sources) and physical function in older adults[19–23], which allowed the creation of perspectives regarding the adequate protein consumption for this population[24–26]. However, few data are available investigating the relationship between diet habits and physical function in populations from different countries.

These information seems to be important since dietary patterns hold significant cultural and regional values[27–29] which might negatively influence the adherence to diet recommendations[30] and health related outcomes[31], whereas understanding the food behavior of some populations may allow the creation of more adequate and specific dietary recommendations to address disparities in diet quality and quantity in older adults.

Therefore, the present study was undertaken to determine the differences in protein consumption and physical function between Brazilian and Italian older women. In addition, we investigated if physical function could be differently associated with different diet patterns among the samples.

MATERIALS AND METHODS

The study approved by the Research Ethics Committee of the University of Mogi das Cruzes (UMC) under the protocol number 621-614. All study procedures were conducted in compliance with the Declaration of Helsinki and the Resolution 196/96 of the National Health Council. All participants were thoroughly informed about the study procedures before providing written consent.

Brazilian study sample

Brazilian older women were recruited by convenience in a community senior center located in Poá, Brazil. Poá is a city located in the southern area of São Paulo with a population of approximately 100 thousand people, being ~3460 older (60 year or over)[32]. The community senior center offers daily sessions of flexibility, aquatic and multicomponent physical exercise, dance classes, adapted sports, nursing and medical care, and cognitive stimulation therapy. Candidate participants were considered eligible if they were 60 or older, lived independently, and possessed sufficient physical and cognitive abilities to perform all of the measurements required by the protocol.

Italian study sample

The "Longevity Check-up" project was an initiative developed by the Department of Geriatric Medicine of the Catholic University of the Sacred Heart in Rome, with the intent to promote a healthy lifestyle in the general population. Milan EXPO 2015 exhibition was chosen as the setting for the initiative because of the chance to meet an unselected population of individuals, not generally referred to traditional healthcare services [33]. In the period between June 1, 2015 and June 15, 2015 (pavilion of Marche Region), and between September 1, 2015 and October 31, 2015 (Casa Ferrarini pavilion), a sample of 3206 persons from different Italian regions underwent individual assessments that consisted of a brief questionnaire, the objective measurement of the seven cardiovascular health metrics, the evaluation of specific anthropometric parameters, and handgrip strength testing. Candidate participants were considered to be eligible for enrolment if they were at least 18 years of age and provided written informed consent. Self-reported pregnancy, inability to perform functional tests, and unwillingness to give written informed consent were considered exclusionary. For the present

study, age- and body mass index (BMI)-matched Italian older women aged 60 or older were randomly selected [34].

Anthropometric measurements

A weight scale with a stadiometer was used to measure body mass and height. The BMI was subsequently calculated as following:

a) body mass (kg)/ height (m^2).

Dietary assessment

Food intake was assessed using a 24-h recall diary. This method uses an open-ended questionnaire to provides a quantitative and subjective estimation of actual food consumption. In the present protocol, trained researchers asked the participants to detailly recall all foods they consumed on a meal-by-meal basis, including snacks, during the previous 24-h period. Interviews occurred on Tuesdays, Wednesdays, Thursdays, and Fridays to avoid bias associated with the weekend. Participants were requested to detailly describe cooking methods (e.g., fried, grilled, roasted), amounts in portions, product brands, sauces, spices, and condiments consumed, and the use of dietary supplements. The amounts of beverages consumed were also recorded, and participants should describe if and how beverages were sweetened. Two-dimensional aids (e.g., photographs), household utensils (e.g., standard measuring cups and spoons), and food models were used as memory aids to assess portion sizes. Diet composition was estimated using the NutWin software, version 1.5 (Federal University of São Paulo, Brazil) for the Brazilian population[35] and MètaDieta (ME.TE.DA, LLC, San Benedetto del Tronto, Italy) for the Italian population [36].

Functional assessments

- *Isometric handgrip strength test (IHG)*

IHG was measured using a Jamar® handheld hydraulic dynamometer (Sammons Preston, Bolingcobrook, IL, USA)[37]. The measure was obtained from the dominant hand with the participant seated on a chair with the shoulders abducted, the elbow of the dominant side near the trunk and flexed at 90°, and the wrist in a neutral position (thumb up). The contralateral

arm remained relaxed under the thigh. To determine the dominant hand, volunteers were asked which of the hands was the strongest. IHG was measured during 4 s under encouragement.

Sit-to-stand test

Participants rose from a chair five times as quick as possible with their arms folded across their chest. Timing began when the participant raised their buttocks off the chair and was stopped when the participant was seated at the end of the fifth stand[38].

Statistical analysis

To determine the differences in the continuous data between the groups (i.e., Brazilian and Italian), the Student's t-test for independent samples was performed. Chi-square (χ^2) test was performed to investigate the association between the dependent categorical variables (i.e., IHG, IHG/BMI, and sit-to-stand) and the independent categorical variables. The median values were chosen as the cutoff values, as following: IHG (Brazilian: 22 kg; Italian: 14 kg), IHG/BMI (Brazilian: 0.8 kg; Italian: 0.5 kg), sit-to-stand (Brazilian: 11.3 s; Italian: 14.7 s), age (Brazilian: 66 years; Italian: 77 years), BMI (Brazilian: 28.7 kg/m²; Italian: 29.7 kg/m²), relative protein consumption (Brazilian: 23.6%; Italian: 17.7%), relative animal-based protein (Brazilian: 41.4%; Italian: 67.3%), relative plant-based protein (Brazilian: 53.7%; Italian: 29.0%), body-weight adjusted protein consumption (Brazilian: 1.0 g/kg/day; Italian: 1.0 g/kg/day), total protein (Brazilian: 68.8g; Italian: 64.6g), animal protein (Brazilian: 29.0g; Italian: 41.8g), plant-based protein (Brazilian: 34.8g Italian: 18.3g), valine (Brazilian: 2573.7 mg; Italian: 2943.2 mg), isoleucine (Brazilian: 2232.9 mg; Italian: 2480.8 mg), leucine (Brazilian: 4184.6 mg; Italian: 4646.2 mg). Independent variables with a $P<0.05$ in the χ^2 test were included in a univariate logistic binary analysis. To be considered as an independent variable associated with physical function, the results were required to have a $P< 0.05$ and a 95% confidence interval (CI 95%) that did not include the value of 1. All analyses were conducted using the IBM SPSS Statistics, version 20.0, software (IBM Corp., Armonk, NY, USA).

RESULTS

The characteristics of the study participants are shown in Table 1. One-hundred twenty-eight (75 Brazilian and 53 Italian) older women were recruited to take part in the study. Brazilian older women had better physical performance in IHG (P<0.001), IHG/BMI (P=0.081), and sit-to-stand (P<0.001) tests, as well as a higher total (P=0.043) and relative (P<0.001) protein consumption. A different intake of specific protein sources was observed among the groups, given that Italian older women consumed more animal-based protein, both relative (P<0.001) and total (P<0.001), while a higher intake of plant-based protein (P<0.001 for both) was found in Brazilian older women.

Table 1. Characteristics of the participants.

Variables		
Characteristics	Brazilian (n= 75)	Italian (n=53)
Age, years	75.2 ± 7.5	77.6 ± 5.5
Body weight, kg	71.4 ± 12.5	70.7 ± 13.1
BMI, kg/m²	28.2 ± 7.0	30.1 ± 5.5
Physical functional tests		
IHG, kg	**20.0 ± 10.9**	**13.1 ± 6.8***
IHG/BMI, kg	**1.2 ± 3.1**	**0.4 ± 0.2***
Sit-to-stand, s	**11.9 ± 3.3**	**16.7 ± 6.0***
Diet		
Protein, %	**22.9 ± 5.3**	**17.6 ± 4.7***
Animal-based protein, %	**39.7 ± 18.5**	**63.9 ± 16.2***
Plant-based protein, %	**52.7 ± 16.4**	**30.5 ± 13.7***
Protein, g/kg/day	1.04 ± 0.41	1.09 ± 0.44
Protein, g/day	**72.7 ± 26.8**	**63.9 ± 19.2***
Animal-based protein, g/day	**29.7 ± 17.2**	**41.5 ± 17.7***
Plant-based protein, g/day	**37.9 ± 17.2**	**19.0 ± 8.4***
Valine, mg	2744 ± 1314	2935 ± 1047

Isoleucine, mg	2409 ± 1155	2512 ± 921
Leucine, mg	4437 ± 2142	4516 ± 1607

BMI = body mass index; IHG= Isometric handgrip strength*P<0.05 vs Brazilian

The association between physical function and dietary characteristics according to the country are shown in Table 2. IHG (P=0.04) and sit-to-stand (P=0.01) were significantly associated with BMI in Brazilian older women. In addition, body weight-adjusted protein consumption was associated with IHG/BMI (P=0.002) and sit-to-stand (P=0.04) performances. In Italian older women, leucine (P=0.03), isoleucine (P=0.03), and valine (P=0.02) were significantly associated with sit-to-stand.

Table 2. Frequency (%) of the distribution of older women according to physical function.

	Brazilian						Italian					
	IHG		IHG/BMI		Sit-to-stand		IHG		IHG/BMI		Sit-to-stand	
Variable	Low	High	Low	High	Low	High	Low	High	Low	High	Low	High
Age, years												
Low	13 (37.1 %)	22 (55.0 %)	17 (39.5 %)	18 (56.3 %)	17 (45.9 %)	18 (47.4 %)	12 (22.6 %)	15 (28.3 %)	15 (28.3 %)	12 (22.6 %)	13 (24.5 %)	14 (26.4 %)
High	22 (62.9 %)	18 (45.0 %)	26 (60.5 %)	14 (43.8 %)	20 (54.1 %)	20 (52.6 %)	10 (18.9 %)	16 (30.2 %)	14 (26.4 %)	12 (22.6 %)	13 (24.5 %)	13 (24.5 %)
BMI (kg/m²)												
Low	**22 (62.9 %)**	**16 (40.0 %)**	20 (46.5 %)	18 (56.3 %)	**24 (64.9 %)**	**14 (36.8 %)**	12 (22.6 %)	14 (26.4 %)	12 (22.6 %)	14 (26.4 %)	13 (24.5 %)	13 (24.5 %)
High	**13 (37.1 %)**	**24 (60.0 %)***	23 (53.5 %)	14 (43.8 %)	**13 (35.1 %)**	**24 (63.2 %)***	10 (18.9 %)	17 (32.1 %)	17 (32.1 %)	10 (18.9 %)	13 (24.5 %)	14 (26.4 %)
Protein, %												

Low	17 (48.6 %)	21 (52.5 %)	24 (55.8 %)	14 (43.8 %)	20 (54.1 %)	18 (47.4 %)	13 (24.5 %)	13 (24.5 %)	17 (32.1 %)	9 (17.0 %)	13 (24.5 %)	13 (24.5 %)
High	18 (51.4 %)	19 (47.5 %)	19 (44.2 %)	18 (56.3 %)	17 (45.9 %)	20 (52.6 %)	9 (17.0 %)	18 (34.0 %)	12 (22.6 %)	15 (28.3 %)	13 (24.5 %)	14 (26.4 %)
Animal-based protein, %												
Low	16 (45.7 %)	22 (55.0 %)	19 (44.2 %)	19 (59.4 %)	17 (45.9 %)	21 (55.3 %)	12 (22.6 %)	15 (28.3 %)	15 (28.3 %)	12 (22.6 %)	14 (26.4 %)	13 (24.5 %)
High	19 (54.3 %)	18 (45.0 %)	24 (55.8 %)	13 (40.6 %)	20 (54.1 %)	17 (44.7 %)	10 (18.9 %)	16 (30.2 %)	14 (26.4 %)	12 (22.6 %)	12 (22.6 %)	14 (26.4 %)
Plant-based protein, %												
Low	20 (57.1 %)	18 (45.0 %)	25 (58.1 %)	13 (40.6 %)	18 (48.6 %)	20 (52.6 %)	9 (17.0 %)	17 (32.1 %)	13 (24.5 %)	13 (24.5 %)	13 (24.5 %)	13 (24.5 %)
High	15 (42.9 %)	22 (55.0 %)	18 (41.9 %)	19 (59.4 %)	19 (51.4 %)	18 (47.4 %)	13 (24.5 %)	14 (26.4 %)	16 (30.2 %)	11 (20.8 %)	13 (24.5 %)	14 (26.4 %)
Protein, g/kg/day												
Low	14 (40.0 %)	15 (37.5 %)	**23 (53.% %)**	**6 (18.8 %)**	**10 (27.0 %)**	**19 (50.0 %)**	8 (15.1 %)	18 (34.0 %)	11 (20.8 %)	15 (28.3 %)	15 (28.3 %)	11 (20.8 %)
High	21 (60.0 %)	25 (62.5 %)	**20 (46.5 %)**	**26 (81.3 %)***	**27 (73.0 %)**	**19 (50.0 %)***	14 (26.4 %)	13 (24.5 %)	18 (34.0 %)	9 (17.0 %)	11 (20.8 %)	16 (30.2 %)
Protein, g/day												

Low	16 (45.7 %)	22 (55.0 %)	24 (55.8 %)	14 (43.8 %)	18 (48.6 %)	20 (52.6 %)	14 (26.4 %)	12 (22.6 %)	17 (32.1 %)	9 (17.0 %)	10 (18.9 %)	16 (30.2 %)
High	19 (54.3 %)	18 (45.0 %)	19 (44.2 %)	18 (56.3 %)	19 (51.4 %)	18 (47.4 %)	8 (15.1 %)	19 (35.8 %)	12 (22.6 %)	15 (28.3 %)	16 (30.2 %)	11 (20.8 %)
Animal-based protein, g/day												
Low	18 (51.4)	21 (52.5 %)	22 (51.2 %)	17 (53.1 %)	20 (54.1 %)	19 (50.0 %)	12 (22.6 %)	14 (26.4 %)	16 (30.2 %)	10 (18.9 %)	10 (18.9 %)	16 (30.2 %)
High	17 (48.6 %)	19 (47.5 %)	21 (48.8 %)	15 (46.9 %)	17 (45.9 %)	19 (50.0 %)	10 (18.9 %)	17 (32.1 %)	13 (24.5 %)	14 (26.4 %)	16 (30.2 %)	11 (20.8 %)
Plant-based protein, g/day												
Low	15 (42.9 %)	21 (52.5 %)	23 (53.5 %)	13 (40.6 %)	15 (40.5 %)	21 (55.3 %)	14 (26.4 %)	14 (26.4 %)	18 (34.0 %)	10 (18.9 %)	12 (22.6 %)	16 (30.2 %)
High	20 (57.1 %)	19 (47.5 %)	20 (46.5 %)	19 (59.4 %)	22 (59.5 %)	17 (44.7 %)	8 (15.1 %)	17 (32.1 %)	11 (20.8 %)	14 (26.4 %)	14 (26.4 %)	11 (20.8 %)
Valine, mg												
Low	16 (45.7 %)	19 (47.5 %)	22 (51.2 %)	13 (40.6 %)	15 (40.5 %)	20 (52.6 %)	13 (24.5 %)	14 (26.4 %)	17 (32.1 %)	10 (18.9 %)	**9 (17.0 %)**	**18 (34.0 %)**
High	19 (54.3 %)	21 (52.5 %)	21 (48.8 %)	19 (59.4 %)	22 (59.5 %)	18 (47.4 %)	9 (17.0 %)	17 (32.1 %)	12 (22.6 %)	14 (26.4 %)	**17 (32.1 %)**	**9 (17.0 %)***
Isoleucine, mg												
Low	16 (45.7 %)	21 (52.5 %)	22 (51.2 %)	15 (46.9 %)	17 (45.9 %)	20 (52.6 %)	13 (24.5 %)	13 (24.5 %)	17 (32.1 %)	9 (17.0 %)	**9 (17.0 %)**	**17 (32.1 %)**

High	19(54.3%)	19 (47.5 %)	21 (48.8 %)	17 (53.1 %)	20 (54.1 %)	18 (47.4 %)	9 (17.0 %)	18 (34.0 %)	12 (22.6 %)	15 (28.3 %)	**17 (32.1 %)**	**10 (18.9 %)***
Leucine, mg												
Low	16 (45.7 %)	21 (52.5 %)	23 (53.5 %)	14 (43.8 %)	16 (43.2 %)	21 (55.3 %)	11 (20.8 %)	15 (28.3 %)	16 (30.2 %)	10 (18.9 %)	**9 (17.0 %)**	**17 (32.1 %)**
High	19 (54.3 %)	19 (47.5 %)	20 (46.5 %)	18 (56.3 %)	21 (56.8 %)	17 (44.7 %)	11 (20.8 %)	16 (30.2 %)	13 (24.5 %)	14 (26.4 %)	**17 (32.1 %)**	**10 (18.9 %)***

BMI = body mass index; IHG= Isometric handgrip strength*P<0.05

Table 3 presents the unadjusted OR and 95% CI results for physical function. The binary logistic regression analysis indicated that body weight-adjusted protein consumption was positively associated with IHG/BMI (unadjusted OR = 1.6; CI 95% = 1.708–14.543; P-value = 0.003) and negatively associated with sit-to-stand (unadjusted OR = -0.993; CI 95% = 0.141-0.972; P-value = 0.04) in Brazilian. In the Italian sample, valine (unadjusted OR = -1.329; CI 95% = 0.085-0.825; P-value = 0.02), isoleucine (unadjusted OR = -1.167; CI 95% = 0.101-0.958; P-value = 0.04), and leucine (unadjusted OR = -1.167; CI 95% = 0.101-0.958; P-value = 0.04) were significantly associated with sit-to-stand performance.

Table 3. Unadjusted Or and 95% confidence intervals (CI) for physical function Brazilian.

	IHG/BMI		Sit-to-stand	
Variable	Unadjusted OR	CI 95%	Unadjusted OR	CI 95%
Protein, g/kg/day				
High	1.6	1.708-14.543	-0.993	0.141-0.972*
Low	Ref.		Ref.	

Italian

	Sit-to-stand	
Variable	Unadjusted OR	CI 95%
Valine, mg		

High	-1.329	0.085-0.825*
Low	Ref.	
Isoleucine, mg		
High	-1.167	0.101-0.958*
Low	Ref.	
Leucine, mg		
High	-1.167	0.101-0.958*
Low	Ref.	

BMI = body mass index; IHG= Isometric handgrip strength*P<0.05; Ref = reference; OR = odds ratio; CI = confidence interval.

DISCUSSION

The present study investigated the main differences in physical function and diet characteristics between Brazilian and Italian community-dwellers older women. Our results revealed that Brazilian older women had a better physical function and a higher intake of plant-based protein, while higher animal-based protein intake was observed in Italian older women. Furthermore, we tested the hypothesis that physical function could be differently associated with different patterns of protein intake among the samples. We observed that body weight-adjusted protein consumption was significantly associated with IHG/BMI and sit-to-stand tests in the Brazilian sample. On the other hand, branched-chain amino acids (BCAA) were negatively associated with sit-to-stand performance in Italian participants.

These results provide an interesting perspective about the influence of sociocultural factors on dietary consumption and physical function. In Brazilian, the higher intake of plant-based protein may be explained by a rich diet of legumes, vegetables and animal derived foods (e.g., dairy products), given that this diet pattern is commonly observed in Brazilian older women[39,40]. Beans, for example, are a widely known source of plant protein[41], one of the most consumed foods in Brazil[40], and were present in at least one of the main meals (i.e., lunch or dinner) of the Brazilian participants.

An additional explanation may be that meat consumption had for a long time a high symbolic value due to its high cost and status of great cultural importance, which could have collaborated with changes in the diet patterns of the Brazilian population[42].

One may argue that the diet pattern observed in the Brazilian population was more likely to be found in the Italian population because legumes and vegetables are the basis of Mediterranean diet[43]. However, our sample recruitment occurred prevalently in the Northern part of Italy and a populational study found higher adherence to the Mediterranean diet in the Southern Italy, but not in the Northern part[27].

These different patterns of protein consumption likely impact on the relationship between protein intake and physical performance. In the present study, a body weight-adjusted protein consumption ≥1 g/kg/day were significantly associated with IHG/BMI and sit-to-stand tests in the Brazilian sample.

A possible explanation for these findings may reside in the fact that plant-based protein generally contains smaller amounts of essential amino acids and stimulates protein synthesis as well as inhibits protein breakdown in a less extent than animal-based protein[44], which leads to the recommendation that greater amounts of plant-based protein may be necessary to elicit the same protein anabolism evoked by smaller quantities of animal-based protein[41]. In fact, we recently observed that plant-based protein intake was significantly associated with walking speed in Brazilian older adults who consumed twofold more plant-based protein than the Framingham cohort[45,46].

On the other hand, physical function was significantly associated with valine, leucine, and isoleucine intake in Italian older women. Notably, animal-based protein is the main source of BCAA[47] and it represented more than 60% of the protein source consumed by Italians. Once in the body, BCAA, and specially leucine, stimulates muscle protein synthesis[48] via the activation of the downstream cascade of the mammalian target of rapamycin (mTOR)[49]. Researchers have argued that BCAA have a key role in muscle mass and physical function regulation during aging[41] and an increasing number of evidence have demonstrated lower systemic concentrations of BCAA in older adults with sarcopenia[48].

Based on these premises, it is possible to suggest that the association between BCAA and physical function observed in Italian older adults occurred due to a high intake of animal-based protein.

It is worth mentioning that the median values of body weight-adjusted protein consumption of Brazilian older women were higher than the recommended dietary allowance (RDA, 0.8 g kg−1 day−1). These findings are in line with a recent systematic review and meta-analysis that found better physical performance in older adults who had higher protein intake than the RDA[20].

Many researchers have questioned if the current RDA is enough to maintain the functional status or even prevent its decline in older adults[24,41], given that the amount of recommended protein is based on nitrogen balance studies, which may be associated with a methodological bias[24,25]. A further consideration regarding the RDA is that it has no specific recommendations for older adults[24,25], although the aging muscle shows a state of anabolic resistance characterized by blunted protein synthesis in response to protein ingestion or amino acid infusion[50].

Taken together, these findings support increasing the protein RDA for older adults and suggest that country-based recommendations should take into consideration the cultural factors and the regional diet patterns to ensure the optimal protein intake to avoid impairments on physical function.

We recognize some limitations to this study. Different sample recruitments were used in the present study, so that Brazilian participants were limited to a unique city, while Italian participants included people from different regions. The possibility cannot be ruled out that results could be different with a randomly multicentric Brazilian sample. In addition, our study is based in a relatively small number of participants, and no power calculation was performed. Body composition[51], physical activity levels[52], and oral health status[53]are associated with protein consumption in older adults and were not controlled in the present study. Finally, the diet evaluation through the 24-h recall diary should also be acknowledged as a limitation of the study.

CONCLUSION

Our findings indicate that Brazilian and Italian community-dwellers older women show different patterns of protein consumption, given that a higher consumption of plant-based protein was observed in the Brazilian sample, while Italians consumed more animal-based protein. These diet pattern likely influenced the relationship between physical function and protein intake found in these samples. Indeed, body weight-adjusted protein consumption was significantly associated with IHG/BMI and sit-to-stand tests in the Brazilian sample. On the other hand, BCAA were negatively associated with sit-to-stand performance in Italian participants.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest: The authors declare that they have no conflict of interest.

Research involving human participants: All procedures performed in the present study were approved by the Research Ethics Committee of the University of Mogi das Cruzes (UMC) under the protocol number 621-614 and were conducted in compliance with the Declaration of Helsinki and the Resolution 196/96 of the National Health Council.

Informed consent: Informed consent was obtained from all individual participants included in the study.

DATA AVAILABILITY

The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

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ARTICLE 8

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ORIGINAL ARTICLE

High relative consumption of vegetable protein is associated with faster walking speed in well-functioning older adults

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Abstract

Background Adequate nutrition and, especially, optimal protein intake are necessary to preserve physical function during aging. Increased consumption of animal-derived protein is often advocated as a strategy to support physical performance in old age. However, there is a lack of empirical evidence to support this claim. **Aims** To assess the relationship of protein consumption and specific protein sources with physical function in older adults. **Methods** Participants were community dwellers aged 60 years and older recruited in São Paulo, Brazil. Enrollees had their medical books reviewed and were evaluated for anthropometry, physical performance, and diet. Physical performance was evaluated by isometric handgrip strength and walking speed (WS) tests. Diet was assessed using a 24-h recall diary. **Results** Ninety older adults were recruited (mean age: 68.0 ± 6.7 years; 87.0% women). Body weight-adjusted protein consumption was significantly associated with upper-limb muscle strength ($r = 0.21$; $p < 0.05$), but not with usual ($r = 0.09$; $p > 0.05$) or fast WS ($r = 0.08$; $p > 0.05$). Conversely, relative protein consumption was correlated with usual WS ($r = 0.13$; $p < 0.05$), while fast WS was negatively associated with relative animal protein intake ($r = -0.18$; $p < 0.05$) and positively associated with relative plant-based protein ingestion ($r = 0.15$; $p < 0.05$). **Discussion** Findings of the present study indicate that different measures of protein intake are associated with distinct components of physical function. In addition, high relative ingestion of vegetable protein is associated with faster WS. **Conclusions** A comprehensive dietary evaluation is necessary to appreciate the impact of specific nutrients on physical performance in older people. Future interventional studies are needed to establish the optimal blend of protein sources to support physical performance in old age.

Keywords Diet · Physical performance · Muscle strength · Gait speed · Animal protein · Nutrition

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Introduction

The aging process is a continuous phenomenon resulting from derangements in multiple body systems and marked by increased risk of developing chronic diseases and death [1]. Among the changes that accompany aging, declining physical performance has received considerable attention because of its association with a vast array of negative health-related outcomes, including disability, falls, dementia, institutionalization, and mortality [2–7]. Indeed, preservation of physical function is acknowledged as a key determinant of successful aging [8].

Adequate nutrition and, especially, optimal protein intake are core elements for preserving physical function and promoting healthy aging [9, 10]. Yet, the prevalence of protein–energy malnutrition is concernedly high among older people [11, 12]. What is more, the aging muscle shows a state of anabolic resistance characterized by blunted myofibrillar protein synthesis (MPS) in response to protein ingestion or amino acid infusion [13]. Hence, protein intake above the recommended dietary allowance (RDA, 0.8 g kg^{-1} day^{-1}) is advisable to maintain muscle mass and function into old age [14, 15]. Indeed, a recent systematic review and metaanalysis showed that very high (≥ 1.2 g kg^{-1} day^{-1}) and high protein intake (≥ 1.0 g kg^{-1} day^{-1}) were associated with better physical performance compared with low protein intake (< 0.8 g kg^{-1} day^{-1}) in community-dwelling older adults [16]. Notwithstanding, the possible differential effect of specific protein sources on physical function is not clearly established. Animal-derived foods are thought to provide higher quality protein than plant-based aliments [17]. Though, low protein intake, especially of animal origin, has been associated with reduced all-cause mortality [9, 18]. Such an association was not observed in people older than 65 years [9]. The mechanisms underlying the switch from the detrimental to the protective effect of high protein ingestion in old age are presently unclear. However, the lower responsiveness of the aged muscle to dietary protein and amino acids may explain the higher protein requirements of older adults [19]. Notably, animal-derived protein was reported to stimulate MPS to a greater extent than soy protein in older men under both at rest and post-exercise [20]. Furthermore, greater protein consumption, particularly of animal origin, has been associated with higher levels of function in communitydwelling older people [21].

In the attempt to increase the understanding of protein requirements in old age, the present study was undertaken to assess the impact of total protein consumption and protein from different sources on physical function in communitydwelling older adults.

Methods

Informed consent

The study was approved by the Research Ethics Committee of the University of Mogi das Cruzes (UMC) under the protocol number 621-614. All study procedures were conducted in compliance with the Declaration of Helsinki and the Resolution 196/96 of the National Health Council. All participants were thoroughly informed about the study procedures before providing written consent.

Study participants

This study was designed as a cross-sectional investigation. Participants were recruited based on convenience in the metropolitan area of São Paulo, Brazil. The study was advertised through posters placed in public sites (e.g., parks, city hall, public offices, bus stops, train stations) as well as local radio and newspapers. People were also invited to participate by direct contact. Candidate participants were considered to be eligible if they were ≥ 60 years of age and possessed sufficient physical and cognitive abilities to perform all the measurements required by the protocol.

Dietary assessment

Food intake was assessed using a 24-h recall diary. The method is based on an open-ended questionnaire to provide a quantitative and subjective estimation of food consumption. Trained researchers asked participants to recall all foods they consumed on a meal-by-meal basis, including snacks, during the previous 24 h. Interviews occurred on Tuesdays, Wednesdays, Thursdays, and Fridays to avoid possible bias associated with the weekend. Participants were requested to report cooking methods (e.g., fried, grilled, roasted), amounts in portions, product brands, sauces, spices, and condiments consumed, and the eventual use of supplements. The amount of beverages consumed was also recorded, and participants were asked to report if and how beverages were sweetened. Two-dimensional aids (e.g., photographs), household utensils (e.g., standard measuring cups and spoons), and food models were used as memory aids to assess portion sizes. Diet composition was estimated using the NutWin software, version 1.5 (Federal University of São Paulo, Brazil) [22].

Functional assessments

All functional tests were administered by two experienced researchers (H.J.C.-J. and I.O.G.). While one was responsible for detailing the operational procedures, demonstrating the test before the assessment, quantifying the performance, and evaluating the motor pattern, the other ensured participant safety. After the end of the explanation and before each test, volunteers performed a familiarization trial to ensure they had fully understood the test. Then, volunteers performed all tests twice, and the best result obtained was considered for the analysis. The tests were administered in a dedicated room and were performed in a sequential order with 1-min interval between trials, as follows: isometric handgrip strength (IHG) [23], walking speed (WS) at usual pace, and WS fast pace [24].

Isometric handgrip strength test

IHG was measured using a Jamar® handheld hydraulic dynamometer (Sammons Preston, Bolingcobrook, IL, USA) [23]. The measure was obtained from the dominant hand with the participant seated on a chair with the shoulders abducted, the elbow of the dominant side near the trunk and flexed at 90°, and the wrist in a neutral position (thumb up). The contralateral arm remained relaxed under the thigh. To determine the dominant hand, volunteers were asked which of the hands was the strongest. IHG was measured during 4 s under encouragement.

Walking speed tests

WS was measured over 3 m [24]. This distance was chosen because of the space limitations. However, high concordance has been observed between the results recorded on 3- and 6-m courses [25]. For the test, volunteers were required to walk 5 m (including 1-m acceleration and 1-m deceleration) at their usual and fastest possible pace (without running). Before the evaluation, both feet were to remain on the starting line. The measurement was started when a foot reached the 1-m line and was stopped when a foot reached the 4-m line. The 1-m intervals at the beginning and at the end of the course were used to avoid early acceleration and/ or deceleration.

Anthropometric measurements

A weight scale with a Filizola® (Brazil) stadiometer was used to measure body mass and height. The body mass index (BMI) was subsequently calculated as the ratio between body mass (kg) and the square of height (m^2). A flexible and inextensible anthropometric tape (Sanny®, São Paulo, Brazil) was used to measure waist (WC) and hip (HC) circumferences. WC was assessed at the mid-point between the last floating rib and the highest point of the iliac crest. HC was taken at the highest point of the buttocks [26].

Comorbid conditions

Information pertaining to comorbidities was collected through self-report and careful review of medical charts including medication use.

Statistical analysis

Normality of data was ascertained using the KolmogorovSmirnov test. For the analysis, participants were categorized into two subgroups (i.e., low and high) for each physical function test (i.e., IHG, IHG/BMI, and WS at usual and fast pace). Data are presented as mean ± standard deviation (SD) or absolute numbers and percentages for continuous and categorical variables, respectively. Differences in continuous variables between groups were assessed via independent *t* test statistics. Comparisons of categorical variables were performed by Chi-square (χ^2) statistics. Pearson's correlations were used to explore relationships between results of the physical function tests and diet characteristics. For all tests, the level of significance was set at 5% ($p < 0.05$). All analyses were conducted using the IBM SPSS Statistics software, version 20.0 (IBM Corp., Armonk, NY, USA).

Results

Participant characteristics

Ninety people were recruited. The main characteristics of enrollees are shown in Table 1. The mean age was 68.0 ± 6.7 years (range 60–85 years), and 78 (87.0%) participants were women. The mean BMI was 29.3 ± 5.4 kg/ m^2. The average IHG (23.5 ± 8.4 kg) and WS at both usual (1.2 ± 0.4 m/s) and fast pace (1.5 ± 0.5 m/s) were higher than the proposed cutoffs for sarcopenia [27]. Participant diet was hierarchically composed of carbohydrates (56.6%),

protein (23.3%), and fat (20.5%). The average body weight-adjusted protein consumption was 1.1 ± 0.4 g kg^{-1} day^{-1}, which is higher than the RDA, with a predominance of plant-derived proteins over those of animal origin (53.4% vs. 40.3%).

Table 1. Main characteristics of study participants

Demographics and anthropometry	
Age, years (mean ± SD)	68.0 ± 6.7
Women, *n* (%)	78 (87.0)
Body weight, kg (mean ± SD)	72.0 ± 13.0
Height, m (mean ± SD)	1.60 ± 0.10
BMI, kg/m^2 (mean ± SD)	29.3 ± 5.4
WC, cm (mean ± SD)	97.6 ± 11.9
HC, cm (mean ± SD) *Physical function tests*	104.5 ± 10.8
Handgrip strength, kg (mean ± SD)	23.5 ± 8.4
Handgrip strength/BMI (mean ± SD)	0.8 ± 0.4
Usual walking speed, m/s (mean ± SD)	1.2 ± 0.4
Fast walking speed, m/s (mean ± SD) *Diet*	1.5 ± 0.5
Energy intake, kcal (mean ± SD)	1146 ± 146
Fat, % kcal	20.5
Carbohydrates, % kcal	56.6
Protein, % kcal	23.3
Animal protein, % total protein	40.3
Plant protein, % total protein	53.4
Protein, g d ay^{-1} (mean ± SD)	74.5 ± 26.0
Protein, g k g^{-1} day^{-1} (mean ± SD)	1.1 ± 0.4
Animal protein, g d ay^{-1} (mean ± SD)	31.3 ± 16.6
Plant protein, g d ay^{-1} (mean ± SD)	39.4 ± 16.6
Leucine, mg day^{-1} (mean ± SD)	4627 ± 2127
Isoleucine, mg day^{-1} (mean ± SD)	2511 ± 1142
Valine, mg day^{-1} (mean ± SD)	2860 ± 1298

BMI body mass index, *HC* hip circumference, *WC* waist circumference

Participant characteristics and diet parameters according to physical function

Table 2 shows participant characteristics according to categories of physical performance. Overall, participants with high physical performance were younger than those with low performance. The high IHG subgroup showed greater BMI and HC than the low IHG subgroup. Similarly, body circumferences were significantly greater in the high fast WS subgroup than in the low WS subgroup.

As for diet characteristics, specific patterns were observed between groups. Participants with high IHG/BMI showed lower relative carbohydrate consumption than those with low IHG/BMI. In contrast, higher relative protein consumption was observed in the high usual WS subgroup compared with the low usual WS counterpart. There were no differences in relative protein consumption between high and low fast WS subgroups. However, participants with high fast WS showed lower consumption of animal protein and higher consumption of plant protein.

Table 2. Characteristics of study participants according to physical function categories.

	IHG		IHG/BMI		Usual WS		Fast WS	
	Low (< 25 kg)	High (≥ 25 kg)	Low (< 0.82 kg)	High (≥ 0.82 kg)	Low (< 1.3 m/s)	High (≥ 1.3 m/s)	Low (< 1.6 m/s)	High (≥ 1.6 m/s)
Demographics and anthropometry								
Age, years (mean ± SD)	69.7 ± 7.5		66.4 ± 5.5*	70.0 ± 7.6	66.1 ± 5.2*	70.9 ± 7.4	65.3 ± 4.6*	71.5 ± 7.6	65.5 ± 4.6*
Women, *n* (%)	36 (85.8)		41 (87.3)	38 (86.1)	39 (86.7)	41 (82.5)	37 (89.6)	44 (80.0)	32 (90.6)
Body weight, kg (mean ± SD)	70.3 ± 13.5		73.5 ± 12.5	72.6 ± 14.0	71.6 ± 12.1	69.9 ± 14.3	73.2 ± 11.4	69.4 ± 13.3	73.2 ± 12.5
BMI, kg/m^2 (mean ± SD)	28.3 ± 5.3		30.1 ± 5.4*	29.4 ± 6.8	29.2 ± 4.4	28.8 ± 5.9	29.4 ± 4.8	28.3 ± 5.9	29.6 ± 4.9
WC, cm (mean ± SD)	96.3 ± 14.5		98.8 ± 9.0	98.9 ± 13.7	96.7 ± 9.9	96.7 ± 14.1	98.3 ± 9.9	93.1 ± 10.8	100.5 ± 11.8*
HC, cm (mean ± SD)	101.6 ± 12.1		107.1 ± 8.7*	104.9 ± 12.0	104.2 ± 9.6	102.0 ± 11.2	106.1 ± 9.9	101.3 ± 10.7	106.2 ± 10.2*
Physical functional tests									
Handgrip strength, kg (mean ± SD)	9.7 ± 8.4		28.6 ± 4.8*	10.6 ± 9.5	28.4 ± 5.2*	17.9 ± 10.6	20.6 ± 12.4	18.7 ± 11.3	19.9 ± 11.9
Handgrip strength/ BMI, kg (mean ± SD)	0.4 ± 0.3		1.0 ± 0.2*	0.3 ± 0.3	1.0 ± 0.2*	0.62 ± 0.36	0.70 ± 0.43	0.6 ± 3.9	0.6 ± 4.1
Usual walking speed, m/s (mean ± SD)	1.0 ± 0.5		1.1 ± 0.6	1.0 ± 0.5	1.1 ± 0.6	0.56 ± 0.43	1.46 ± 0.23*	0.5 ± 0.5	1.3 ± 0.2*
Fast walking speed, m/s (mean ± SD)	1.3 ± 0.6		1.3 ± 0.8	1.3 ± 0.6	1.3 ± 0.7	0.77 ± 0.64	1.77 ± 0.27*	0.6 ± 0.5	1.7 ± 0.2*
Diet									
Energy intake, kcal (mean ± SD)	1294 ± 417		1136 ± 161	1152 ± 164	1136 ± 161	1238 ± 279	1316 ± 439	1241 ± 249	1307 ± 439
Fat, % kcal	19.4		21.4	20.9	20.1	19.4	20.9	19.5	20.7

Carbohydrates, % kcal	58.2	55.1*	57.3	55.9	58.1	55.7	56.9	56.7
Protein, % kcal	23.0	23.5	22.5	23.9	22.3	23.9*	23.4	23.0
Animal protein, % protein	41.7	39.0	41.2	39.1	41.6	38.4	45.6	36.2*
Plant protein, % protein	55.0	52.0	53.3	53.6	53.4	54.1	49.7	56.4*
Protein, g day^{-1} (mean ± SD)	73.5 ± 23.0	75.4 ± 28.7	68.9 ± 21.0	79.2 ± 29.2	70.6 ± 25.5	77.7 ± 26.4	73.5 ± 23.2	75.2 ± 28.0
Protein, g kg^{-1} day^{-1} (mean ± SD)	1.1 ± 0.4	1.0 ± 0.4	0.9 ± 0.3	1.1 ± 0.4	1.0 ± 0.4	1.0 ± 0.3	1.1 ± 0.4	1.0 ± 0.3
Animal protein, g day^{-1} (mean ± SD)	31.5 ± 16.1	30.4 ± 17.7	28.9 ± 14.6	32.2 ± 18.5	30.8 ± 16.0	30.5 ± 17.6	34.3 ± 14.9	28.3 ± 17.7
Plant protein, g day^{-1} (mean ± SD)	39.4 ± 12.7	39.3 ± 19.6	36.2 ± 13.6	42.1 ± 18.8	37.3 ± 16.2	41.5 ± 16.4	36.6 ± 15.4	41.6 ± 16.8

Table 2 (continued)

	IHG		IHG/BMI		Usual WS		Fast WS	
	Low (< 25 kg)	High (≥ 25 kg)	Low (< 0.82 kg)	High (≥ 0.82 kg)	Low (< 1.3 m/s)	High (≥ 1.3 m/s)	Low (< 1.6 m/s)	High (≥ 1.6 m/s)
Leucine, mg day^{-1} (mean ± SD)	4817 ± 1749	4453 ± 2427	4400 ± 1722	4773 ± 2432	4653 ± 2162	4614 ± 2141	4785 ± 2051	4533 ± 2206
Isoleucine, mg day^{-1} (mean ± SD)	2620 ± 250	2411 ± 1295	2388 ± 932	2593 ± 1310	2527 ± 1159	2501 ± 1151	2609 ± 1106	2450 ± 1181
Valine, mg day^{-1} (mean ± SD)	2981 ± 1088	2748 ± 1467	2717 ± 1046	2956 ± 1492	2875 ± 1312	2847 ± 1313	2965 ± 1249	2791 ± 1347

BMI body mass index, *HC* hip circumference, *IHG* isometric handgrip strength, *WC* waist circumference, *WS* walking speed test. *$p < 0.05$ vs. low

Relationship between physical function and diet characteristics

Pearson's correlations were performed to explore the relationship between age, diet composition, and performance tests (Table 3). Age was negatively associated with both usual and fast WS. IHG/BMI was negatively correlated with relative carbohydrate consumption and positively correlated with body weight-adjusted protein consumption. A positive correlation was also observed between relative protein consumption and usual WS. Finally, fast WS was negatively correlated with relative animal protein intake and positively correlated with consumption of plant-based protein.

Table 3. Relationship between dietary factors and results of physical tests as assessed by Pearson's correlation.

	IHG	IHG/BMI	Usual WS	Fast WS
Age, years	− 0.18	− 0.14	− 0.35**	− 0.38**
Energy intake, kcal	− 0.001	0.04	0.11	0.03
Fat, % kcal	0.10	0.04	0.06	0.02
Carbohydrates, % kcal	− 0.30	− 0.27*	− 0.13	− 0.05
Protein, % kcal	0.17	0.20	0.13*	0.06
Animal protein, % protein	0.06	0.04	− 0.16	− 0.18*
Plant protein, % protein	− 0.20	− 0.16	0.10	0.15*
Protein, g day^{-1}	0.12	0.17	0.16	0.04
Protein, g kg^{-1} day^{-1}	0.07	0.21*	0.09	− 0.08
Animal protein, g day^{-1}	0.12	0.13	− 0.02	− 0.10
Plant protein, g day^{-1}	− 0.02	0.05	0.20	0.12
Leucine, mg day^{-1}	0.04	0.07	0.03	− 0.04
Isoleucine, mg day^{-1}	0.03	0.07	0.03	− 0.04
Valine, mg day^{-1}	0.04	0.07	0.03	− 0.04

BMI body mass index, *HC* hip circumference, *WC* waist circumference, *WS* walking speed *$p < 0.05$, **$p < 0.01$

Discussion

The present study investigated the association between dietary factors and physical performance in a sample of well-functioning older community dwellers. Our analyses revealed that upper-limb muscle strength was positively associated with body weight-adjusted protein consumption and negatively associated with relative carbohydrate consumption. In addition, high relative protein consumption was associated with faster usual WS. Finally, fast WS was negatively correlated with relative animal protein ingestion and positively correlated with relative plant protein intake.

In keeping with the present study, Gregório et al. [28] found that postmenopausal women who consumed dietary protein above the RDA performed better in the one-leg stand and the short physical performance battery than those reporting a protein intake below the RDA. Similarly, Isanejad et al. [29] found that older women who consumed ≥ 1.2 g kg^{-1} day^{-1} of protein had better performance in IHG, knee extension, one-leg stand, and chair rise tests. While WS was found to be positively associated with relative protein intake, no significant correlations were determined between body weight-adjusted protein consumption and gait speed at either usual or fast pace (Table 3). Noticeably, prospective studies showed that older adults with higher protein intake at baseline experienced milder decline in muscle strength over

the follow-up, with no impact on mobility [29, 30]. Taken together, these findings suggest that protein consumption might be associated with muscle strength, but not mobility. It may be hypothesized that the loss of muscle mass might have a greater impact on muscle strength [31, 32] than on muscle function [32], which instead relies on multiple organ systems (e.g., central and peripheral nervous system, cardiovascular system, respiratory system) [4]. Hence, a greater protein consumption may increase the availability of essential amino acids (EAAs), thereby stimulating MPS and overcoming anabolic resistance [14, 15]. Other cross-sectional studies and meta-analyses observed that mobility (e.g., WS), but not muscle strength was associated with protein consumption [16, 28]. These discrepancies may derive from differences in physical activity levels [33] and methods used to assess muscle mass [34].

Our analyses showed that relative protein consumption was associated with usual WS, while fast WS was negatively correlated with relative animal protein intake and positively related to plant-based protein ingestion. These findings suggest that different measures of protein intake are associated with specific components of physical function. Future studies are warranted to conclusively establish the relationship between various measures of protein consumption and domains of physical performance to refine dietary recommendations for older adults.

Animal-derived foods are regarded as a source of highquality protein enriched with EAAs readily available for MPS [35, 36]. Several studies have demonstrated that a high animal protein consumption is associated with lean body mass [15, 35–37] and upper-limb muscle strength in older adults [15, 38]. In contrast, higher ingestion of plant-derived protein has been related with lower skeletal muscle index [36] and IHG in older people [38]. No association between protein sources and muscle strength was observed in our sample. Indeed, physical performance in fast WS was better in participants with higher vegetable protein consumption.

A possible explanation for these findings may reside in the fact that our sample of Brazilian older adults showed higher absolute (0.39 g day^{-1}) and relative (53.4%) plant protein consumption than that reported in other studies [36, 38]. Specifically, a twofold greater intake was observed relative to the Framingham study [38]. It should also be considered that a saturable dose–response relationship between the amount of protein ingested per meal and MPS rate has been determined in healthy older adults, such that MPS becomes maximally stimulated by 0.4 g of protein per kg of body weight per meal [39]. Although the main concern regarding

plant-based protein is associated with its low quality [36, 37], it is suggested that the co-ingestion of protein from foods such as soy, bean and nuts, could provide the quantity of EAAs requested for muscle homeostasis [36].

Albeit dealing with a highly relevant subject, our study presents some limitations that need to be discussed. First, the results shown in this work derive from cross-sectional observations. The possibility cannot be ruled out that differences in birth cohort might have influenced some of the assessed parameters. For the same reason, reverse causality between dietary patterns and physical performance cannot be excluded. Indeed, it is possible that dietary choices were somewhat influenced by the level of physical function rather than vice versa. In addition, since enrollees were recruited on a voluntary basis, it is possible that those who accepted to participate were more engaged in their health management than those who declined. Therefore, future studies adopting probabilistic random sampling are needed to rule out such a potential source of bias. The relatively small number of participants, the lack of power calculation, diet evaluation through the 24-h recall diary, and the lack of direct measures of body composition should also be acknowledged as limitations of the study. Furthermore, neither objectively measured nor self-reported physical activity throughout the life course was collected. Hence, the impact of physical activity on functional tests and dietary choices could not be established. Finally, in older adults, protein intake distribution has shown to impact physical performance more than the amount of protein ingested throughout the day [33]. Because of the small sample size, the pattern of protein ingestion according to food sources could not be analyzed. Future investigations should clarify whether the distribution of protein intake from different sources has an impact on physical performance in old age.

Conclusions

Findings from the present study indicate that physical performance is associated with dietary factors in well-functioning older community dwellers. Based on our analyses, different measures of protein intake are associated with specific components of physical function. Specifically, body weight adjusted protein consumption was correlated with upper limb muscle strength and relative protein consumption was positively associated with usual WS. In addition, our findings add new evidence to the relationship between protein sources and physical function, since fast WS was negatively correlated with relative animal protein

consumption and positively correlated with relative plant protein intake. Future interventional studies are needed to establish the optimal blend of protein sources to support physical performance in old age.

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Data availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest: The authors declare that they have no conflict of interest.

Statement of human and animal rights: All procedures performed in the present study were approved by the Research Ethics Committee of the University of Mogi das Cruzes (UMC) under the protocol number 621-614 and were conducted in compliance with the Declaration of Helsinki and the Resolution 196/96 of the National Health Council.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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The physical capabilities underlying timed "Up and Go" test are timedependent in community-dwelling older women

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ARTICLEINFO ABSTRACT

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Timed 'Up and Go' (TUG) has been widely used in research and clinical practice to evaluate physical function and mobility in older adults. However, the physical capabilities underlying TUG performance are not well elucidated. Therefore, the present study aimed at investigating a selection of physical capacities underlying TUG performance in community-dwelling older women. Four hundred and sixty-eight apparently healthy older women independent to perform the activities of daily living (mean age: 65.8 ± 6.0 years) were recruited from two specialized healthcare centers for older adults to participate in the study. Volunteers had their medical books reviewed and underwent evaluations of anthropometric data as well as physical and functional capacities. Pearson's correlation results indicate that TUG performance was significantly associated with upper (i.e., handgrip strength) and lower (i.e., sit-to-stand) limb muscle strength, balance (i.e., one-leg stand), lower limb muscle power (i.e., countermovement jump), aerobic capacity (i.e., 6-minute walk test), and mobility (i.e., usual and maximal walking speeds). When the analyses were performed based on TUG quartiles, a larger number of physical capabilities were associated with TUG > 75% in comparison with TUG < 25%. Multiple linear regression results indicate that the variability in TUG (~20%) was explained by lower limb muscle strength (13%) and power (1%), balance (4%), mobility (2%), and aerobic capacity (< 1%), even after adjusted by age and age plus body mass index (BMI). However, when TUG results were added as quartiles, a decrease in the impact of physical capacities on TUG performance was determined. As a whole, our findings indicate that the contribution of physical capabilities to TUG performance is altered according to the time taken to perform the test, so that older women in the lower quartiles — indicating a higher performance — have an important contribution of lower limb muscle strength, while volunteers in the highest quartile demonstrate a decreased dependence on lower limb muscle strength and an increased contribution of other physical capabilities, such as lower limb muscle power and balance.

Abbreviations: ADLs, activities of daily living; BMI, body mass index; DP, double product; GUG, get up and go; HC, hip circumference; iTUG, instrumented TUG; MAP, mean arterial pressure; NC, neck circumference; ANOVA, one-way analysis of variance; 6MWT, six-minute walk test; TUG, timed 'Up and Go'; UMC, University of Mogi das Cruzes; WC, waist circumference

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Introduction

The aging process is accompanied by several alterations in the neuromuscular apparatus (Deschenes, 2004), causing among others a significant decrease in strength and power generation (Lauretani et al., 2003). The ultimate consequence of such a deterioration is the progressive decrease of the ability to perform activities of daily living (ADLs) and loss of independence (Millan-Calenti et al., 2010; Vermeulen et al., 2011).

In this sense, a number of tools have been developed to objectively measure physical function and mobility in older adults with the aim of identifying people at risk of negative health events and assessing the

effectiveness of therapeutic interventions. Among the available tools, the timed 'Up and Go' (TUG) test has shown to be reliable, inexpensive, and easy and quick to perform tool, repeatedly validated in several populations (Barry et al., 2014; Benavent-Caballer et al., 2016; Bischoff et al., 2003; Bohannon, 2006; Kamide et al., 2011; Lorefice et al., 2017; Podsiadlo and Richardson, 1991; Pondal and del Ser, 2008; Zarzeczny et al., 2017).

TUG was developed by Podsiadlo and Richardson (Podsiadlo and Richardson, 1991) as a modified version of the "Get-up and go" (GUG) test. The main concern of the researchers regarding the GUG test was the absence of a direct evaluation of the test scores, once the results were based on the observer's perception of the patient's risk of falling. In their updated version, Podsiadlo and Richardson maintained the test protocol, which consists of, on the word "go", get up from a chair, walk 3 m at a comfortable and safe pace, turn, return to the chair, and sit down again. However, the score given was based in the time taken to complete the test. When the authors tested the validity of TUG (Podsiadlo and Richardson, 1991), results demonstrated that TUG scores were significantly correlated with balance, gait speed, and functional capacity in frail older adults, indicating that this test may be a useful clinical tool to evaluate basic mobility skills.

In the last years, several evidence have expanded the initial knowledge about TUG, demonstrating that TUG scores are associated with risk of falls (Alexandre et al., 2012; Rydwik et al., 2011; ShumwayCook et al., 2000; Viccaro et al., 2011), hospitalization (Viccaro et al., 2011), nursing home placement (Nikolaus et al., 1996), health status (Viccaro et al., 2011), capacity to perform the ADLs (Rydwik et al., 2011; Viccaro et al., 2011), physical function (van Iersel et al., 2008; Rydwik et al., 2011; Viccaro et al., 2011), and some cognitive domains (e.g.,

executive function) (Donoghue et al., 2012). In addition, modified versions (i.e., rising from the chair without using hands, walk at maximum pace) have been proposed to contemplate its usefulness in different groups (Barry et al., 2014; Kamide et al., 2011; Rydwik et al., 2011), as well as reference values have been suggested to different populations (Alexandre et al., 2012; Bischoff et al., 2003; Bohannon, 2006; Kamide et al., 2011; Kojima et al., 2015; Rydwik et al., 2011). Lastly, is important to mention that changes on TUG scores are used to verify the effectiveness of physical exercise programs (Coelho Junior et al., 2017a).

Regarding physical function, — pragmatically — authors have proposed that TUG performance basically reflects the balance and gait skills, which is a product of the seminal study published by Podsiadlo and Richardson (1991). However, recent evidence have suggested that the physical capacities underlying TUG performance are sample-dependent (Benavent-Caballer et al., 2016; Zarzeczny et al., 2017).

Studying a sample composed of a mixture of community-dwelling and institutionalized older adults, for example, Benavent-Caballer et al. (Benavent-Caballer et al., 2016) confirmed the importance of functional balance (i.e., evaluated by Berg Balance Scale) in TUG performance. On the other hand, findings from Zarzeczny et al., (2017) indicate that the results of 30-s chair stand test and 6-minute walk test were significantly correlated with TUG performance in very old volunteers (> 80 years). This view is supported by Nur et al., (2017) who showed that muscle strength was central to TUG performance in patients with knee osteoarthritis.

The aforementioned mentioned studies indicate that several physical capabilities may be associated with TUG performance, and, therefore, indicate that this test is only dependent on balance and gait seems to be a very simplistic view. Despite the interesting results from these studies, experiments were performed in small sample sizes, composed of a mixture of different populations, and using a limited number of evaluations. To overcome such a limitation, the current study was designed to investigate the contribution of a selection of different physical capabilities to the variability of TUG in a large sample of apparently healthy community-dwelling older women.

Materials and methods

This study had a cross-sectional design and was approved by the Research Ethics Committee of the University of Mogi das Cruzes (UMC) under the protocol number 621–614 and was conducted in accordance with the Declaration of Helsinki and with Resolution 196/96 of the National Health Council. Experiments were developed in the city of Poá, state of São Paulo, Brazil, starting in January 2015 and ending in November 2015.

Study participants

The study participants were recruited from two specialized healthcare centers for older adults in a town located in the metropolitan area of São Paulo, Brazil. Volunteers were recruited by convenience and asked verbally by the medical team and researchers about their willingness to take part in the study. All participants were apparently healthy and provided informed consent before enrolment.

The participants were identified as apparently healthy according to the capacity to perform the ADL, walking without the aid of assistive devices, and the absence of disease likely to impact physical function.

Participants were eligible to participate in the present study if they had age ≥ 60 years, were community-dwelling older women, showed independence to perform the ADL according to Katz Index (6 points) (Shelkey and Wallace, 1999), and did not present clinical signs of cognitive impairment, since they scored higher than the cutoff points adjusted for schooling on the Mini-Mental State Examination (MMSE) (Herrera Jr et al., 2002).

Exclusion criteria were as follows: nursing home residence, missing values, taking hormone replacement and/or psychotropic drugs, cerebrovascular disease, pulmonary diseases with respiratory insufficiency (e.g., chronic obstructive pulmonary disease), neurological or psychiatric diseases, musculoskeletal disorders, complaints of any kind of dizziness, blurred vision or lightheadedness when rising or standing for long time, indicative of orthostatic hypotension and/or vestibular disorders. The presence of hypertension (HTN), type II diabetes mellitus (T2DM), arthritis, cardiovascular diseases (CVD) and osteoporosis was not considered an exclusion criterion provided that the clinical symptoms were pharmacologically controlled. The evaluations regarding the exclusion criteria, and the clinical and pharmacological control of the abovementioned diseases was performed by a physician and a certified nurse.

After the application of the exclusion and inclusion criteria, 468 older women were included in the analyses (Fig. 1).

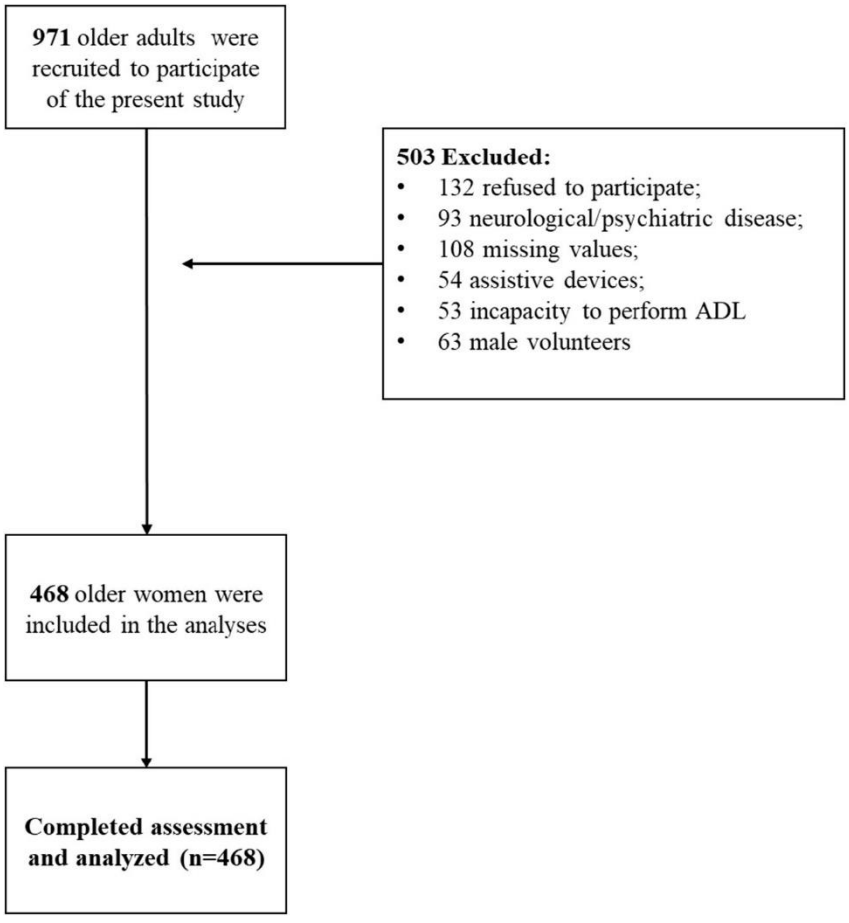

Fig. 1. Flow diagram of the sample selection process.

Functional assessments

Two experienced researchers applied each test. While one was responsible for detailing the operational procedures, demonstrate the test before the evaluation, quantify the evaluation time and evaluate the motor gesture; the other, ensured the safety of the participant. After the end of the explanation and before the start of the tests, volunteers performed a familiarization trial to ensure the understanding of the test. Then, the volunteers performed all tests twice (except for the six-minute walk test), and the best result obtained in each test was used in the analysis. The tests were distributed in a room as stations, and were performed in a circuited fashion one after the other. A one-minute interval between trials was provided. During

all tests, verbal encouragement was provided to ensure that volunteers achieved the best possible performance without compromising safety. During TUG, walking speed test at maximal pace, and sit-to-stand tests researchers provided stimulus such as: Come on, faster!; A little more!; and; Lets go! During OLS, verbal encouragement was provided to keep the participant focused on the test. Therefore, the volunteers were stimulated with the sentences: Focus! Keep your posture!; Very good!. During handgrip test, the researchers repeatedly used the sentences: as much force as possible!; Lest go!; and more strength! For the countermovement jump test, verbal encouragement was only provided before the test, with the sentence: Jump as high as you can using all your strength! Regarding Six-minute walk test, researchers told the volunteers that they were close to finalizing the test (i.e., Come on! Force! There is little left!). The protocol used in this study has been used by our group elsewhere (Coelho Junior et al., 2015, 2016; Coelho Junior et al., 2017b).

TUG test

The TUG test involves getting up from a chair (total height: 87 cm; seat height: 45 cm; width: 33 cm;), walking three meters around a marker placed on the floor, coming back to the same position, and sitting back on the chair. The subjects started the test wore their regular footwear, with their back against the chair, arms resting on the chair's arms, and with the feet in contact with the ground. A researcher instructed the volunteers to, on the word ‘go’, get up and walk as fast as possible without compromising safety in the demarcation of three meters on the ground, turn, returns to the chair, and sit down again. Timing was started when the volunteer got up from the chair and was stopped when the participant's back touches the backrest of the chair (Podsiadlo and Richardson, 1991). A stopwatch (1/100 s accuracy) was used for time evaluation, and a longer time taken to perform the test indicates a lower performance.

Participants were divided into quartiles based on TUG performance:
TUG quartiles: < 25% ≤6.07 s; 25%–50% = 6.07 s–6.81 s; 50%–75% = 6.82 s–7.65 s; > 75%≥ 7.65 s. The main reason to choose this approach is because there is no standard cutoff for apparently health Brazilian older adults, so that the use of any suggested cutoff to divide our sample could be associated with a great risk of bias. Therefore, quartiles seem to be the best approach since volunteers are allocated in the subgroups according to results of the whole sample.

Handgrip strength

The handgrip strength was measured using a Jamar® (USA) dynamometer while the participants remained seated in a chair with the shoulders abducted, elbows near the trunk and flexed at 90°, and wrists in a neutral position (thumbs up). The contralateral arm remained relaxed under the thigh. To determine handgrip strength, the volunteers performed a maximal contraction during 4 s with the dominant hand (Mathiowetz et al., 1984). To determine the dominant hand, the volunteers were asked which of the hands was the strongest. Results were recorded in kgf.

One-leg stand test

The one-leg stand test was performed with the volunteers standing in a unipodal stance with the dominant lower limb, the contralateral knee remaining flexed at 90°, the arms folded across the chest, and the head straight. A stopwatch was activated when the volunteer raised their foot off the floor and was stopped when the foot touched the floor again. The maximum performance time was up to 30 s, considered the best test result (Vellas et al., 1997).

Sit-to-stand test

Volunteers were requested to rise from a chair five times as quick as possible with. arms folded across the chest. The stopwatch was activated when the volunteer raised their buttocks off the chair and was stopped when the volunteer seated back at the end of the fifth stand (Guralnik et al., 1994).

Walking speed test

Walking speed was measured over three meters. This distance was chosen due to space limitations (Middleton et al., 2016). It is worth to mentioning, that a high concordance has been observed between the results recorded after 3-meter and 6-meter courses (Lyons et al., 2015). In the test, volunteers were required to walk five meters at their usual and fastest possible cadences (without running). Before the evaluation, both feet of each volunteer were to remain on the starting line. The measurement was started when a foot reached the one-meter line and was stopped when a foot reached the four-meter line. The one-meter intervals at the beginning

and at the end of the course were used to avoid early acceleration and/or deceleration (Lyons et al., 2015).

Countermovement jump

The countermovement jump was performed to evaluate lower limb muscle power. In the initial position, the volunteers stood on a jump platform (Jump System Pro, Cefise, Brazil), their feet remained approximately parallel at shoulder width, and their hands rested on their hips. When instructed, the volunteers flexed their knees at approximately 90° and jumped the maximum height possible. The maximum height was adopted and expressed in centimeters (cm) (RamírezCampillo et al., 2014).

6-minute walk test (6MWT)

The 6-minute walk test was performed according to the American Thoracic Society guidelines (2002) (Enright, 2003). The test was performed indoors on a 30-meter track. Briefly, after remaining seated for 15 min, the volunteers were asked to walk on the track as fast as possible for 6 min. In the case the volunteers experienced chest pain, substantial dyspnea, leg cramps, stagger, diaphoresis, pale or ashen appearance, or any other complaint, the test was interrupted. The distance walked by the volunteers in meters was used in the analysis.

Anthropometric measurements

A weight scale with a Filizola® (Brazil) stadiometer was used to measure body mass (kg) and height (cm). The body mass index (BMI) was determined by using the formula body mass (kg)/height (m^2). An anthropometric tape (flexible and inextensible) (Sanny®, Brazil) was used to obtain all measurements (i.e., waist circumference [WC], hip circumference [HC], and neck circumference [NC]). Participants remained in a standing position, head held erect, eyes forward, with the arms relaxed at the side of the body, feet kept together, wearing light clothes. The WC was assessed at the mid-point between the last floating rib and the highest point of the iliac crest. HC was evaluated at the highest point of the buttocks. NC was measured right above the cricoid cartilage and perpendicular to the long axis of the neck (Coelho Junior et al., 2016).

Evaluation of hemodynamic parameters at rest

The procedures for measurement of blood pressure were adapted from the VII Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) (Chobanian et al., 2003). All procedures occurred in the morning

(08:30 am–10:30 am). In summary, volunteers remained in a sitting position on a comfortable chair for 15 min in a quiet room. Afterwards, an appropriate cuff was placed at approximately the midpoint of the upper left arm (heart level). An automatic, noninvasive and validated arterial blood pressure monitor (Microlife-BP 3BT0A, Microlife, Widnau, Switzerland) was used to measure systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) (Cuckson et al., 2002). During blood pressure recording, volunteers remained relaxed in the sitting position, with parallel feet at shoulder width, both forearm and hands on the table, supinated hands, back against the chair, without move or talk. The volunteer did not have access to blood pressure values during measurement. The evaluation lasted approximately 80 s and was performed three times with one-minute interval between the measurements. The mean value was used in the analysis. Mean arterial pressure (MAP) and double product (DP) were calculated according to the following equations:

$$MAP = [SBP + (2 * DBP)]/3 \quad (1)$$

$$DP = SBP\ HR * . \quad (2)$$

Statistical analysis

Normality of data was tested using the Kolmogorov-Smirnov test. To determine the differences in continuous and categorical data among groups (i.e., TUG quartiles: < 25% ≤6.07 s; 25%–50% = 6.07 s–6.81 s; 50%–75% = 6.82 s–7.65 s; > 75%≥ 7.65 s), one-way analysis of variance (ANOVA) followed by Dunnett's posthoc test and the chi-square (Lauretani et al., 2003) test were performed, respectively. Pearson's correlation was used to explore correlations between continuous variables and TUG performance. Multiple linear regression was applied to examine how the variability in TUG performance could be explained by physical capacities (i.e., muscle strength [sit-to-stand and handgrip strength] and power [countermovement jump], ambulation [usual and maximal walking speeds], balance [one-leg stand], aerobic capacity [6MWT]). The level of significance was 5% ($p < 0.05$) and all analyses were conducted using

the IBM SPSS Statistics, version 20.0, software (IBM Corp., Armonk, NY, USA). Data are presented as mean ± standard deviation (SD).

Results

The final study sample included 468 older women. Table 1 shows the general characteristics of the study population. Volunteers showed a normal to overweight BMI classification (28 kg/m^2) according to cutoff values for older adults (Corona et al., 2014), while an elevated cardiovascular risk was indicated based on circumferences evaluation (WC, HC, and NC). HTN was the most prevalent morbidity (59.0%), followed by osteoarthritis (31.2%), osteoporosis (26.3%), T2DM (18.2%), and CVD (4.7%).

BMI = body mass index; WC = waist circumference; HC = hip circumference; NC = neck circumference; TUG = timed up and go; 6MWT = 6-minute walk test; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; HR = Heart rate; HTN = hypertension; T2DM = type 2 diabetes mellitus; CVD = cardiovascular disease.

Table 1. Characteristics of older women.

Variables	Total (n = 468)	Minimum-Maximum
Anthropometric characteristics		
Age (years)	65.8 ± 6.0	60–89
Weight (kg)	69.7 ± 13.2	35.5–122.0
Height (m)	1.57 ± 0.02	1.00–1.93
BMI (kg/m^2)	28.0 ± 5.0	16.2–45.7
WC (cm)	97.0 ± 12.8	50–136
HC (cm)	104.7 ± 11.1	56–144
NC (cm)	36.3 ± 3.3	30–58
Physical functional tests		
TUG (s)	7.0 ± 1.3	4.6–14.3
Handgrip strength (kgf)	23.6 ± 5.0	6.7–42.0
One-leg stand (s)	15.2 ± 12.7	0–30
Sit-to-stand (s)	10.8 ± 2.3	5.2–25.1
Usual walking speed (m/s)	1.2 ± 0.2	0.47–2.94
Maximal walking speed (m/s)	1.7 ± 0.4	0.45–3.09
Countermovement jump (cm)	11.2 ± 7.9	0–108
6MWT (m)	580.9 ± 141.6	72–2.560
Hemodynamic parameters		
SBP (mm Hg)	135.1 ± 61.7	89–194
DBP (mm Hg)	77.1 ± 10.6	53–144
MAP (mm Hg)	96.5 ± 11.6	68.3–160.7
HR (bpm)	77.0 ± 11.3	51–119
Disease prevalence		
HTN(%)	59.0	–
Osteoarthritis (%)	31.2	–
Osteoporosis (%)	26.3	–
T2DM(%)	18.2	–
CVD (%)	4.7	–

The main characteristics of study participants according to TUG quartiles are shown in Table 2. Age increased across TUG quartiles, with participants in the last quartile were older than volunteers of all other subgroups. With regard to anthropometry, TUG > 75% showed an obesity classification according to BMI, as well as an elevated cardiovascular risk as defined by WC, HC and NC. A similar pattern was observed in TUG 25–50% and TUG 50–75%, but not in TUG < 25%. Hypothesis test indicated that BMI and WC were higher in TUG > 75% and TUG 50–75% comparing to TUG < 25%. A reduced performance on all physical functional tests was observed in TUG > 75% compared with TUG < 25%, TUG 25–50%, and TUG 50–75%. As expected, physical performance was reduced according to TUG quartiles. Indeed, TUG 50–75% showed a lower performance in one-leg stand, sit-tostand, usual and maximal walking speeds, and 6MWT tests in comparison to TUG < 25% and TUG 25–50% (only for one-leg stand test).

Table 2. Characteristics of older women according to TUG.

Total (n = 468)							
Variables	< 25%	Minimum-Maximum	25%–50%	Minimum-Maximum	50%–75%	Minimum-Maximum	> 75% Minimum-Maximum
	(n = 117)		(n = 117)		(n = 117)		(n = 117)
Anthropometric characteristics							
Age (years)	63.3 ± 4.4	60–81	64.4 ± 4.5	60–76	66.0 ± 5.7[a]	60–88	69.4 ± 7.1[a,b,c]
Weight (kg)	67.3 ± 12.7	38.8–108.3	69.8 ± 11.4	44.7–113.8	70.3 ± 14.0	35.5–109.4	71.0 ± 14.4
Height (m)	1.58 ± 0.08	1.0–1.93	1.57 ± 0.06	1.37–1.75	1.57 ± 0.07	1.41–1.82	1.56 ± 0.06
BMI (kg/m^2)	26.7 ± 4.8	16.2–43.3	28.3 ± 4.5	20.4–45.7	28.6 ± 4.8[a]	17.3–42.1	29.1 ± 5.3[a]
WC (cm)	92.5 ± 12.0	63–128	96.7 ± 11.6	68–129	98.2 ± 13.3[a]	50–133	100.6 ± 13.1[a]
HC (cm)	103.4 ± 10.4	81–144	104.9 ± 10.1	69–133	104.9 ± 12.3	56–135	105.4 ± 11.3
NC (cm)	36.0 ± 2.9	30–46	36.6 ± 3.8	30–58	36.4 ± 3.2	30–47	36.4 ± 3.1
Physical functional tests							
TUG (s)	5.6 ± 0.34	4.6–6.0	6.4 ± 0.19	6.1–6.8	7.1 ± 0.23	6.8–7.6	8.9 ± 1.1
Handgrip strength (kgf)	24.9 ± 4.7	9.4–42	24.1 ± 4.7	6.7–34.1	23.7 ± 5.2	12.5–41.5	21.6 ± 5.1[a,b,c]
One-leg stand (s)	20.7 ± 12.9	0–30	21.2 ± 11.3	0–30	12.9 ± 11.3[a,b]	0–30	6.6 ± 9.4[a,b,c]
Sit-to-stand (s)	9.5 ± 1.4	5.2–16.0	10.2 ± 1.6[a]	7.4–15.3	10.8 ± 1.9[a]	7.1–19.9	12.7 ± 2.8[a,b,c]
Usual walking speed (m/s)	1.36 ± 0.31	0.50–2.94	1.31 ± 0.29	0.60–2.66	1.24 ± 0.22[a]	0.58–2.11	1.10 ± 0.25[a,b,c]
Maximal walking speed (m/s)	1.97 ± 0.52	0.45–3.00	1.88 ± 0.41	0.77–3.09	1.75 ± 0.39[a]	0.77–3.00	1.46 ± 0.38[a,b,c]
Countermovement jump (cm)	13.9 ± 5.5	2.0–85.0	11.1 ± 3.8[a]	0–25.5	12.1 ± 12.1	3.4–108	7.6–3.8[a,b,c]
6MWT (m)	637.9 ± 130.7	211–1248	592.7 ± 203.8	384–2.560	573 ± 82.4[a]	352–960	499.5 ± 114.1[a,b,c]
Hemodynamic parameters							
SBP (mm Hg)	129.1 ± 18.0	90–182	132.5 ± 18.7	90–185	132.5 ± 18.1	96–192	136.5 ± 19.4[a]
DBP (mm Hg)	76.8 ± 11.1	52–112	77.2 ± 9.6	56–104	77.0 ± 10.0	57–103	77.0 ± 11.8
MAP (mm Hg)	94.1 ± 11.8	68.3–121.7	95.6 ± 11.2	70–131	95.5 ± 11.0	74.6–126.7	96.8 ± 12.4
HR (bpm)	76.9 ± 10.7	52–113	74.8 ± 10.3	55.0–102	77.6 ± 11.3	54–117	78.7 ± 12.7
Disease prevalence							
HTN (%)	47.9	–	53.8	–	59.8	–	74.4*
T2DM (%)	10.3	–	18.8	–	21.4	–	22.2

Arthritis (%)	27.4	–	28.2	–	30.8	–	38.5
CVD (%)	2.6	–	6.0	–	4.3	–	6.0
Osteoporosis (%)	21.4	–	26.5	–	29.1	–	28.2

BMI = body mass index; WC = waist circumference; HC = hip circumference; NC = neck circumference; TUG = timed up and go; 6MWT = 6-minute walk test; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; HR = Heart rate; HTN = hypertension; T2DM = type 2 diabetes mellitus; CVD = cardiovascular disease. [a] $P < 0.05$ vs < 25%. [b] $P < 0.05$ vs 25%–50%. [c] $P < 0.05$ vs 50%–75%. * $P < 0.05$ vs 25% (chi-square test).

Similar to TUG 50–75%, TUG 25–50% demonstrated worse results in the sit-to-stand and countermovement jump tests relative to TUG < 25%. Hemodynamic parameters indicated higher blood pressure levels in TUG > 75% compared with TUG < 25%. Lastly, TUG > 75% had a higher prevalence of HTN compared to TUG < 25%.

Table 3 depicts the Pearson's correlation between TUG and physical functional tests. In the total sample (n = 468), TUG was significantly correlated with handgrip strength (r = −0.24), sit-to-stand (r = 0.53), countermovement jump (r = −0.27), 6MWT (r = −0.36), and usual (r = −0.27) and maximal (r = −0.19) walking speeds. When the analyses were performed based on TUG quartiles, TUG < 25% was correlated with sit-to-stand (r = 0.46) and usual walking speed (r = −0.26), while TUG 25%–50% and TUG 50%–75% were only significantly correlated with sit-to-stand (r = 0.21 and 0.19, respectively). A greater number of correlations was found in the TUG > 75%. In fact, significant correlations were observed between TUG and sit-to-stand (r = 0.34), countermovement jump (r = −0.30), 6MWT (r = −0.23), and usual walking speed (r = −0.20).

Table 3. Pearson's correlation between TUG and physical capabilities.

Total (n = 468)

Variables	TUG_Total	TUG_ < 25%	TUG_25%–50%	TUG_50%–75%	TUG_ > 75%
Handgrip strength (kgf)	−0.242*	−0.045	0.150	−0.092	−0.039
One-leg stand (s)	−0.391*	0.170	−0.030	−0.023	−0.087
Sit-to-stand (s)	0.533*	0.464*	0.218*	0.196*	0.347*
Usual walking speed (m/s)	−0.271*	0.262*	0.031	−0.032	−0.201*
Maximal walking speed (m/s)	−0.195*	−0.035	−0.136	−0.136	−0.118
Countermovement jump (cm)	−0.270*	0.031	−0.218*	−0.031	−0.307*
6MWT (m)	−0.366*	0.139	−0.099	−0.039	−0.239*

TUG = timed up and go; 6MWT = 6-minute walk test. * $P < 0.05$.

Table 4 shows the results from multiple linear regression to predict TUG. Results indicate that the variability in TUG was explained by lower limb muscle strength (i.e., sit-to-stand; 13%), balance (i.e., oneleg stand; 4%), mobility (i.e., usual walking speed; 2%), lower limb muscle power (i.e., countermovement jump; 1%), and aerobic capacity (i.e., 6MWT; < 1%). When age (Model 2) and age plus BMI (Model 3) were added as independent variables, results became less remarkable but remained statically significant. However, when TUG results were added as quartiles (Model 4), a decrease in the impact of physical capacities on TUG performance was determined, as it may be observed for lower limb muscle strength (3%), lower limb muscle power (< 1%), usual walking speed (< 1%), and balance (< 1%).x′ The collaboration of aerobic capacity remained near 0%. The addition of age (Model 5) and age plus BMI (Model 6) as independent variables did not cause marked changes in the model.

Table 4. Results from multiple linear regression to predict TUG performance.

Dependent variable	Predictor variable	Unstandardized Beta	Standardized Beta	P	R∗	R2∗	Adjustated R^{2*}	sr^2
Model 1								
TUG	Sit-to-stand	0.235	0.398	0.001				0.13
	Countermovement jump	−0.019	−0.122	0.040				0.01
	One-leg stand	−0.026	−0.232	0.001				0.04
	6MWT	−0.001	−0.093	0.038				0.00
	Usual walking speed	−0.840	−0.165	0.001	0.654	0.428	0.416	0.02
Model 2								
TUG	Sit-to-stand	0.226	0.382	0.001				0.12
	Countermovement jump	−0.015	−0.097	0.017				0.00
	One-leg stand	−0.021	−0.187	0.001				0.03
	6MWT	−0.001	−0.088	0.039				0.00
	Usual walking speed	−0.550	−0.108	0.015				0.00
	Age	0.064	0.269	0.001	0.700	0.490	0.478	0.06
Model 3								
TUG	Sit-to-stand	0.226	0.383	0.001				0.12
	Countermovement jump	−0.014	−0.088	0.028				0.00
	One-leg stand	−0.020	−0.178	0.001				0.02
	Usual walking speed	−0.531	−0.104	0.018				0.00
	6MWT	−0.001	−0.084	0.045				0.00
	Age	0.068	0.287	0.001				0.06
	BMI	0.029	0.115	0.004	0.709	0.502	0.489	0.01
Model 4								
TUG	Sit-to-stand	0.130	0.220	0.001				0.03
	Countermovement jump	−0.007	−0.043	0.189				0.00
	One-leg stand	−0.007	−0.065	0.063				0.00
	Usual walking speed	−0.299	−0.059	0.102				0.00

	6MWT	−0.054	−0.020	0.593				0.00
	TUG Quartiles	2.023	0.623	0.001	0.815	0.664	0.656	0.23
Model 5								
TUG	Sit-to-stand	0.130	0.221	0.001				0.03
	Countermovement jump	−0.005	−0.032	0.313				0.00
	One-leg stand	−0.005	−0.046	0.173				0.00
	Usual walking speed	−0.146	−0.029	0.414				0.00
	6MWT	0.000	−0.018	0.598				0.00
	TUG Quartiles	1.894	0.584	0.001				0.19
	Age	0.041	0.174	0.001	0.830	0.689	0.681	0.02
Model 6								
TUG	Sit-to-stand	0.132	0.224	0.001				0.03
	Countermovement jump	−0.005	−0.029	0.355				0.00
	One-leg stand	−0.005	−0.045	0.185				0.00
	Usual walking speed	−0.144	−0.028	0.419				0.00
	6MWT	0.000	−0.017	0.605				0.00
	TUG Quartiles	1.864	0.574	0.001				0.18
	Age	0.044	0.184	0.001				0.02
	BMI	0.013	0.051	0.104	0.832	0.692	0.682	0.00

TUG = Timed up and go; 6MWT = 6 min walking test; BMI = body mass index; sr^2 = square of semipartial correlation. * Values for the model.

Discussion

Findings from the present study indicate that the contribution of physical capabilities to TUG performance is altered according to the time necessary to complete the test, so that older women in the lower quartiles — indicating higher performance — have an important contribution of muscle strength, while those in the highest quartile — indicating reduced performance — demonstrate a decreased dependence on muscle strength and an increased contribution of other physical capabilities, such as lower limb muscle power, balance, and aerobic capacity.

It is worth mentioning that our sample was composed of non-institutionalized older women, with total ADL independence, and able to walk without the use of assistive devices. A number of available normative values for TUG in clinical and nonclinical settings have been proposed in the last years, but they were typically developed in nonLatin American countries and the TUG was performed at a normal pace which limits the characterization of our sample in relation to these studies (Bohannon, 2006; Kamide et al., 2011; Pondal and del Ser, 2008).

Nevertheless, when the TUG values of the highest quartile group (8.9 ± 1.1 s) were compared with other studies it was possible observed that, although these values were characterized as weak in the current study, they were lower than those reported in patients with

hip fracture (35.9 s) (Kristensen et al., 2009), multiple sclerosis (14.02 s) (Lorefice et al., 2017), and Parkinson's disease (10.0 s) (Son et al., 2017): Similarly, values were lower than the proposed cut-offs (i.e., 10–19 s, 12 s, 12.6 s, 13.5 s) for impaired mobility, dependency to perform basic and extended ADL (e.g., chair transfers, climb stairs), and risk of falls (Barry et al., 2014; Bischoff et al., 2003; Kojima et al., 2015; Podsiadlo and Richardson, 1991), indicating that our volunteers showed a "healthy" status and may not represent the reality of many older adults.

In the current study, the association between lower limb muscle strength (i.e., sit-to-stand; 13%), balance (one-leg stand; 4%), and mobility (usual walking speed; 2%), explained a great variability in the TUG results (~19%). These data are supported by several evidence in the scientific literature which demonstrated that TUG performance is strongly determined by these variables (Benavent-Caballer et al., 2016; Jung and Yamasaki, 2016; Nur et al., 2017; Shimada et al., 2010; Zarzeczny et al., 2017).

Indeed — in an experiment similar to the present study — BenaventCaballer et al. (Benavent-Caballer et al., 2016) asked older adults to complete a battery of functional performance-based tests (e.g., handgrip strength, one-leg stand) to investigate the physical factors underlying TUG. These researchers observed that balance and lower limb muscle strength explained together 45.1% of the variation in TUG. However, the balance was the most significant factor explaining TUG performance.

It should be stressed that Benavent-Caballer et al. (BenaventCaballer et al., 2016) investigated a sample composed of a mix of apparently healthy community-dwelling and institutionalized older adults (TUG performance = 11.1; 77.8% female). This may be one of the key determinants for the difference between the results because, as demonstrated in the current study, volunteers with an impaired performance demonstrated a greater need for other physical capacities than lower limb muscle strength. Interestingly, this hypothesis is in line with evidence from Zarzeczny et al., (Zarzeczny et al., 2017) who demonstrated that TUG performance in very old women (> 80 years) living in nursing home is strongly associated with 6MTW, which may represent an evaluation of aerobic capacity (Coelho Junior et al., 2017b; Ohtake, 2005; Ross et al., 2010; Rostagno and Gensini, 2008). Results of the present study support these data since the pattern shown in Pearson's correlation analyses (Table 2 and Table 3) differed according to TUG quartiles.

In fact, when the analysis was conducted in the entire sample, lower limb muscle strength (sit-to-stand) demonstrated the strongest correlation between the variables and TUG (0.53); whereas its influence decreased according to TUG quartiles in the subgroup analysis

(from 0.46 to 0.19). In addition, other physical capabilities, such as lower limb muscle power and aerobic capacity (i.e., 6MWT), were significantly associated with TUG performance in the > 75% quartile, but not in the other quartiles. Lastly, the impact on TUG performance is shown by the multiple linear regression, where the addition of TUG quartiles as an independent variable decreased the unstandardized and standardized beta of the models, as well as the square of semipartial correlation (Table 4).

Taken together, these data indicate that TUG performance is not circumscribed to balance and walk, as widely stated in the literature, and that the physical capabilities underlying this phenomenon are dependent on TUG levels.

Unfortunately, our sample size (n = 117) did not allow further inferences regarding the physical capabilities associated with TUG performance in the > 75% quartile. Nevertheless, it is noteworthy that, when the multivariable linear regression was performed using these volunteers, lower limb muscle strength (i.e., sit-to-stand; 5%), lower limb muscle power (i.e., countermovement jump; 4%), and mobility (i.e., usual walking speed; 4%) explained the variations in TUG performance (Supplementary material Table SM 1), suggesting that the variables underlying TUG performance may be dependent of the time taken to perform the test.

In fact, when compared to the analysis performed in the whole sample (Table 4), it is possible to observe a marked decrease in the collaboration of lower limb muscle strength (−12%), followed by an increase in the collaboration of lower limb muscle power (+3%) and mobility (+2%), in TUG performance. However, more data investigating and comparing populations with different levels of performance are still necessary for a better understanding.

TUG scores have been widely used in the clinical setting as predictors of poor outcomes, screening tools to identify older adults at risk of reduced functionality, and, even, as sensitivity analysis to identify the effectiveness of therapeutic interventions (Benavent-Caballer et al., 2016). Our results have a great practical application because propitiate an additional understanding about the physical capabilities that explaining TUG performance, collaborating with the development of interventions focused on the variables. In this sense, is possible to suggest that older women with a TUG value ≤7.65 s may benefit from therapies composed exclusively — or with a high component — of resistance training (Häkkinen et al., 1998, 2001; Henwood et al., 2008; Kalapotharakos et al., 2004), leading to a significant increase in muscle strength. On the other hand, a larger number of physical stimuli should be offered to people with TUG values > 7.65 s, such as approached in multicomponent exercise programs (MCEP), propitiating improvements in more than one physical capability (Cadore and Izquierdo, 2015; Cadore et al., 2013; Coelho Junior et al., 2017a; Marzetti et al., 2017a).

Our study had several limitations. First, aging is strongly associated with the sarcopenic process, which, in turn, is a major determinant of functional impairment (Cruz-Jentoft et al., 2010; Marzetti et al., 2017b). Although previous findings did not indicate an association between the cross-sectional area of rectus femoris and TUG performance (Benavent-Caballer et al., 2016), volunteers of the current study were not classified into sarcopenic and non-sarcopenic due to the lack of muscle mass evaluations. Second, in the experiment of Zarzeczny et al., (Zarzeczny et al., 2017) authors not only indicated that 6MWT and lower limb muscle strength were associated with the TUG performance, but — after fragmented TUG performance using the instrumented TUG (iTUG) analysis — they suggested that this phenomenon occurred due the association of these factors with the moment when the volunteer speeds up vertically to get up from the chair. Therefore, future studies must approach these limitations to a better understanding of the relation among TUG and physical capabilities in older women.

Conclusions

In conclusion, data of the current study indicate that the determinist thought regarding the physical capabilities associated with TUG performance is not totally correct since the contribution of physical capabilities to TUG performance is altered according to the time taken to perform the test. Indeed, older women who perform TUG at velocities ≤7.65 s use a high component of muscle strength, while other variables, such as aerobic capacity have only a small participation. On the other hand, when TUG is performed at velocities > 7.65 s the participation of muscle strength decreases, and a number of other physical capacities seem to be required.

Supplementary data to this article can be found online at https:// doi.org/10.1016/j.exger.2018.01.025.

Authors' contributions

All authors participated in the development of the research project, analysis, and interpretation of the data, and preparation of the manuscript.

Declaration of interest statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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ARTICLE 10

Cross-sectional Associations Between Physical Function and Frailty Status Across 4 Frailty Different Instruments

Abstract

Aims: The present study investigated the associations of frailty status using 4 different frailty instruments and physical performance tasks in community-dwelling older adults. **Methods:** One-hundred ninety-nine people participated of the present study. Frailty were identified using Fried frailty phenotype, FRAIL, SOF, and Gérontopôle Frailty Screening Tool (GFST). Physical performance tests included isometric handgrip strength (IHG), sit-to-stand test, timed "Up-and-Go" test, and one-leg stand. **Results:** No significant associations were observed when individuals were identified using FRAIL and SOF instruments. On the other hand, IHG ($P<0.001$ and $P=0.004$), TUG ($P<0.0001$), and one-leg stand ($P=0.003$ and $P=0.004$) performances were significantly associated with frailty status when participants were identified by Fried frailty phenotype and GFST indexes. Z scores identified that most frail participants identified by Fried frailty phenotype showed low IHG (Z score= 5.6) and one-leg stand performance (Z score= 3.3), while most frail participants identified by GFST showed low IHG (Z score= 2.2) and TUG (Z score= 7.0) scores. **Conclusions:** Our findings suggest that the relationship between physical function and frailty status in community-dwelling older adults is tool-dependent. A possible explanation for these findings is based on the fact that Fried frailty phenotype and GFST involve performance-based physical function tests, while FRAIL and SOF include self-reported assessments. Additionally, low IHG and one-leg stand performances were observed in most frail participants identified by Fried frailty phenotype, while most frail participants identified by GFST showed low IHG and TUG scores.

Keywords: Elderly; Diet; Physical function; Disability; Sarcopenia

Introduction

Frailty is a highly prevalent condition among older adults, and is defined as a state of increased vulnerability to negative health-related outcomes [1], which occurs as a result of multisystem physiological derangements and poor social support that impact the individual's ability to maintain homeostasis after a stressor event [2–4]. Frailty progress increase the risk for many negative events, such as fractures, disability, hospitalization, nursing home placement, and death [5,6]. As such, frailty represents a major public health problem [1] and researchers have been looking for therapies to counteracting this condition.

Nowadays, two main theorical models of frailty have been proposed: a) the phenotype model [7] and b) the cumulative deficit model or multidomain model [8]. The frailty phenotype [7] is the most utilized model for frailty diagnosis and many instruments [3,9] have been created in the last years in attempt to propitiate a deeper and faster analysis.

Although most studies have found a similar association between different frailty indexes and many negative health-related outcomes, such as disability, hospitalization, and death [6,10,11], Lin et al.[12] observed differences among frailty indexes to predict disability and hospitalization in prefrail older adults, suggesting that frailty instruments may reflect different pathogenic bases.

Physical function has a key role in frailty [13] and many researchers [13,14] have stressed that dynapenia, loss of muscle power and poor mobility may be considered substrate for frailty development and progression. Indeed, the phenotype model is alternatively called as physical frailty model, given that its characterization is based on changes on physical function [3].

Nevertheless, physical function is a construct that includes different physical capacities and abilities, so that it is possible to suggest that be frail does not mean have poor physical function in all domains. However, evidence regarding this topic are still scarce.

Based on these premises, the present study investigated the association between frailty status and physical function in community-dwelling older adults using 4 different frailty instruments.

Materials and Methods

The study approved by the Research Ethics Committee of the University of Campinas. All study procedures were conducted in compliance with the Declaration of Helsinki and the Resolution 196/96 of the National Health Council. All participants were thoroughly informed about the study procedures before providing written consent.

Participants

Participants were recruited by convenience in a community senior center located in Poá, Brazil. Poá is a city located in the southern area of São Paulo with a population of approximately 100 thousand people, being ~3460 older (60 year or over) [15]. The community senior center offers daily sessions of flexibility, aquatic and multicomponent physical exercises, dance classes, adapted sports, nursing and medical care, and cognitive stimulation therapy. Candidate participants were considered eligible if they were 60 or older, were community-dwellers, and possessed sufficient physical and cognitive abilities to perform all of the measurements required by the protocol.

Anthropometric measurements

A weight scale with a stadiometer was used to measure body mass and height. The body mass index (BMI) was subsequently calculated as following:
a) body mass (kg)/ height (m^2).

Frailty assessment

- *Frailty phenotype*

The frailty phenotype was first described by Fried et al. [7]. The instrument incorporates measures of multiple physical domains, including weight loss, exhaustion, weakness, slowness, and sedentary behavior [16,17]. People are respectively identified as robust, prefrail and frail according to the presence of none, 1-2, and ≥3 of the following criteria: (1) unintentional weight loss of ≥5 kg in the prior year; (2) self-reported fatigue; (3) weakness, grip strength lower than 0.8 kg; (4) slowness, defined by Timed “Up-and-Go” (TUG) performance [18] equal or higher than 4.4 s; and (5) low physical activity levels according to the short form of the International Physical Activity Questionnaire (IPAQ) [19]. Gender- and BMI-specific cutoff points were used for grip strength and height-specific cutoff points were used for TUG based in the median values of our sample. Gender-specific cutoffs were used for physic activity levels [17].

- *FRAIL index*

FRAIL scale consists of 5 simple questions require a yes or no answer, with 1 point given to any affirmative response [20]. Instrument scores range from 0 to 5 points, and people are identified as robust (0 points), prefrail (1-2 points), and frail (≥3 points) according to the following criteria: (1) self-reported fatigue; (2) poor resistance, based on the inability to climb a flight of stairs; (3) limited ambulation, based on the inability to walk 1 block; (4) illnesses, presence of ≥ 5 illnesses; and (5) unintentional weight loss of ≥5% in the past 6 months.

- *SOF index*

SOF is derived from the Study of Osteoporotic Fractures [21]. The instrument is based on 3 criteria: (1) unintentional weight loss of ≥4.5 kg in the prior year; (2) self-reported exhaustion; (3) inability to rise from a chair 5 times without using arms. SOF scores range from 0 to 3, and people are identified as robust, prefrail, and frail according to the presence of 0, 1, and 2-3 criteria.

- *Gérontopôle Frailty Screening Tool*

The Gérontopôle Frailty Screening Tool (GFST) is an 8-item questionnaire assessing individual's social, physical, functional and cognitive situation. In the present study, only the first six self-reported questions were used to analysis given that the last two questions are dependent of general practitioner's personal view. The GFST is based on the following criteria: (1) living alone; (2) unintentional weight loss in the prior 3 months; (3) self-reported fatigue in the last 3 months; (4) self-reported mobility difficulties in the last 3 months; (5) complains of memory problems; and (6) slowness, defined by a Timed "Up-and-Go" (TUG) performance equal or higher than 4.4 s. Once there is no clear cut-off point to classify the patient as frail or not [22], we proposed the following cutoffs for robust, prefrail and frail individuals, respectively, 0, 1-2, ≥3 components.

- *Functional Assessments*

All physical function tests were administered by two experienced exercise physiologists. One examiner was responsible for detailing the operational procedures, demonstrating the test before the assessment, quantifying performance and evaluating motor patterns. The other examiner ensured participant safety by providing occasional verbal and/or tactile cueing, if needed, without interfering with the physical function tests. After the explanation and before each test, participants performed a familiarization trial to ensure they

had fully understood each test. Except for the one-leg stance test, participants performed all tests twice with the best result used for analysis.

- *Isometric Handgrip Strength (IHG)*

IHG strength of the dominant hand was measured using a Jamar® handheld hydraulic dynamometer (Sammons Preston, Bolingbrook, IL, USA)[23]. To determine the dominant hand, participants were asked which of their hands was the strongest. The measure was obtained while the participant was seated on a chair with the shoulder abducted, the elbow near the trunk and flexed at 90°, and the wrist in a neutral position (thumbs up). The contralateral arm remained relaxed under the thigh. To measure handgrip strength, participants performed a maximal contraction during 4 s. The test reliability in the present study was ≥0.8 (κ= 0.96). Results were recorded in kg.

- *Five Times Sit to Stand Test*

Participants rose from a chair five times as quick as possible with their arms folded across their chest. Timing began when the participant raised their buttocks off the chair and was stopped when the participant was seated at the end of the fifth stand [24]. The test reliability in the present study was ≥0.8 (κ= 0.97).

- *Timed-Up-and-Go Test (TUG)*

The TUG test involved getting up from a chair (total height: 87 cm; seat height: 45 cm; width: 33 cm), walking three meters around a cone placed on the floor, coming back to the same position, and sitting back on the chair [25]. Participants wore regular footwear, placed their back against the chair, rested their arms on the chair's arms, and put their feet on the ground. A researcher instructed the participant to, on the word “go”, get up, walk three meters as fast as possible without compromising safety, turn, walk three meters back to the chair, and sit down. Timing began when the participant got up from the chair and was stopped when the participant’s back touched the backrest of the chair. The test reliability in the present study was of ≥0.8 (κ= 0.94).

- *One-Leg Stance Test*

The one-leg stance test was performed with the participant standing in a unipodal stance on the dominant lower limb, with the contralateral knee flexed at 90°, arms folded across the chest, and head held straight [26]. Timing began when the participant raised the non-

dominant foot off the floor and was stopped when the foot touched the floor again. The maximum performance time was set at 30 s.

- *Statistical Analysis*

Continuous and categorical variables were compared among the three groups (i.e., robust, prefrail, and frail) via one-way analysis of variance (ANOVA) and chi-square (χ^2) statistics, respectively. Bonferroni posthoc analyses were performed to determine whether there were significant differences between groups. χ^2 and Z-score were further used to explore the association between diet characteristics and frailty status across frailty instruments. Median values were chosen as the cutoff values for IHG (23 kg), sit-to-stand (13 s), TUG (6.7 s), and one leg stance (16 s) tests. For all tests, alpha was set at 5% ($p < 0.05$) and Z-score was set at 1.96. All analyses were conducted using the IBM SPSS Statistics, version 20.0, software (IBM Corp., Armonk, NY, USA).

Results

Clinical Characteristics

One-hundred ninety-nine people participated of the present study. Table 1 shows clinical, sociodemographic, and physical function of study participants according to frailty status and frailty instruments. Frailty frequency was 26.1% using FRAIL index, 22.6% using SOF, 15.5% using Fried frailty phenotype, and 12.0% using GFST. There were no differences on clinical, sociodemographic and physical function among frailty status when participants were identified using FRAIL and SOF indexes. On the other hand, significant differences in age and physical function were observed using Fried and GFST. Frail participants identified by both Fried frailty phenotype and GFST were older and had poor physical function in all tests when compared to prefrail and robust individuals. In addition, prefrail older adults identified by Fried frailty phenotype had poorer performance on IHG/BMI and sit-to-stand tests in comparison to robust counterparts.

Table 1. Characteristics of the participants according to frailty status.

	FRAIL			Fried Frailty Phenotype			GFST			SOF		
Variables	Robust (n=22)	Prefrail (n=125)	Frail (n=52)	Robust (n=14)	Prefrail (n=154)	Frail (n=31)	Robust (n=38)	Prefrail (n=137)	Frail (n=24)	Robust (n=27)	Prefrail (n=127)	Frail (n=45)
Characteristics												
Age, years	66.0 ± 4.5	68.8 ± 7.3	67.6 ± 6.4	**65.1 ± 7.5**	**67.8 ± 6.1**	**71.2 ± 9.1ab**	**65.2 ± 3.8**	**67.8 ± 6.3**	**75.1 ± 9.0ab**	68.6 ± 8.0	68.2 ± 6.9	68.0 ± 6.1
Body weight, kg	66.5 ± 11.7	69.6 ± 12.7	68.2 ± 10.4	63.5 ± 9.2	69.9 ± 12.1	66.4 ± 12.4	71.3 ± 11.1	68.9 ± 11.7	65.3 ± 14.5	68.8 ± 12.2	69.7 ± 12.0	66.7 ± 12.0
BMI, kg/m²	28.1 ± 4.4	28.9 ± 5.3	28.5 ± 4.3	27.7 ± 3.6	28.9 ± 5.0	28.4 ± 5.5	28.6 ± 4.6	29.0 ± 4.9	27.5 ± 5.8	29.4 ± 5.2	29.0 ± 4.8	27.5 ± 5.1
Sex, f (%)	18 (9.0)	103 (81.7)	45 (86.5)	13 (6.5)	125 (62.8)	27 (13.6)	31 (81.6)	115 (83.9)	20 (80.0)	22 (81.5)	106 (83.5)	38 (82.6)
Tabagism, n (%)	0 (0.0)	3 (2.4)	3 (5.8)	1 (7.1)	4 (2.6)	1 (3.2)	1 (2.6)	3 (2.2)	2 (8.0)	0 (0.0)	3 (2.4)	3 (6.5)
Race, n (%)												
Asian	0 (0.0)	8 (4.0)	3 (1.5)	0 (0.0)	9 (4.5)	2 (1.0)	1 (5.0)	7 (3.5)	3 (1.5)	0 (0.0)	7 (3.5)	4 (2.0)
Black	3 (1.5)	22 (11.0)	12 (6.0)	2 (1.0)	28 (14.1)	7 (3.5)	9 (4.5)	23 (11.5)	5 (2.5)	6 (3.0)	22 (11.0)	9 (4.5)
Caucasian	19 (9.5)	96 (48.0)	37 (18.5)	12 (6.0)	117 (58.8)	22 (11.1)	28 (14.0)	107 (53.5)	17 (8.5)	21 (10.5)	98 (49.0)	33 (16.5)
Physical function												
IHG, kg	25.6 ± 14.2	24.1 ± 11.6	21.9 ± 8.8	**35.5 ± 18.2**	**25.0 ± 9.2**	**11.9 ± 7.4ab**	**28.8 ± 12.1**	**24.2 ± 9.9**	**12.7 ± 10.7ab**	22.6 ± 8.1	24.5 ± 12.8	22.0 ± 7.7
Sit-to-stand, s	12.5 ± 2.4	14.8 ± 7.9	13.6 ± 3.5	**11.5 ± 3.7**	**13.6 ± 5.4a**	**19.4 ± 10.9ab**	**13.4 ± 2.5**	**13.5 ± 5.7**	**21.2 ± 12.3ab**	14.1 ± 5.8	14.4 ± 6.7	13.9 ± 7.0
TUG, s	6.9 ± 2.3	16.2 ± 43.2	7.2 ± 2.0	**8.1 ± 2.2**	**9.0 ± 19.7**	**34.0 ± 7.3ab**	**5.7 ± 0.6**	**8.6 ± 15.0**	**46.9 ± 85.0ab**	15.0 ± 33.4	10.3 ± 22.6	18.7 ± 56.0
One-leg stand, s	18.5 ± 10.4	16.5 ± 11.4	15.3 ± 10.2	**21.0 ± 11.5**	**17.6 ± 10.4**	**8.1 ± 9.8ab**	**19.6 ± 9.6**	**17.3 ± 10.3**	**7.2 ± 10.4ab**	15.0 ± 2.2	17.3 ± 10.7	15.0 ± 11.0

BMI= Body mass index; GFST= Gérontopôle Frailty Screening Tool; IHG= Isometric handgrip strength; SOF= Study of Osteoporosis Fractures; TUG= Timed "Up-and-Go"; aP<0.05 vs Robust; bP<0.05 vs Prefrail.

The association between physical function and frailty status across the different frailty indexes are shown in Table 2. No significant associations were observed when individuals were identified using FRAIL and SOF instruments. On the other hand, IHG ($P<0.001$ and $P=0.004$), TUG ($P<0.0001$), and one-leg stand ($P=0.003$ and $P=0.004$) performances were significantly associated with frailty status when participants were identified by Fried frailty phenotype and GFST indexes. Z scores identified that most frail participants identified by Fried frailty phenotype showed low IHG (Z score= 5.6) and one-leg stand performance (Z score= 3.3), while most frail participants identified by GFST showed low IHG (Z score= 2.2) and TUG (Z score= 7.0) scores.

Table 2. Frequency (%) of the distribution of older adults according to frailty status.

	FRAIL			Fried Frailty Phenotype			GFST			SOF		
Variables	Robust (n=22)	Prefrail (n=125)	Frail (n=52)	Robust (n=14)	Prefrail (n=154)	Frail (n=31)	Robust (n=38)	Prefrail (n=137)	Frail (n=24)	Robust (n=27)	Prefrail (n=127)	Frail (n=45)
IHG, kg												
<23	12 (6.0)	60 (30.2)	27 (13.6)	**1 (5.0)**	**69 (34.7)**	**29 (14.6)**	**12 (6.0)**	**69 (34.7)**	**18 (9.0)**	14 (7.0)	60 (30.2)	25 (12.6)
≥23	10 (5.0)	65 (32.7)	25 (12.6)	**13 (6.5)**	**85 (42.7)**	**2 (1.0)***	**26 (13.1)**	**68 (34.2)**	**6 (3.0)***	13 (6.5)	67 (33.7)	20 (10.1)
Sit-to-stand, s												
<13	11 (5.8)	39 (20.6)	20 (10.6)	8 (4.2)	53 (28.0)	9 (4.8)	14 (7.4)	51 (27.0)	5 (2.6)	11 (5.8)	40 (21.2)	19 (10.1)
≥13	11 (5.8)	79 (41.8)	29 (15.3)	6 (3.2)	96 (50.8)	17 (9.0)	24 (12.7)	80 (42.3)	15 (7.9)	15 (7.9)	84 (44.4)	20 (10.6)
TUG, s												
<6.7	20 (10.0)	106 (53.0)	49 (24.5)	**12 (6.0)**	**145 (72.9)**	**17 (8.5)**	**38 (19.0)**	**126 (63.0)**	**11 (5.5)**	20 (10.0)	115 (57.5)	40 (20.0)
≥6.7	2 (1.0)	20 (10.0)	3 (1.5)	**2 (1.0)**	**9 (4.5)**	**14 (7.0)***	**0 (0.0)**	**11 (5.5)**	**14 (7.0)***	7 (3.5)	12 (6.0)	6 (3.0)
One-leg stand, s												
<16	9 (4.5)	64 (32.0)	27 (13.5)	**5 (2.5)**	**71 (35.7)**	**24 (12.1)**	**15 (7.5)**	**65 (32.5)**	**20 (10.0)**	15 (7.5)	60 (30.0)	25 (12.5)
≥16	13 (6.5)	62 (31.0)	25 (12.5)	**9 (4.5)**	**83 (41.7)**	**7 (3.5)***	**23 (11.5)**	**137 (68.5)**	**25 (12.5)***	12 (6.0)	67 (33.5)	21 (10.5)

BMI= Body mass index; GFST= Gérontopôle Frailty Screening Tool; IHG= Isometric handgrip strength; SOF= Study of Osteoporosis Fractures; TUG= Timed "Up-and-Go"; *P<0.05

Discussion

The main findings of the present study indicate that the relationship between physical function and frailty status in community-dwelling older adults is tool-dependent. A possible explanation for these findings is based on the fact that Fried frailty phenotype [7] and GFST [22] involve performance-based physical function tests, while FRAIL [20] and SOF [21] include self-reported assessments.

In fact, self-reported physical function may be more influenced by gender, cognitive function, pain, culture, language and education than performance based-assessments [27–29], leading to the suggestion that different physical constructs are captured by these tools [30]. These premises are supporting by empirical evidence that observed a weak to moderate correlation between self-reported and performance-based physical function assessments [27–30].

In this context, our results suggest that Fried frailty phenotype and GFST should be prioritize by health professionals responsible for older adults care that are looking for frailty instruments that may reflect current patient's physical function, given that both tools offer a better comprehension of performance-based physical function in comparison to FRAIL and SOF.

Additionally, we observed a significant correlation between physical function tests and frailty status. Particularly, low IHG and one-leg stand performances were observed in most frail participants identified by Fried frailty phenotype, while most frail participants identified by GFST showed low IHG and TUG scores. Although these results are at last partially expected, given that IHG is part of the criteria for frailty diagnosis [7] our findings expand this view to indicate that frail individuals identified by Fried frailty phenotype are also at increased risk for poor balance.

This phenomenon likely occurs because these physical functions are controlled by similar neuromuscular mechanisms since age-related changes in sensory receptors and peripheral nerves, as well as decreased visual acuity and vestibular function affect both postural control and strength production [31].

Regarding GFST, our findings are supported by prior studies that observed a significant association between TUG performance and balance, lower-limb muscle power, and lower- and upper-limb muscle strength in older adults [18,32,33]. According to Benavent-Caballer et al. [32], TUG incorporates many functional tasks, such as sit-to-stand, walking, and turning. In this context, even if upper-limb muscle strength is not strictly necessary for TUG performance, Lauretanni et al. [34] found a significant correlation between IHG and mobility,

which might indicate that the existing relationship between TUG and IHG may reflect that frail older adults identified by GFST show limited physical function.

These discoveries have high clinical applicability and collaborate to the creation of more specific therapies to counteract frailty in older adults. The practice of exericse training [35,36] and adequate protein consumption [37], for example, have been associated with low prevalence of frailty and high physical performance scores, and could be interesting alternatives to reverse frailty in the present sample.

One may argue that frail participants identified by Fried frailty phenotype should also have low mobility, given that it is part of the criteria for frailty diagnosis [7]. However, mobility limitations in only one of the five criteria for frailty and it is possible that participants with low mobility did not meet other criteria.

The present study has some limitations that should be acknowledged. Frist, the study population was relatively small and composed exclusively by community-dwellers, limiting inferences to older adults from other settings (i.e., nursing homes) and deeper statistical analysis. Second, both Fried frailty phenotype and GFST were adapted given that walking speed test was replaced by TUG. Third, the relationship between TUG and mobility seems to be age-dependent and we cannot rule out the possibility that different associations could be observed in an older sample. Finally, the cross-sectional design of the study does not allow inference to be drawn on the time course of changes of the variables considered and on cause-effect relationships.

Conclusions

Our findings suggest that the relationship between physical function and frailty status in community-dwelling older adults is tool-dependent. A possible explanation for these findings is based on the fact that Fried frailty phenotype and GFST involve performance-based physical function tests, while FRAIL and SOF include self-reported assessments. Additionally, low IHG and one-leg stand performances were observed in most frail participants identified by Fried frailty phenotype, while most frail participants identified by GFST showed low IHG and TUG scores.

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ARTICLE 11

Frailty is not associated with hypertension, blood pressure or antihypertensive medication in community-dwelling older adults: A comparison using 4 frailty instruments

Abstract

Aims: The present study investigated the associations of frailty status using 4 different frailty instruments and a) office blood pressure, b) hypertension prevalence, c) antihypertensive treatment in community-dwelling older adults. **Methods:** One-hundred eighty older adults were recruited to take part of the present study. Frailty were identified using Fried frailty phenotype, FRAIL, SOF, and Gérontopôle Frailty Screening Tool (GFST). Office blood pressure was measured using an oscilometric blood pressure monitor. Information concerning hypertension diagnosis and antihypertensive therapy were obtained through self-report and careful review of medical charts. **Results:** No significant associations were observed between any hypertension-associated parameter and frailty status. **Conclusions:** Findings of the present study indicate that hypertension, office blood pressure levels and antihypertensive medication were not associated with frailty status in community-dwelling older adults, regardless of the frailty index used to frailty identification.

Keywords: Elderly; Cardiovascular disease; Physical function; Disability; Sarcopenia

Introduction

Frailty is a highly prevalent condition among older adults, and is defined as a state of increased vulnerability to negative health-related outcomes[1], which occurs as a result of multisystem physiological derangements and poor social support that impact the individual's ability to maintain homeostasis after a stressor event[2–4]. Frailty progress increase the risk for many negative events, such as fractures, disability, hospitalization, nursing home placement, and death[5,6]. As such, frailty represents a major public health problem[1].

Hypertension is another great health concern for older adults. As frailty, hypertension is highly prevalent in older adults[7] and represents a major risk factor for cardiovascular and cerebrovascular diseases[7]. Notably, many researchers have proposed a theorical model supporting that hypertension progression may predispose the development of frailty due to many different mechanisms[8–12].

Investigations in animal models of hypertension [13–15] and hypertensive patients [16,17] have found that chronic elevations on blood pressure levels may affect cerebral blood flow. Although changes on cerebral integrity have been observed on areas responsible for autonomic control [14], researchers [16,18,19] have proposed that this phenomenon could also be observed in cerebral areas responsible for motor control and explain the relationship between hypertension and impaired physical performance observed in some studies [16,19,20].

On the other hand, continuous use of angiotensin-converting enzyme (ACE) inhibitors seems to reduce muscle loss and physical function decline in older adults with and without disability[21,22], suggesting that the antihypertensive therapy may delay frailty development and progression.

Nevertheless, although a theorical bases supporting the relationship between hypertension and antihypertensive medication with frailty exists, results of empirical evidence are still uncertain, so that positive [8–12] and null[8,9,23] associations have been observed. Notably, a recent systematic review and meta-analysis of observational studies did not find longitudinal or cross-sectional associations between hypertension and frailty status in adults[24].

Based on these premises, the present study investigated if hypertension, blood pressure, and antihypertensive therapy were significantly associated with frailty status in community-dwelling older adults. In addition, we tested the hypothesis that a similar association could be observed using different frailty instruments.

Materials and Methods

The study approved by the Research Ethics Committee of the University of Campinas. All study procedures were conducted in compliance with the Declaration of Helsinki and the Resolution 196/96 of the National Health Council. All participants were thoroughly informed about the study procedures before providing written consent.

Participants

Participants were recruited by convenience in a community senior center located in Poá, Brazil. Poá is a city located in the southern area of São Paulo with a population of approximately 100 thousand people, being ~3460 older (60 year or over)[25]. The community senior center offers daily sessions of flexibility, aquatic and multicomponent physical exercises, dance classes, adapted sports, nursing and medical care, and cognitive stimulation therapy. Candidate participants were considered eligible if they were 60 or older, were community-dwellers, and possessed sufficient physical and cognitive abilities to perform all of the measurements required by the protocol.

Anthropometric measurements

A weight scale with a stadiometer was used to measure body mass and height. The body mass index (BMI) was subsequently calculated as following:

a) body mass (kg)/ height (m^2).

Frailty assessment

- *Frailty phenotype*

The frailty phenotype was first described by Fried et al.[26]. The instrument incorporates measures of multiple physical domains, including weight loss, exhaustion, weakness, slowness, and sedentary behavior[27,28]. People are respectively identified as robust, prefrail and frail according to the presence of none, 1-2, and ≥3 of the following criteria: (1) unintentional weight loss of ≥5 kg in the prior year; (2) self-reported fatigue; (3) weakness, grip strength lower than 0.8 kg; (4) slowness, defined by Timed "Up-and-Go" (TUG) performance[29] equal or higher than 4.4 s; and (5) low physical activity levels according to the short form of the International Physical Activity Questionnaire (IPAQ)[30]. Gender- and BMI-specific cutoff points were used for grip strength and height-specific cutoff points were used for TUG based in the median values of our sample. Gender-specific cutoffs were used for physic activity levels [28].

- *FRAIL index*

FRAIL scale consists of 5 simple questions require a yes or no answer, with 1 point given to any affirmative response [31]. Instrument scores range from 0 to 5 points, and people are identified as robust (0 points), prefrail (1-2 points), and frail (≥3 points) according to the following criteria: (1) self-reported fatigue; (2) poor resistance, based on the inability to climb a flight of stairs; (3) limited ambulation, based on the inability to walk 1 block; (4) illnesses, presence of ≥ 5 illnesses; and (5) unintentional weight loss of ≥5% in the past 6 months.

- *SOF index*

SOF is derived from the Study of Osteoporotic Fractures [32]. The instrument is based on 3 criteria: (1) unintentional weight loss of ≥4.5 kg in the prior year; (2) self-reported exhaustion; (3) inability to rise from a chair 5 times without using arms. SOF scores range from 0 to 3, and people are identified as robust, prefrail, and frail according to the presence of 0, 1, and 2-3 criteria.

- *Gérontopôle Frailty Screening Tool*

The Gérontopôle Frailty Screening Tool (GFST) is an 8-item questionnaire assessing individual's social, physical, functional and cognitive situation. In the present study, only the first six self-reported questions were used to analysis given that the last two questions are dependent of general practitioner's personal view. The GFST is based on the following criteria: (1) living alone; (2) unintentional weight loss in the prior 3 months; (3) self-reported fatigue in the last 3 months; (4) self-reported mobility difficulties in the last 3 months; (5) complains of memory problems; and (6) slowness, defined by a Timed "Up-and-Go" (TUG) performance equal or higher than 4.4 s. Once there is no clear cut-off point to classify the patient as frail or not [33], we proposed the following cutoffs for robust, prefrail and frail individuals, respectively, 0, 1-2, ≥3 components.

Hemodynamic parameters

The procedures for measurement of blood pressure were adapted from the VII Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7)[34]. For the evaluation, participants remained sitting on a comfortable chair for 15 minutes in a quiet room. An appropriate cuff was selected after measuring the arm circumference of each participant (Sanny, São Paulo, Brazil) and was placed at approximately

the midpoint of the upper left arm (heart level). An automatic, noninvasive, and validated[35] arterial blood pressure monitor (Microlife-BP 3BT0A, Microlife, Widnau, Switzerland) was used to measure systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR). During blood pressure recording, participants remained relaxed in the sitting position, with parallel feet at one shoulder width, both forearm and hands on the table, supinated hands, back against the chair, without move or talk. The evaluation lasted approximately 80 seconds and was performed three times with 1-min rest among the measurements. Mean values were used in the final analysis. The size of the arm cuff was selected after measuring the arm circumference of each participant (Sanny, São Paulo, Brazil).

Disease conditions and pharmacological treatment

Information pertaining to disease conditions was collected by two researchers through self-report and careful review of medical charts of the community senior center. Medical charts, which are updated every six months by a local physician, were reviewed to determine the prevalence of disease conditions.

Statistical Analysis

Continuous and categorical variables were compared among the three groups (i.e., robust, prefrail, and frail) via one-way analysis of variance (ANOVA) and chi-square (χ^2) statistics, respectively. Bonferroni posthoc analyses were performed to determine whether there were significant differences between groups. χ^2 was used to explore the association between hemodynamic parameters and frailty status across the different frailty instruments. For all tests, alpha was set at 5% ($p < 0.05$). All analyses were conducted using the IBM SPSS Statistics, version 20.0, software (IBM Corp., Armonk, NY, USA).

Results

Clinical Characteristics

One-hundred eighty older adults were recruited to take part of the present study. Table 1 shows clinical and sociodemographic characteristics of study participants according to frailty status. Frailty frequency was 26.6% using FRAIL index, 20.5% using SOF, 10.0% using Fried frailty phenotype, and 7.2% using GFST. There were no differences on clinical, sociodemographic, and diseases prevalence among frailty status when participants were identified using FRAIL and SOF indexes. On the other hand, significant differences in the prevalence of diseases were observed using Fried frailty phenotype and GFST instruments, so

that prefrail older adults according to Fried frail phenotype and GFST showed a higher frequency of dyslipidemia and osteoporosis, and a higher frequency of diabetes mellitus and CVD using the GFST.

Table 1. Characteristics of the participants according to frailty status.

	FRAIL			Fried Frailty Phenotype			GFST			SOF		
Variables	Robust (n=22)	Prefrail (n=110)	Frail (n=48)	Robust (n=14)	Prefrail (n=148)	Frail (n=18)	Robust (n=38)	Prefrail (n=129)	Frail (n=13)	Robust (n=26)	Prefrail (n=117)	Frail (n=37)
Characteristics												
Age, years	66.0 ± 4.5	68.8 ± 7.3	67.6 ± 6.4	65.1 ± 7.5	67.8 ± 7.1	71.2 ± 9.1	65.2 ± 3.8	67.8 ± 6.3	75.1 ± 9.0	68.6 ± 8.0	68.2 ± 6.9	68.2 ± 6.9
Body weight, kg	66.5 ± 11.7	69.6 ± 12.7	68.2 ± 10.4	63.5 ± 9.2	69.9 ± 12.1	66.4 ± 12.4	71.3 ± 11.1	68.9 ± 11.7	65.3 ± 14.5	68.8 ± 12.2	69.7 ± 12.0	66.7 ± 12.0
BMI, kg/m²	28.1 ± 4.4	28.9 ± 5.3	28.5 ± 4.3	27.7 ± 3.6	28.9 ± 5.0	28.4 ± 5.5	28.6 ± 4.6	29.0 ± 4.9	27.5 ± 5.8	29.4 ± 5.2	29.0 ± 4.8	27.5 ± 5.1
Sex, f (%)	18 (9.0)	103 (51.5)	45 (22.5)	13 (6.5)	125 (62.8)	27 (13.6)	31 (15.5)	115 (57.5)	20 (10.0)	22 (11.0)	106 (53.0)	38 (19.0)
Tabagism, n (%)	0 (0.0)	3 (1.5)	3 (1.5)	1 (5.0)	4 (2.0)	1 (5.0)	1 (5.0)	3 (1.5)	2 (1.0)	0 (0.0)	3 (1.5)	3 (1.5)
Race, n (%)												
Asian	0 (0.0)	8 (4.0)	3 (1.5)	0 (0.0)	9 (4.5)	2 (1.0)	1 (5.0)	7 (3.5)	3 (1.5)	0 (0.0)	7 (3.5)	4 (2.0)
Black	3 (1.5)	22 (11.0)	12 (6.0)	2 (1.0)	28 (14.1)	7 (3.5)	9 (4.5)	23 (11.5)	5 (2.5)	6 (3.0)	22 (11.0)	9 (4.5)
Caucasian	19 (9.5)	96 (48.0)	37 (18.5)	12 (6.0)	117 (58.8)	22 (11.1)	28 (14.0)	107 (53.5)	17 (8.5)	21 (10.5)	98 (49.0)	33 (16.5)
Comorbidities, n (%)												
Dyslipidemia	4 (2.0)	17 (8.5)	11 (5.5)	**4 (2.0)**	**17 (8.5)**	**10 (5.0)**	**7 (3.5)**	**16 (8.0)**	**9 (4.5)**	7 (3.5)	20 (10.0)	5 (2.5)
Osteoporosis	4 (2.0)	30 (15.0)	15 (7.5)	**3 (1.5)**	**27 (13.6)**	**19 (9.5)**	**2 (1.0)**	**33 (16.5)**	**14 (7.0)**	8 (4.0)	28 (14.0)	13 (6.5)
Diabetes mellitus	2 (1.0)	34 (17.0)	18 (9.0)	5 (2.5)	39 (19.6)	10 (5.0)	**9 (4.5)**	**33 (16.5)**	**12 (6.0)**	6 (3.0)	35 (17.5)	13 (6.5)
Cardiovascular disease	2 (1.0)	15 (7.5)	10 (5.0)	2 (1.0)	18 (9.0)	17 (3.5)	**3 (1.5)**	**15 (7.5)**	**9 (4.5)**	6 (3.0)	15 (7.5)	6 (3.0)

BMI= Body mass index; GFST= Gérontopôle Frailty Screening Tool; SOF= Study of Osteoporosis Fractures; *P<0.05

Figure 1 shows SBP, DBP, and HR distribution according to frailty status across the different frailty indexes. No significant differences in hemodynamic parameters were observed among frailty status, regardless of the frailty index.

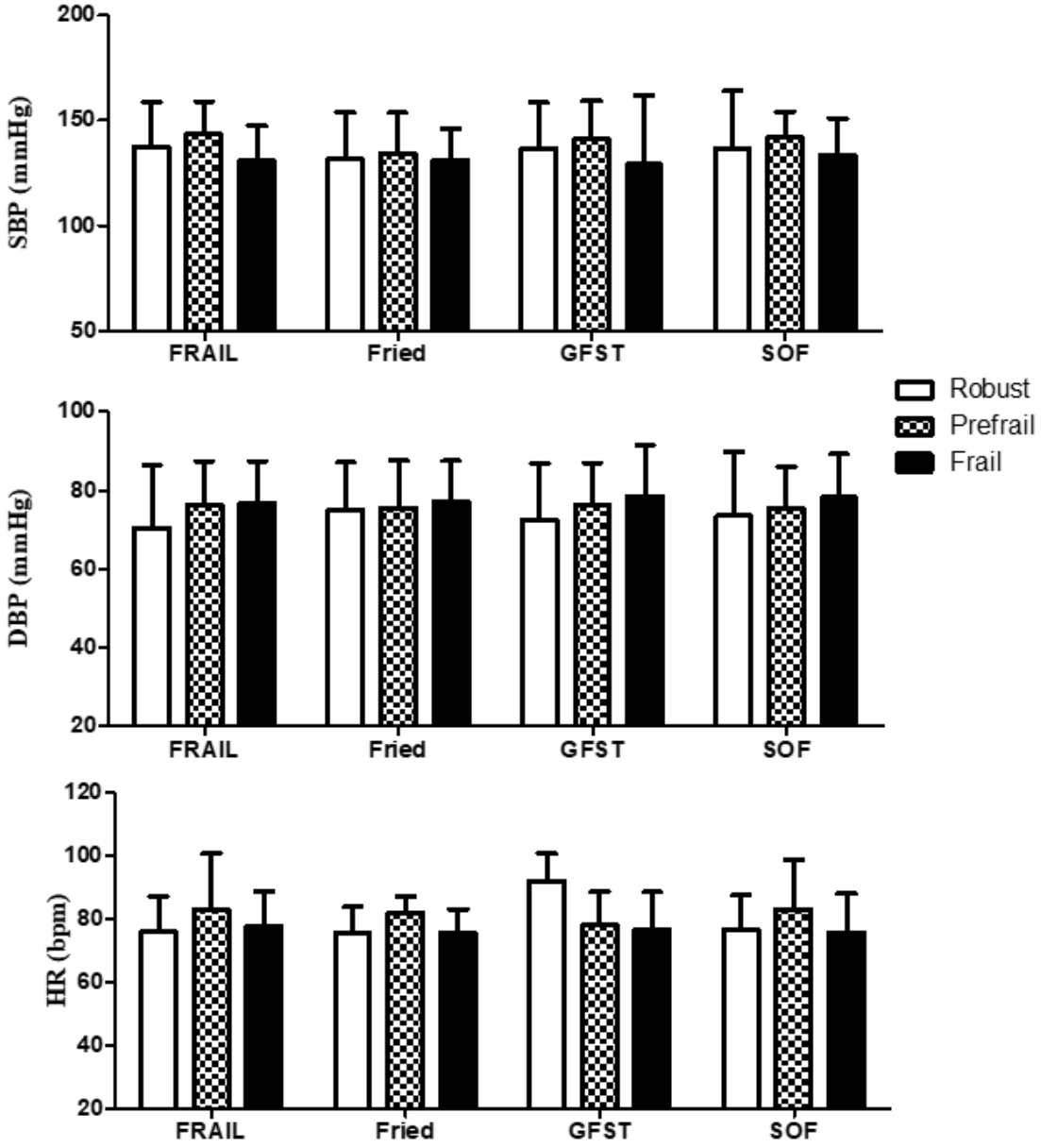

Figure 1. Hemodynamic parameters according to frailty status across the different frailty indexes. SBP= Systolic blood pressure; DBP= Diastolic blood pressure; GFST= Gérontopôle Frailty Screening Tool; HR= Heart rate; SOF= Study of Osteoporosis Fractures.

The association between hypertension, pharmacological therapy and frailty status across the different frailty indexes is shown in Table 2. No significant associations were observed between any hypertension-associated parameter and frailty status.

Table 2. Frequency (%) of the distribution of older adults according to frailty status.

	FRAIL			Fried Frailty Phenotype			GFST			SOF		
Variables	Robust (n=22)	Prefrail (n=110)	Frail (n=48)	Robust (n=14)	Prefrail (n=148)	Frail (n=18)	Robust (n=38)	Prefrail (n=129)	Frail (n=13)	Robust (n=26)	Prefrail (n=117)	Frail (n=37)
Hypertension												
Yes	13 (6.5)	73 (36.5)	31 (15.5)	9 (4.5)	90 (45.2)	17 (8.5)	25 (12.5)	74 (37.0)	18 (9.0)	19 (9.5)	71 (35.5)	27 (13.5)
No	9 (4.5)	53 (26.5)	21 (10.5)	5 (2.5)	64 (32.2)	14 (7.0)	13 (6.5)	63 (13.5)	7 (3.5)	8 (4.0)	56 (28.0)	19 (9.5)
β-Blocker												
Yes	3 (1.5)	26 (13.0)	9 (4.5)	3 (1.5)	29 (14.6)	6 (3.0)	8 (4.0)	22 (11.0)	8 (4.0)	6 (3.0)	23 (11.5)	9 (4.5)
No	19 (9.5)	100 (50.0)	43 (21.5)	11 (5.5)	125 (62.8)	25 (12.6)	30 (15.0)	115 (57.5)	17 (8.5)	21 (10.5)	104 (52.0)	37 (18.5)
Diuretics												
Yes	4 (2.0)	23 (11.5)	5 (2.5)	3 (1.5)	25 (12.6)	4 (2.0)	6 (3.0)	18 (9.0)	8 (4.0)	7 (3.5)	17 (8.5)	8 (4.0)
No	18 (9.0)	103 (51.5)	47 (23.5)	11 (5.5)	129 (64.8)	27 (13.6)	32 (16.0)	119 (59.5)	17 (8.5)	20 (10.0)	110 (55.0)	38 (19.0)
ACE inhibitors												
Yes	3 (1.5)	8 (4.0)	4 (2.0)	1 (5.0)	13 (6.5)	1 (5.0)	3 (1.5)	9 (4.5)	3 (1.5)	3 (1.5)	11 (5.5)	1 (5.0)
No	19 (9.5)	118 (59.0)	48 (24.0)	13 (6.5)	141 (70.9)	30 (15.1)	35 (17.5)	128 (64.0)	22 (11.0)	24 (12.0)	116 (58.0)	45 (22.5)
Angiotensin II receptor antagonists												
Yes	4 (2.0)	37 (18.5)	12 (6.0)	2 (1.0)	43 (21.6)	8 (4.0)	14 (7.0)	31 (15.5)	8 (4.0)	10 (5.0)	35 (17.5)	8 (4.0)
No	18 (9.0)	89 (44.5)	40 (20.0)	12 (6.0)	111 (55.8)	23 (11.6)	24 (12.0)	106 (53.0)	17 (8.5)	17 (8.5)	92 (46.0)	38 (19.0)
Calcium channel blocker												
Yes	2 (1.0)	2 (1.0)	3 (1.5)	0 (0.0)	5 (2.5)	2 (1.0)	2 (1.0)	4 (2.0)	1 (5.0)	2 (1.0)	3 (1.5)	2 (1.0)
No	20 (10.0)	124 (62.0)	49 (24.5)	14 (7.0)	149 (74.9)	29 (14.6)	36 (18.0)	133 (66.5)	24 (12.0)	25 (12.5)	124 (62.0)	44 (22.0)

ACE= Angiotensin converting enzyme; BMI= Body mass index; GFST= Gérontopôle Frailty Screening Tool; SOF= Study of Osteoporosis Fractures; *P<0.05

Discussion

An increasing number of studies have investigated the association between frailty and hypertension in the last years, but results are still uncertain. In the present study, we add knowledge to the current literature to suggest that hypertension, blood pressure levels and antihypertensive medication were not associated with frailty status in community-dwelling older adults, regardless of the frailty index used to frailty identification.

Although some evidence suggests a significant association between hypertension and blood pressure levels with frailty[8–12], a recent systematic review and meta-analysis of observational studies support our findings, given that no significant association was found between frailty and hypertension in adults[24].

Discrepancy in results among the studies may be explained by differences in age, time of diagnosis, controlled blood pressure levels, setting, lesions in physiological systems, type of blood pressure measurement, and sample size.

Regarding age, frail participants of the present study had a mean age of 70.2 years, while a mean age ≥ 72.6 years was observed in most investigations in which frailty was significantly associated with hypertension and blood pressure[8,9,12,36].

As time goes by, hypertension progresses and blood pressure levels remain increasing continuously[7]. This phenomenon affects cerebral microcirculation by provokes cerebral microbleeds, white-matter damage, and vessel rarefaction, to quote a few, potentially reducing cerebral blood flow in areas responsible for mobility (e.g. motor cortex) [17,18], causing substantial impairments on physical performance[37]. Indeed, a prospective study using data from the Cardiovascular Health Study (CHS), observed that older adults (~72 years) with previous diagnosis of hypertension and uncontrolled blood pressure levels had faster progression on vascular brain abnormalities over the follow-up than those with controlled hypertension[37].

Besides that, results from preclinical models found that hypertension progression is accompanied by increase in inflammatory and oxidative markers in the brain [13,15] and blood-brain barrier leakage[14,15], which allows the interaction between many potentially harmful molecules with the brain parenchyma[14,15].

As a whole, this data might suggest that the association between frailty and hypertension can be dependent of the time of diagnosis and age, so that very old adults with a greater time since diagnosis may show structural and functional changes on brain areas and vessels responsible for body movement, consequently collaborating with frailty progression.

Nevertheless, prior investigations observed that the relationship between frailty and cardiovascular abnormalities occurred in hypertensive outpatients[11] in the light of impaired

function of organ systems (e.g., reduced glomerular filtration rate)[10,38], while participants of the present study were community-dwelling older adults whose showed controlled blood pressure levels and lower prevalence of diseases in comparison with other studies[11].

Another potential explanation for our findings might be the time and type of blood pressure measurement used in the present study, since some authors proposed that frailty was significant associated with ambulatory blood pressure, but not office blood pressure[8].

However, any of the abovementioned confounding factors were controlled in the present study limiting the extrapolation of our findings and future studies targeting these limitations would be welcome.

Finally, we tested the hypothesis that hypertension would be differently associated with frailty status across the frailty instruments. Even though most studies have found a similar association between different frailty indexes and cognitive function, falls, disability, fractures, hospitalization, and all-cause mortality [33–35], Lin et al.[28] observed differences to predict disability and hospitalization among frailty indexes in prefrail older adults, suggesting that the pathogenic bases associated with frailty progress might be tool-dependent. In this context, understanding the association of hypertension and frailty according to each instrument may collaborate to a better patient's view and management.

It is worth mentioning that frailty instruments used in the present study are based on physical frailty and future studies should investigate other frailty concepts (e.g., cumulative deficit model)[39], given that hypertension may be associated with cognitive decline[40,41]

The present study has some limitations that should be acknowledged in addition to the lack of control of many confounding factors, such as a) our relatively small sample composed exclusively by community-dwellers, limiting inferences to older adults from other settings (e.g., nursing homes) and deeper statistical analysis, b) the adaptations performed in Fried frailty phenotype and GFST regarding walking speed test, c) and the cross-sectional design of the study, which does not allow inference to be drawn on the time course of changes of the variables considered and on cause-effect relationships.

Conclusion

Findings of the present study indicate that hypertension, office blood pressure levels and antihypertensive medication were not associated with frailty status in community-dwelling older adults, regardless of the frailty index used to frailty identification.

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ARTICLE 12

Effects of Low-Speed and High-Speed Resistance Training Programs on Frailty Status, Physical Performance, Cognitive Function, and Blood Pressure in Prefrail and Frail older adults

INTRODUCTION

Frailty is defined as a reversible state of increased vulnerability to adverse outcomes, including disability and mortality, which occurs separated and faster than a normal aging process in response to a multisystem impairment of the human body and social factors (1–4). Frailty is highly prevalent in older adults (2,4) with an incidence estimated as 43.4 new cases per 1000 person-years (5). In South America, a recent systematic review and metanalysis indicates an average frailty prevalence of 21.7% (Coelho-Junior et al., 2019; Article 2). As frailty progress, patients may present many negative health-related parameters, such as cardiovascular abnormalities, cognitive dysfunction, fractures, disability, hospitalization, nursing home placement, and death (6–10). As such, frailty represents a major public health problem (11).

The pathophysiological bases of frailty are still not totally elucidated, and many possibilities have been proposed, including endocrine dysregulation (3,12), low-grade inflammation (13), myokines activity (14), to quote a few. Sarcopenia, a neuromuscular disease characterized by significant dynapenia, reduced muscle function, and muscle loss, has been proposed as a substrate for frailty development and the physiopathologic pathway through which the negative consequences of frailty succeed (15,16). These statements are based on the fact that the clinical presentation of sarcopenia and frailty present substantial overlap, mainly when frailty presentation is based on the physical domain (15,16).

In this context, low-speed resistance training (LSRT), a type of exercise performed against a resistance with concentric muscle contractions performed at low-to-moderate velocity (17), has been recommended (18,19) as a first-line therapy to counteract sarcopenia-related parameters, given the numerous studies (20–23) that found improved muscle strength in response to LSRT protocols. However, there is still no consensus regarding the effects of LSRE on other frailty diagnosis criteria, as mobility (24).

Mobility is one of the five cardinal points of frailty (25) and represents the individual's ability to transfer from a place to another as comfortable as possible with a reduced risk of falls. Mobility impairments are a well-established risk factor for falls (26) and mortality

(27), as well as part of the clinical presentation of many diseases, such as stroke and Parkinson's.

Notably, many investigations in the early 2000's began to suggest that muscle power, the capacity to exert force in a short time interval, was more associated with mobility tasks than muscle strength (28–30). These findings led researchers (31–35) to examine if high-speed resistance training (HSRT) could cause greater improvements in mobility tasks than LSRT, and most studies have found superior effects of the former in robust community-dwelling older adults (31,32,35,36) and mobility-limited older adults (33), but no studies were performed in frail patients. Systematic reviews and metanalyses (37,38) supported these results but indicated that data must be carefully extrapolated to the clinical, given that meaningless differences were found among RT protocols.

Expert opinions (39–42) have encouraged the inclusion of HSRT on exercise programs for frail older adults. According to researchers, perform concentric muscle contractions as fast as possible would be crucial to improve mobility and restore independence.

Nevertheless, empirical evidence investigating the impact of HSRT programs on frail people are scarce. In one of the few investigations, Cadore et al. (43) found increased physical function and reduced incidence of falls in institutionalized frail older adults who performed exercise programs with a muscle power component.

Based on these premises, the current study investigated the effects of HSRT and LSRT on frailty status. Secondarily, we examined the effects of both RT programs on physical performance, cognitive function, and blood pressure, given its close association with frailty.

MATERIALS AND METHODS

Study design

This is a three-arm randomized controlled trial that investigated the effects of two types of RT on frailty status, physical performance, cognitive function, and blood pressure of prefrail and frail older adults. Ethics approval was granted by the University of Campinas Human Research Ethics Committee (Protocol No. 835.733). All participants provided written informed consent prior to participating. All study procedures were conducted following the principles of the Declaration of Helsinki. Figure 1 shows the experimental design of the present study.

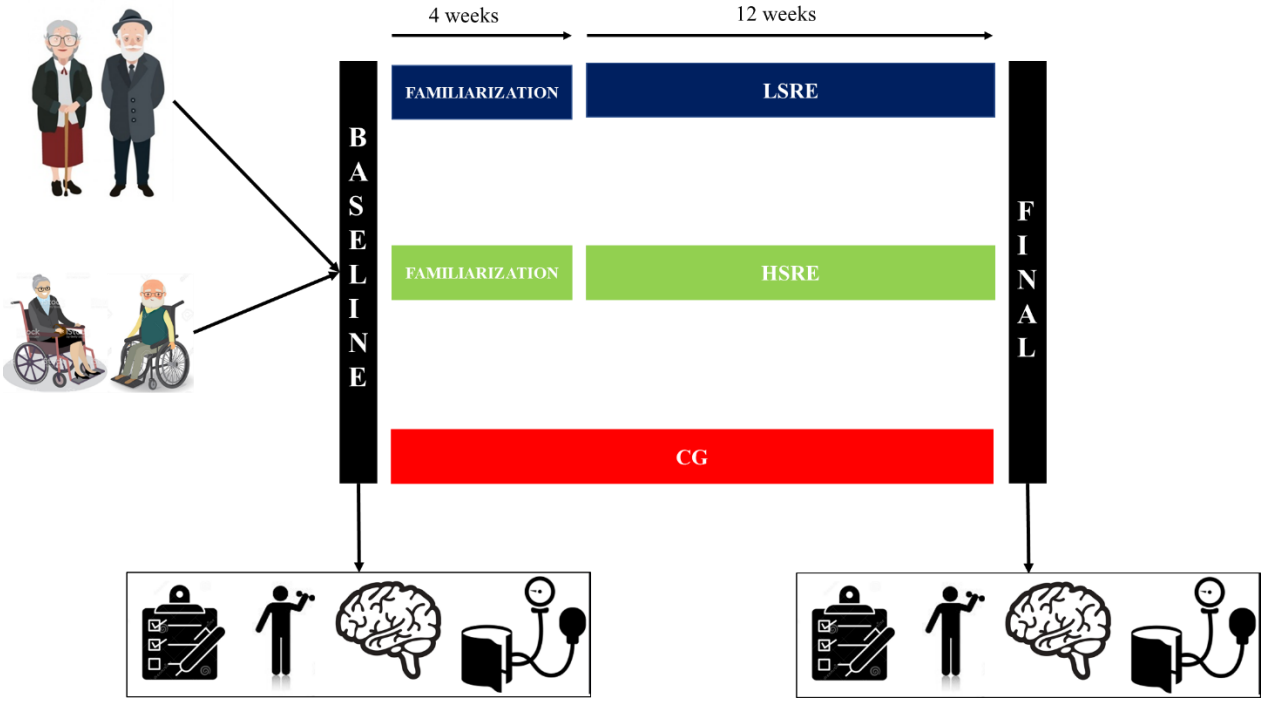


Figure 1. Experimental design of the present study.

Participants

Candidate participants were recruited from two different places. Prefrail volunteers (60-76 years) were recruited from the Center for Older Adults of the city of Poá, SP, Brazil. The study was advertised through posters placed in public sites (e.g., parks, city hall, public offices, bus stops, train stations) as well as via local radio and newspapers. People were also invited to participate by direct contact. Volunteers were on the waiting list to take part in one of the exercise groups offered by the Center for Older Adults and attended the center for primary health care (e.g., blood pressure measurement) and dancing classes.

Frail volunteers (66-99 years) were recruited from the Lar Mãe Mariana Nursing Home, SP, Brazil. The nursing home is a philanthropic institution structured with male and female accommodations, kitchen, dining room, TV room, nursing unit, rehabilitation unit, and psychological stimulation room. Most residents arrive at the nursing home due to abandonment, maltreatment, and/or financial, cognitive and physical disabilities. Patients are accommodated in the rooms according to gender and health status. On an ordinary day, residents commonly wake up around 0700 am, are monitored by nurses, and attend to the rehabilitation unit according to their self-will, where physiotherapists offer analgesia, massages, and physical movements without load up to 45 minutes. In the evenings, older patients watch movies, perform artworks, are visited by people, and/or remain in the garden. Visits to theaters, cinemas,

parks, and other places occur at least once a month. Meals are offered 5 times per day and no specific nutritional recommendations (e.g., protein consumption) for older adults are followed.

All candidate participants met the following inclusion criteria: a) aged 60 years or over; b) were prefrail or frail according to Fried's criteria (25); c) performed the sit-to-stand test alone, with a mobility aid, or researcher's help; d) possessed sufficient physical and cognitive abilities to perform exercise sessions; and e) had a physician authorization to participate. Exclusion criteria included having participated in a structured physical exercise training program in the past six months, prescription of hormone replacement therapy and/or psychotropic drugs, and any unstable cardiovascular event (e.g., myocardial infarction) or complication in the past 6 months.

The power of the sample size was determined using G*Power version 3.1.9.2 on the basis of the magnitude of the mean differences among the groups (i.e., for prefrail and after frail). Considering an effect size of 0.75 based on changes in muscle strength (44), a power of 80%, a level of significance set at 5%, and a dropout of 16.9% (45), the sample size necessary was estimated to be of 66 volunteers.

A computer-generated list of random numbers was used by an independent researcher to allocate participants into one of three experimental groups according to age, body mass index (BMI), and sit-to-stand performance: Low-speed resistance training (LSRT), High-speed resistance training (HSRT), and control group (CG), before baseline evaluations.

Clinical characteristics

Clinical characteristics were measured at baseline for sample characterization. Body mass and height were measured using an analog weight scale with a Filizola® (Brazil) stadiometer. BMI was calculated according to the following formula:

a) BMI= body mass (kg)/ height (m^2);

Information pertaining to disease conditions, medication, schooling, and time of institutionalization was collected through self-report and careful review of medical charts.

Primary outcome

- *Frailty status (appendix 3)*

The frailty phenotype was first described by Fried et al. (25). The instrument incorporates measures of multiple physical domains, including weight loss, exhaustion, weakness, slowness, and sedentary behavior (46,47). People are respectively identified as robust, prefrail and frail according to the presence of none, 1-2, and ≥3 of the following criteria:

(1) unintentional weight loss of ≥5 kg in the prior year; (2) self-reported fatigue; (3) weakness, based on isometric handgrip strength (IHG); (4) slowness, based on walking speed (WS) performance; and (5) low physical activity levels according to the short form of the International Physical Activity Questionnaire (IPAQ) (47). Gender-specific and gender- and height-specific cutoff points based on the median values of older adults from Poá, São Paulo, Brazil (Coelho-Junior et al., Article 16) were used for IHG and WS, respectively. Gender-specific cutoffs were used for physic activity levels (47).

Secondary outcomes

- *Physical function*

Physical function tests were administered by experienced exercise physiologists and physiotherapists. One examiner was responsible for detailing the operational procedures, demonstrating the test before the assessment, quantifying performance and evaluating motor patterns. The other examiner ensured the participant's safety by providing occasional verbal and/or tactile cueing if needed. Notably, most frail participants needed physical support for performing mobility tests, which was provided by the research team without interfering in the performance. After the explanation and before each test, prefrail participants performed a familiarization trial to ensure they had fully understood each test, while frail participants were requested to verbally explain the tests, to avoid fatigue. Except for the 6-min walking test (6MWT), participants performed all tests twice with the mean result used for analysis. Tests were administered in a sequential order with a 2-10-minute rest interval, as follows: 1) IHG, 2) muscle strength of knee extensors, hip flexors, and ankle extensors; 3) one-leg stand; 4) balance tests of the Short Physical Performance Battery (SPPB); 5) sit-to-stand; 6) Timed "Up and Go" (TUG); 7) WS at usual and fast paces; 8) 6MWT.

- *Isometric Handgrip Strength*

IHG of the dominant and nondominant hands was measured using a Jamar® handheld hydraulic dynamometer (Sammons Preston, Bolingbrook, IL, USA) (Figure 2) (49). The measure was obtained while the participant was seated on a chair with the shoulder abducted, the elbow near the trunk and flexed at 90°, and the wrist in a neutral position (thumbs up). The contralateral arm remained relaxed under the thigh. To measure IHG, participants performed a maximal contraction during 4 s. The test reliability in prefrail and frail participants was 0.97 and 0.98, respectively.

Figure 2. Frail participant performing IHG test.

- *Isometric muscle strength of knee extensors, hip flexors, and ankle extensors*

The isometric strength of knee extensors, hip flexors, and ankle extensors was measured using a handheld dynamometer (mTasF-1; ANIMA, Tokyo, Japão) (50). Before testing, participants remained seated with both hands on their thighs, and their knee and hip flexed at 90°. Muscle strength was assessed with the handheld placed: a) near the midpoint of the tibia, for knee extensors; b) near the midpoint of the femur, for hip flexors; and c) between the patella and the femur, for ankle extensors. Participants were requested to perform as much strength was possible to move their joints for 4 seconds. The test reliability in prefrail and frail participants was 1.0.

Figure 3. Muscle strength of knee extensors (Figure 3a and 3b), hip flexors and ankle extensors (Figure 3c).

One-Leg Stand Test

The one-leg stand test was performed with participants standing in a unipodal stance on the dominant and nondominant lower limbs, with the contralateral knee flexed at 90°,

arms folded across the chest or stretched over the body, and head held straight (51) (Figure 4). Timing began when participants raised one foot off the floor and was stopped when the foot touched the floor again. The maximum performance time was set at 30 s. The test reliability in prefrail and frail participants was 0.8.

Figure 4. Frail participants performing the one-leg stand test.

Balance tests of the SPPB

Participants performed the hierarchical test of standing balance of the SPPB (52). Participants were asked to stand with their feet side by side, followed by the semitandem (heel of one foot alongside the big toe of the other foot) and tandem (heel of one foot directly in front of and touching the other foot) positions for 10 s each. The test reliability in prefrail and frail participants was 0.8.

Sit-to-Stand Test

Participants rose from a chair five times as quick as possible with at least one arm positioned on the waist, while the other arm remained folded across the chest or holding a researchers' hand. Timing began when the participant raised their buttocks off the chair and was stopped when the participant was seated at the end of the fifth stand (Figure 5) (52). A 50-Hz linear encoder (Peak Power, CEFISE, Brazil) was attached to the wrist of the arm that was

at the waist to obtain muscle power (w) and the velocity (m/s^2) of concentric and eccentric contractions. The test reliability in prefrail and frail participants was 1.0 and 7.8, respectively.

Figure 5. Frail participants performing the sit-to-stand test.

Timed-Up-and-Go Test

The TUG test involved getting up from a chair (total height: 87 cm; seat height: 45cm; width: 33 cm), walking three meters around a cone placed on the floor, coming back to the same position, and sitting back on the chair (53). Participants wore regular footwear, placed their back against the chair, rested their arms on the chair's arms, and put their feet on the ground. A researcher instructed the participant to, on the word “go”, get up, walk three meters as fast as possible without compromising the safety, turn, walk three meters back to the chair, and sit down. Timing began when the participant got up from the chair and was stopped when the participant’s back touched the backrest of the chair. TUG was performed at usual and fast paces in the present study. The test reliability in prefrail and frail participants was 0.9.

Timed-Up-and-Go Test with secondary tasks

After performing the traditional TUG task, participants performed b) TUG combined with a verbal fluency task, naming as many animals as they could remember, (c) TUG with a motor task, carrying a full cup of water), and (d) TUG test with both cognitive and

motor tasks; i.e., performing the verbal fluency test while carrying a full cup of water (Figure 6)(54). The test reliability in prefrail and frail participants was 0.98 and 0.94, respectively.

Figure 6. Frail participants performing TUG with motor task.

Walking Speed Tests

WS was measured over four meters (Figure 7)(52). For the test, participants were required to walk six meters (including one-meter acceleration and one-meter deceleration) at their usual and fastest possible pace (without running). Before the evaluation, both feet of each participant were to remain on the starting line. Timing began when a foot reached the 1-meter line and was stopped when a foot reached the 4-meter line. The 1-meter intervals at the beginning and at the end of the course were used to avoid early acceleration and/or deceleration. The test reliability in prefrail and frail participants was 1.0.

Figure 7. Prefrail participants performing WS test.

6-min walking test

The 6MWT was performed according to the American Thoracic Society guidelines (55). The test was performed indoors on a 30-m track. In summary, after remaining seated for 15 min, the volunteers were asked to walk on the track as fast as possible for six minutes. In the case that the volunteers experienced chest pain, intolerable dyspnea, leg cramps, stagger, diaphoresis, pale or ashen appearance, or any other complaint, the test was interrupted. The distance walked by the volunteers in meters was used in the analysis.

Cognitive function

- *Mini-Mental State Examination (MMSE) (appendix 4)*

The participants' cognitive function was assessed using the MMSE, which is a standard test in cognitive aging research to assess mental status with a possible score of 0–30. MMSE evaluates orientation, registration, and short-term recall, attention and concentration, language (naming, sentence writing, and comprehension), and visuospatial abilities. Individual items are summed to generate the total score. If individuals decline or are unable to attempt a task, the value of that particular item would be missing (56,57).

- *Clock Drawing Test (CDT)*

CDT involves draw the face of a large clock, place all the numbers inside the clock and place the pointers indicating 11:10 (eleven hours and ten minutes). No time limit was given to participants and they were allowed to draw as many watches as they wanted as long as only one of them was indicated for analysis. CDT was analyzed according to the method proposed by Shulman et al. (58).

- *Rey's Auditory Verbal Learning Test (RAVLT) (appendix 5)*

RAVLT is a neuropsychological tool used for testing episodic memory (59–62) and its scores have been strongly associated with the atrophy of medial temporal lobe structures (e.g., hippocampus) responsible for memory formation and maintenance after learning (61). In addition, RAVLT is useful to distinguish patients with and without dementia (59) and normative data according to gender and age have been provided to young, middle-aged and older adults (62,63) and patients with stroke, epilepsy, and neoplasm (60). The test consists of read-aloud two lists (A and B) of 15 substantives each (with a 1-s interval between each word). At the beginning of the test, list A was read five consecutive times by a researcher. Then, participants

were requested to recall as many words were possible after each trial (A1-A5). The list B, interference list, with new 15 substantives was read after A5 and words were retrieved (B1). Finally, participants were asked to recall the words from list A immediately after the interference list (A6, immediate recall) and after a delay of 20 minutes (A7, delayed recall), without listening to the list A again (63). Four summary scores were used to assess episodic memory, delayed memory, and susceptibility to interference (63):

a)Verbal learning (VL) score= ΣA1-A5 – (5 * A1);

b)Proactive interference (PI)= B1/A1;

c)Retroactive interference (RI)= A6/A5;

d)Forgetting speed (FS)= A7-A6;

- *Stroop test*

A computerized version of the Stroop test (TESTINPACSTM) was used to provide reaction time (ms) and the number of correct words in each stimulus (control, congruent, incongruent) (Figure 8)(64,65). To the test, participants remained seated in front of a 17-inch color monitor. The distance between the participant and the monitor was chosen according to the participants' vision needs. Stroop was divided into three phases. In the first phase, control stimulus, the monitor exhibited a rectangle painted in green, yellow, blue, or red. Two possible responses, corresponding or not to the color of the rectangle, were exhibited at the lower corners of the monitor, and participants were requested to tell the color corresponding to the rectangle. The second phase was called congruent stimulus and consisted in stimulus (i.e., name of a color) and responses (i.e., name of two colors, one corresponding to the first color and the other not) exhibited as words in white. The correct answer was telling which colors match. The third phase, incongruent stimulus, is called Stroop effect and consisted of four colors exhibited is an incompatible color. The participants were requested to tell the color corresponding to the letters and inhibit the response for the identity of the disclosed word. A total of 36 stimuli (12 attempts each phase) were randomly provided and the time was registered in milliseconds. After the participants' response, a researcher was responsible to immediately press the corresponding key (← or →). This protocol was established after a pilot study in which we observed that participants of the present study took too long or were not able to return the hand to the initial position, if they had to take it off, even if the keyboard was composed only by two keys.

Figure 8. STROOP test: control, congruent and incongruent stimulus.

Blood pressure and heart rate

Blood pressure was measured accordingly to the VII Joint National Committee of High Blood Pressure (JNC7)(66). Pre- and post-intervention blood pressure values were based on the mean values measured in three consecutive visits in three different days. For blood pressure evaluation, participants remained seated in a comfortable chair in a room with artificial light. Blood pressure and heart rate were blindly measured in the left arm using automated oscillometric equipment (BP 3BT0A, Microlife AG, Widnau, Switzerland) (67). At the end of each measurement, the equipment provided systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR).

Exercise interventions

Exercise interventions were carried out over a total of 16 weeks in the mornings (08:00 am–12:00 am) under the supervision of at least two fitness instructors. The first four weeks were dedicated to participants' familiarization. In this period, participants performed four exercises for lower limbs (Figure 9): 1st) squat on the chair, 2nd) seated unilateral hip flexion, 3rd) seated unilateral knee extension, and 4th) bilateral calf raise with 12–15 submaximal repetitions avoiding fatigue (i.e., inability to complete a repetition in a full range of motion). The number of sets was increased linearly during the first month, such that one set was performed in the 1st week, two sets in the 2nd week, 3 sets in the 3rd week, and 4 sets in the 4th week. Subsequently, participants performed the main exercise period. After a brief warm-up, participants performed the same exercises that were performed during the familiarization period using an adjustable weight vest and ankle weights (DOMYOS®, Shangai, China). The total volume (sets x repetitions x load) was equalized among the exercise sessions. However, LSRT and HSRT were designed according to the peculiarities of each type of resistance exercise (17,68). During LSRT, participants performed 4 sets of 8-10 repetitions at 70%-75% of 1-

repetition maximum (1RM). The concentric and eccentric phases should be carried out for ~2.5-s. For HSRT, exercises were performed 8 times (sets) with 3-5 repetitions at 70%-75% of 1RM. The concentric phase was performed as fast as possible and the eccentric phase was carried out for ~2.5-s. Bilateral calf raise was performed with the load of unilateral knee extension. A researcher was responsible for monitoring and ensuring that the velocity of muscle contraction was according to the protocol. Particularly, verbal encouragement was provided in the HSRT.

Figure 9. Resistance exercises used in the present study. 1st) squat on the chair, 2nd) seated unilateral hip flexion, 3rd) seated unilateral knee extension, 4th) bilateral calf raise.

Ten-repetition maximum test (10RM)

10RM tests were performed prior, monthly, and at the end of the exercise programs in the following three exercises: squat on the chair (until 90° knee flexion), seated unilateral hip flexion, and seated unilateral knee extension. Before the tests, individuals performed a brief specific warm-up using light loads. Afterward, the 10RM load was determined up to 5 attempts, with a 3-minute interval between the attempts. The resistance was increased according to the capacity of the volunteer to perform more than one successful repetition maximum with the proper technique. The test was completed when participants were unable to perform more than 10 repetitions using a proper technique (69). All trials were performed with participants using the full range of motion. Subsequently, the 1RM was calculated based on the following formula:

b) 1RM= (10RM/ (1.0278 - [0.0278 × 10])) (70).

Statistical Analysis

Normality of data was ascertained using the Kolmogorov-Smirnov test. Data are presented as mean ± standard deviation (SD) or absolute numbers (percentages) for continuous and categorical variables, respectively. A group × time repeated-measures ANOVA followed by Bonferroni posthoc analyses were performed to determine whether there were significant

differences between groups. For all tests, the level of significance was set at 5% ($p < 0.05$). All analyses were conducted using GraphPad Prism 6.0. (San Diego, CA). The intention-to-treat principle was applied to the analysis of the outcomes for all participants based on their assigned treatment, after excluding volunteers who had missed four or more exercise sessions in a recurrent and sequential manner according to the records.

RESULTS

The flowchart of the present study is shown in Fig. 10. One-hundred twenty-two older adults were recruited and evaluated for eligibility criteria. Of these, 37 were identified as robust and 7 could not attend exercise training in the mornings, leaving a total of 78 older adults, 39 prefrail and 39 frails, who were randomized into the three groups (i.e., LSRT, HSRT, and CG). Adherence to exercise sessions was above 95% in both prefrail and frail groups. Five prefrail and eleven frail participants withdrew from the trial. In prefrail, 3 participants from the CG withdrew to start a programmed exercise program, while two, one from the HSRT and one from the LSRT, withdrew after two weeks because they were not randomized to the same exercise group. In frail, four participants withdrew due to personal reasons, two participants due to the 10RM test, one start to take psychotropic drugs, one could not attend for exercise sessions for two months due to substantial weight loss and complains of muscle fatigue, one had a stroke, one had urinary tract infection, and one died.

Most participants complained of extraneous muscle fatigue during the familiarization period, but not in the main period. Two participants reported pain and one participant from the HSRT group reported epigastric discomfort and nausea during the performance of the squat on the chair exercise.

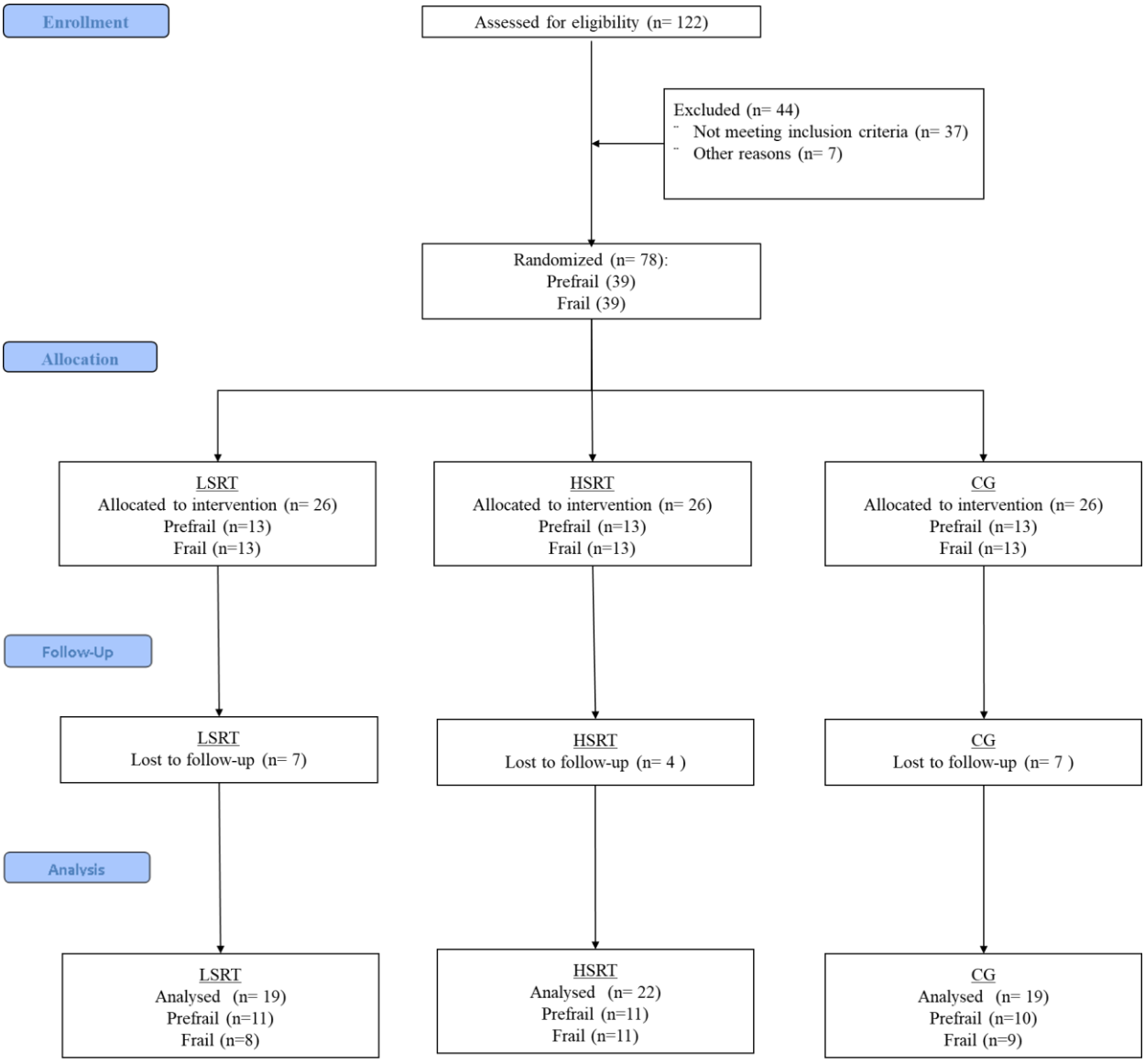


Figure 10. Flowchart of the present study. LSRT= Low-speed resistance training; HSRT= High-speed resistance training; CG= Control group.

Clinical characteristics

Table 1 shows the clinical characteristics of prefrail and frail participants according to group allocation. There were no significant differences between experimental and CG groups regarding the clinical characteristics of study participants. Frail participants were older and had a lower time of formal education in comparison to prefrail. The average BMI was within normal limits for both groups. Hypertension and type II diabetes were highly prevalent in prefrail and frail, while osteoarthritis, stroke, and Parkinson's disease were most notorious in frail. There were significant differences in physical performance between exercise and CG in prefrail and frail. In prefrail, LSRT showed higher right and left muscle strength of knee extensors, right

hip flexor, and balance on one-leg stand test. In addition, CG showed higher TUG performance when compared to LSRT. In frail, LSRT showed higher right and left muscle strength of knee extensors in comparison with HSRT and CG, and lower TUG performance in comparison to HSRT. No differences in cognitive function or blood pressure were observed in any group.

Table 1. Main characteristics of study participants.

	Prefrail (n= 32)			Frail (n= 28)		
	LSRT (n= 11)	HSRT (n= 11)	CG (n= 10)	LSRT (n= 8)	HSRT (n= 11)	CG (n= 9)
Variables						
Clinical Characteristics						
Age, years	65 ± 3.5		65 ± 3.5	75 ± 4.6	73 ± 7.5	75.0 ± 9.2
Gender, female/male	9/2	11/0	11/0	6/2	6/5	6/3
BMI, kg/m²	26.8 ± 5.7	24.5 ± 2.4	25.5 ± 3.3	25.3 ± 3.1	24.6 ± 3.5	25.7 ± 2.4
Schooling, years	7 ± 2.9	4 ± 2.1	8 ± 2.1	2 ± 4.5	0 ± 3.5	0 ± 4.9
Time of institutionalization, years	—	—	—	2 ± 0.9	2.0 ± 3.1	2.0 ± 1.5
Comorbidities, %						
Hypertension	72.7	36.6	100	87.5	63.6	44.4
Osteoarthritis	27.2	27.2	36.3	25.0	36.3	66.6
Stroke	0	0	0	12.5	9.0	11.1
Diabetes	9.0	27.2	9.0	37.5	9.0	11.1
Parkinson's disease	0	0	0	0	9.0	0
Frailty phenotype, %						
Weakness	45.4	72.7	0	87.5	72.7	77.7
Slow walking speed	18.1	45.4	20.0	87.5	81.8	66.6
Unintentional weight loss	0	9.0	40.0	50	63.6	77.7
Exhaustion	45.4	72.7	81.8	100	100	100
Low activity level	0	9.0	20.0	100	100	100
Physical performance						
Right IHG, kg	25.0 ± 4.0	21.9 ± 5.7	25.9 ± 3.2	6.2 ± 5.5	4.8 ± 6.4	13.8 ± 13.7ab
Left IHG, kg	25.5 ± 6.1	21.3 ± 6.0	25.7 ± 3.6	8.5 ± 9.5	9.6 ± 9.3	12.7 ± 12.4ab
Right knee extensor, kgf	17.3 ± 4.2	11.7 ± 2.3a	10.1 ±1.9a	7.0 ± 1.9	7.1 ± 2.8	7.0 ± 5.7

Left knee extensor, kgf	14.8 ± 3.1	12.3 ± 3.4a	10.3 ± 2.3a	6.6 ± 2.0	6.1 ± 3.7	6.6 ± 5.0
Right hip flexor, kgf	11.1 ± 3.2	8.2 ± 3.3a	8.6 ± 3.6a	6.0 ± 1.7	5.4 ± 2.2	4.7 ± 2.8
Left hip flexor, kgf	10.1 ± 2.7	8.1 ± 2.8	8.3 ± 2.5	5.4 ± 1.1	5.1 ± 2.5	4.3 ± 2.5
Right ankle extensor, kgf	6.8 ± 2.1	6.4 ± 1.8	5.8 ± 1.1	5.6 ± 1.5	4.3 ± 2.6	3.8 ± 2.3
Left ankle extensor, kgf	7.1 ± 1.7	6.4 ± 1.8	6.4 ± 1.1	3.8 ± 2.8	4.4 ± 2.4	3.7 ± 2.6
Right one-leg stand, s (30 s max)	19.4 ± 9.7	10.9 ± 11.6a	12.5 ± 12.0a	0.1 ± 0.3	0.1 ± 0.4	2.2 ± 3.1
Left one-leg stand, s (30 s max)	16.4 ± 11.0	13.0 ± 12.2	7.3 ± 10.4a	0.0 ± 0.2	0.2 ± 0.4	2.3 ± 4.4
Normal balance, s (10 s max)	10.0 ± 0.0	9.8 ± 0.6	10.0 ± 0.0	1.2 ± 3.5	1.8 ± 4.0	4.4 ± 5.2
Semi tandem balance, s (10 s max)	10.0 ± 0.0	9.8 ± 0.6	10.0 ± 0.0	0.0 ± 0.0	1.0 ± 3.0	4.4 ± 5.2
Tandem balance, s (10 s max)	10.0 ± 0.0	6.9 ± 0.6	10.0 ± 0.0	0.0 ± 0.0	0.8 ± 2.7	5.5 ± 5.2
Sit-to-stand, s	8.4 ± 1.1	10.0 ± 2.3	8.0 ± 0.6	26.7 ± 11.6	26.2 ± 13.3	28.6 ± 10.9
TUG at usual pace, s	8.0 ± 0.8	10.2 ± 2.7	6.2 ± 1.4a	119.8 ± 180.2	20.8 ± 27.3a	46.4 ± 36.3
TUG at fast pace, s	6.5 ± 1.1	8.4 ± 2.5	5.6 ± 0.9	38.0 ± 46.3	17.4 ± 22.8a	28.5 ± 25.4
TUG with verbal task, s	8.3 ± 1.0	10.7 ± 3.9	7.1 ± 1.2	69.0 ± 109.8	18.4 ± 24.1	37.5 ± 43.2
TUG with motor task, s	8.7 ± 1.7	10.1 ± 2.1	8.0 ± 0.8	14.2 ± 13.0	7.1 ± 12.9	16.1 ± 20.7
TUG with both verbal and motor tasks, s	8.3 ± 1.1	11.6 ± 3.2	10.9 ± 1.4	17.6 ± 19.7	8.3 ± 18.7	17.7 ± 23.2
WS at usual pace, m/s	1.3 ± 0.3	1.2 ± 0.2	1.3 ± 0.3	0.41 ± 0.37	0.81 ± 0.99	0.51 ± 0.41
WS at fast pace, m/s	1.8 ± 0.3	1.5 ± 0.3	1.9 ± 0.3	0.46 ± 0.41	0.66 ± 0.91	0.62 ± 0.50
6MWT, m	480 ± 137	460 ± 151	589 ± 179	150 ± 174	100 ± 136	91.4 ± 107
Cognitive function						
MMSE, points	24.3 ± 1.9	23.2 ± 1.8	23.4 ± 1.5	15.6 ± 4.5	13.8 ± 3.7	16.0 ± 2.0
CDT, points	1.6 ± 0.8	1.6 ± 0.7	2.0 ± 0.7	5.5 ± 1.4	5.5 ± 1.3	4.4 ± 1.4
Hemodynamic parameters						
SBP, mmHg	130.4 ± 14.9	131.6 ±19.5	137.8 ± 13.5	124.0 ± 21.6	114.3 ± 17.0	140.1 ± 15.4
DBP, mmHg	68.0 ± 23.0	72.0 ± 10.0	79.8 ± 11.8	81.9 ± 15.5	67.8 ± 9.4	79.2 ± 11.7
HR, bpm	73.7 ± 11.6	73.7 ± 9.6	73.1 ± 4.2	65.9 ± 5.6	70.5 ± 12.2	86.7 ± 12.3

BMI= Body mass index; IHG= isometric handgrip strength; TUG= Timed "Up-and-Go"; 6MWT= 6-min walking test; MMSE= Mini mental state examination; CDT= Clock Drawing Test; SPB= Systolic Blood Pressure; DBP= Diastolic Blood Pressure; HR= Heart Rate; LSRT= Low-Speed Resistance Training; HSRT= High-Speed Resistance Training; CG= Control Group; aP<0.05 vs LSRT; bP<0.05 vs HSRT.

Frailty Status

The effects of RT on frailty status are shown in Figures 11 and 12. Both LSRT and HSRT reduced the prevalence of frailty criteria in prefrail and frail older adults. Six (54.5%) prefrail participants returned to robust condition after LSRT, while only two (18.1%) participants became robust after HSRT. RT improved weakness, slowness, and exhaustion in prefrail.

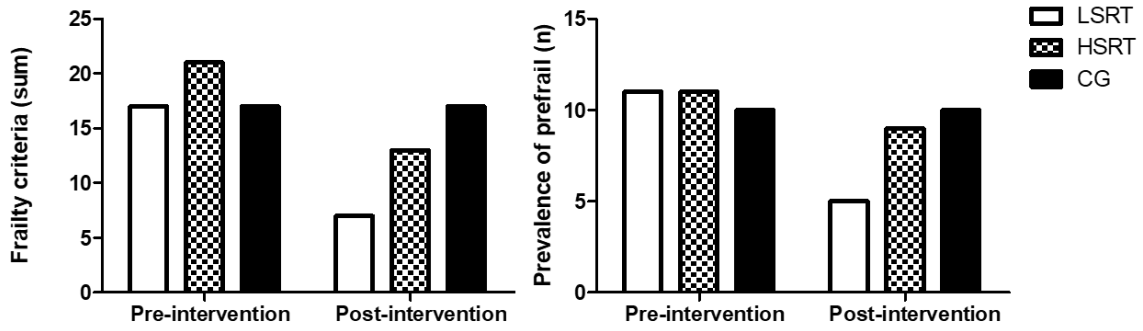


Figure 11. The effects of RT on frailty criteria (a) and status (b) in prefrail older adults. LSRT= Low-speed resistance training; HSRT= High-speed resistance training; CG= Control group.

Regarding frail, ten participants, five in each intervention group (62.5%, 45.4%), returned to prefrail condition, and two participants (12.5%, 9.0%), one in each intervention group, returned to robust condition after LSRT and HSRT. RT improved weight loss, sedentary behavior, and exhaustion.

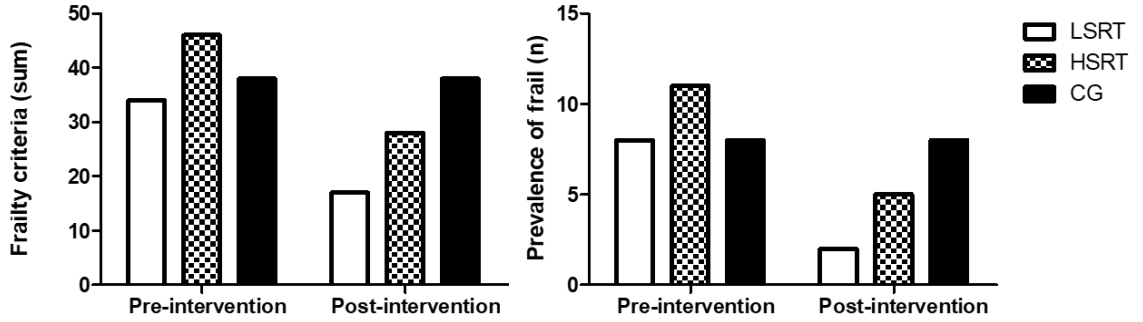
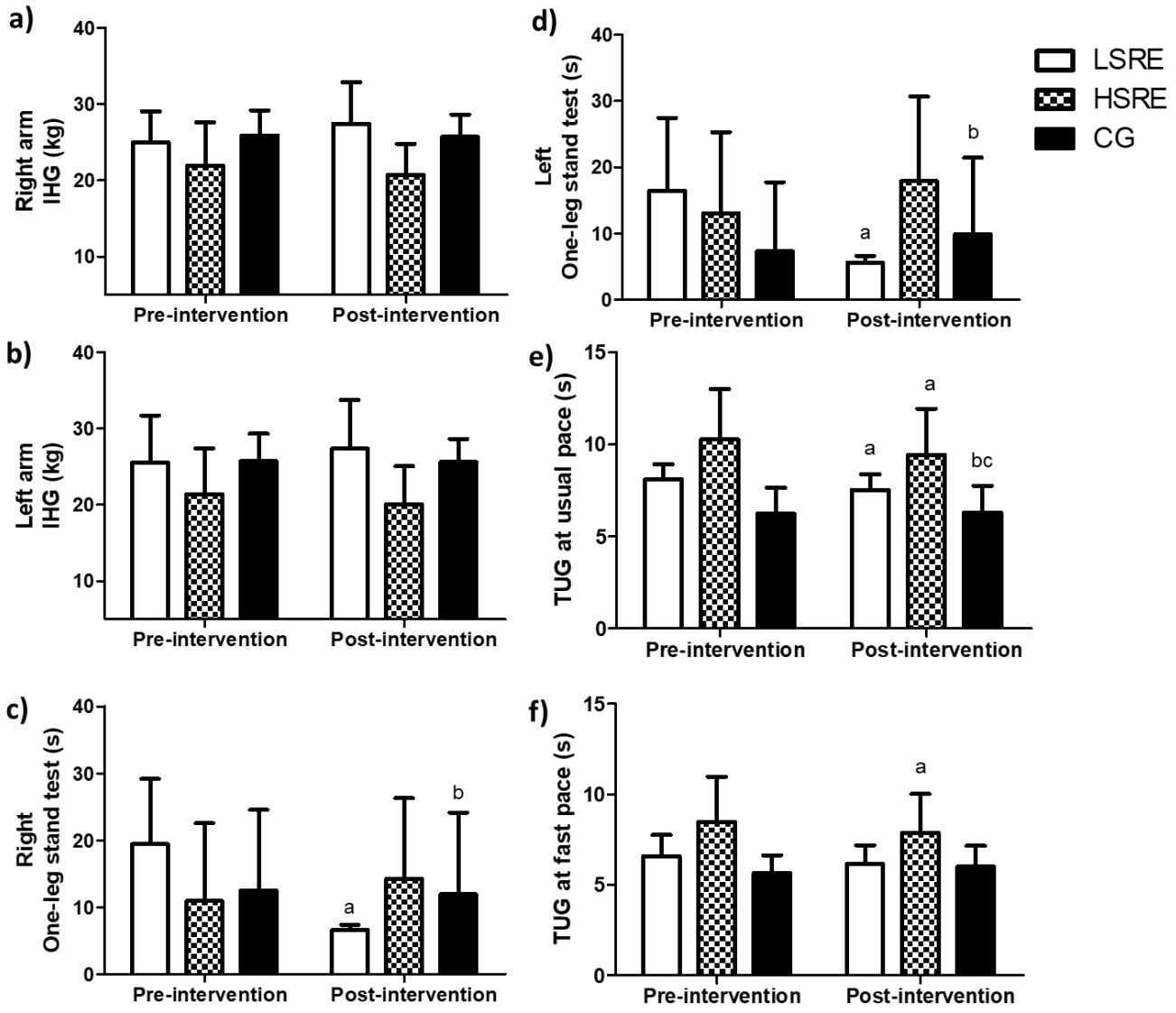
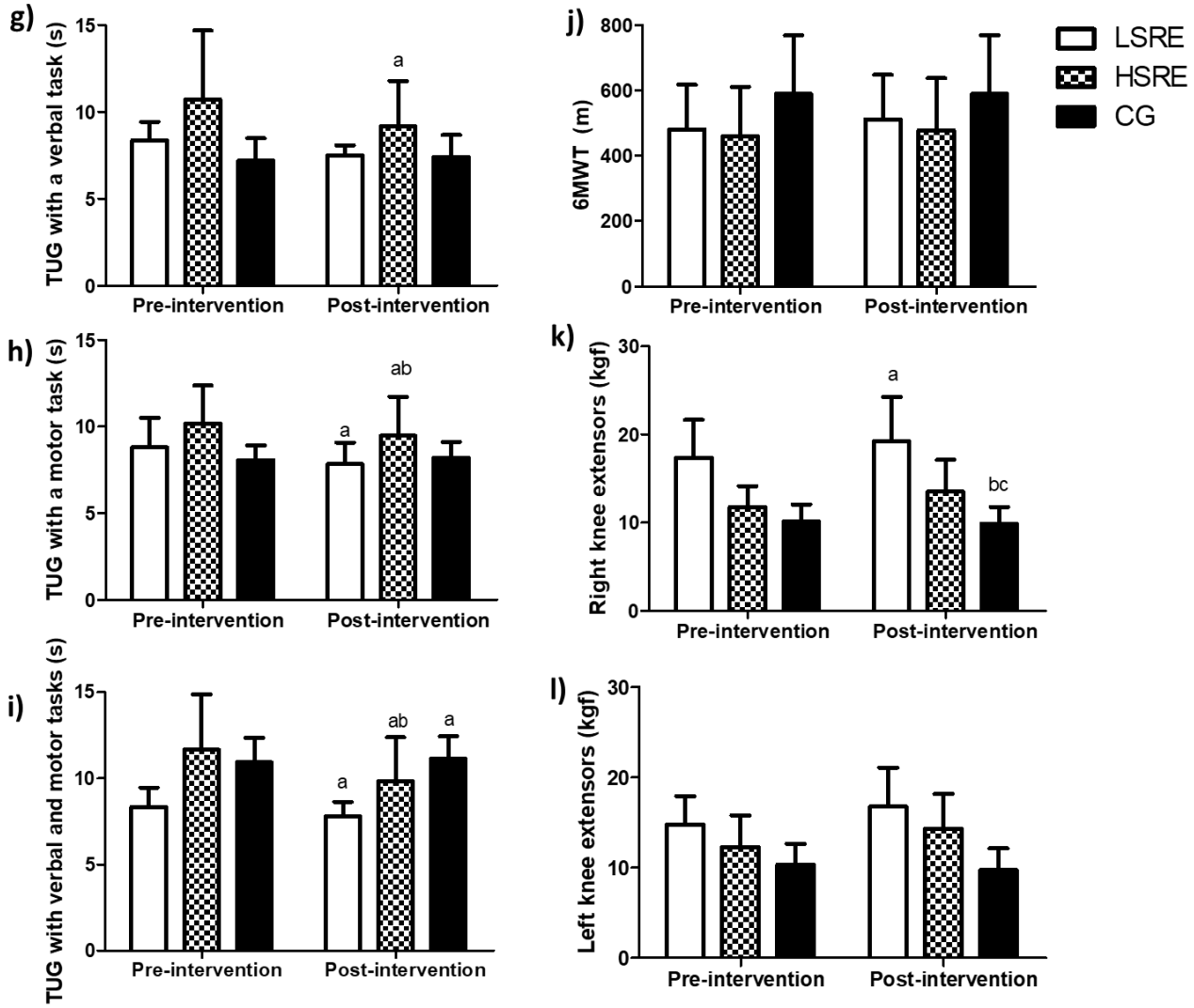


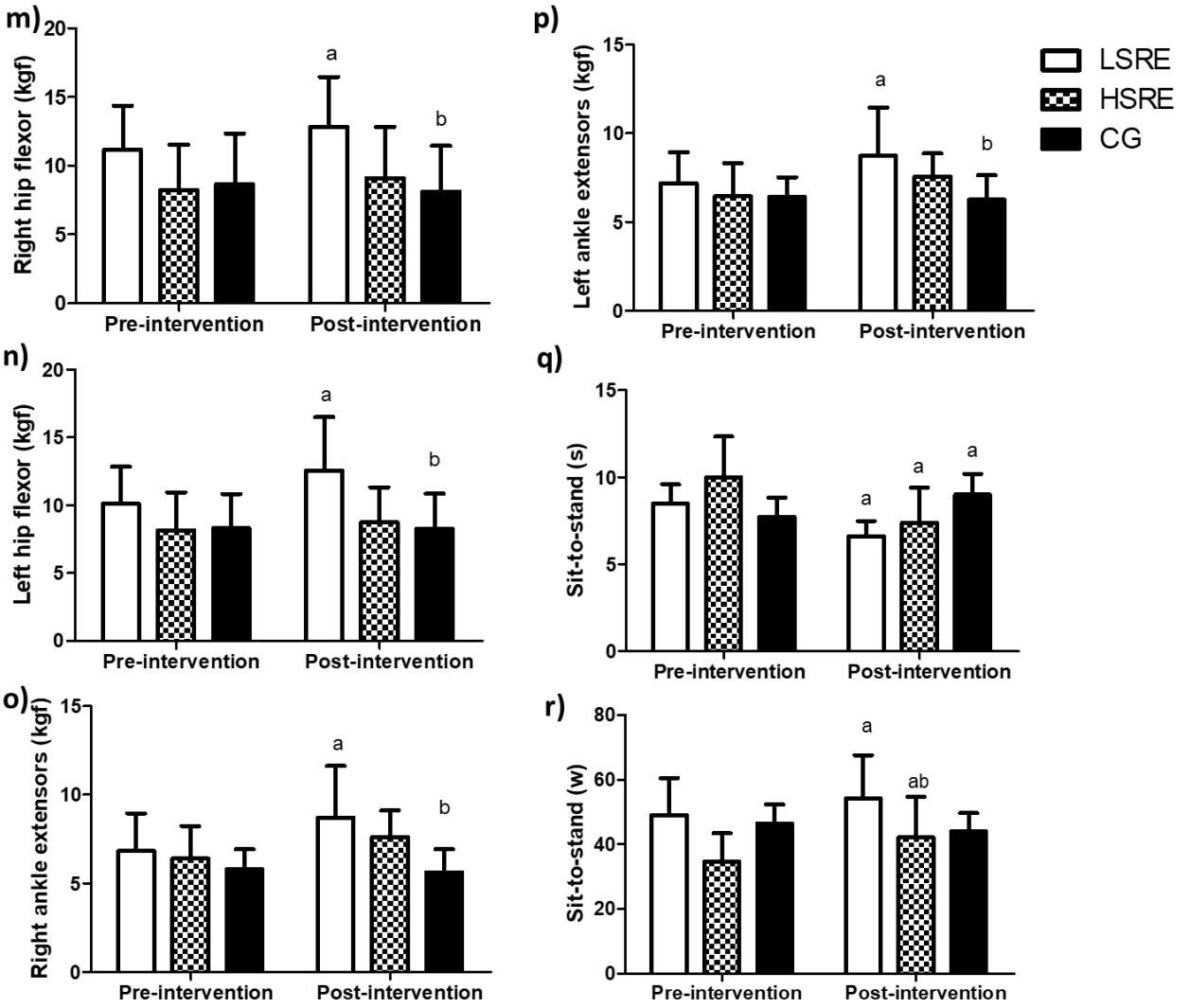
Figure 12. The effects of RT on frailty criteria (a) and status (b) in frail older adults. LSRT= Low-speed resistance training; HSRT= High-speed resistance training; CG= Control group.

Physical function

The effects of RT on physical function are shown in Figures 13 and 14. LSRT and HSRT caused different patterns of improvements in physical function in prefrail. LSRT improved muscle strength of the right knee extensors (P=0.01), right (P=0.01) and left (P=0.001) hip flexors, and right (P=0.001) and left (P=0.01) ankle extensors, while the right (P<0.001) and left (P=0.01) one-leg stand performances were significantly reduced. In contrast, TUG at fast pace (P=0.01), TUG associated with a verbal task (P=0.001), TUG associated with motor and verbal tasks (P<0.001), and tandem balance (P=0.01) were only improved after HSRT. Performance time (P<0.001), power (P=0.05, P<0.001), and the velocity of muscle contraction (P<0.001) in the sit-to-stand test, TUG at usual pace (P=0.01, P<0.001), and TUG associated with a motor task (P=0.01, P<0.001) were significantly improved in response to LSRT and HSRT. CG showed a significant increase in the time on the sit-to-stand (P<0.001) test. At the end of the protocol, higher TUG performance (P<0.001) and muscle strength of the right (P<0.001) and left knee extensors (P<0.001) were observed in exercise groups in comparison to CG, while only LSRT showed lower right and left one-leg stand performances (P<0.001) and higher muscle strength of the right (P=0.01) and left (P<0.01) hip flexors, and right (P<0.01) and left (P<0.01) ankle extensors in comparison to CG. Significant differences in TUG associated with motor task (P=0.01), TUG associated with motor and verbal tasks (P=0.01), and power (P=0.01) in the sit-to-stand test were found between LSRT and HSRT.


a)
Right arm IHG (kg)
40
30
20
10
Pre-intervention
Post-intervention
b)
Left arm IHG (kg)
40
30
20
10
Pre-intervention
Post-intervention
c)
Right One-leg stand test (s)
40
30
20
10
0
a
b
Pre-intervention
Post-intervention
d)
Left One-leg stand test (s)
40
30
20
10
0
a
b
Pre-intervention
Post-intervention
LSRE
HSRE
CG
e)
TUG at usual pace (s)
15
10
5
0
a
a
bc
Pre-intervention
Post-intervention
f)
TUG at fast pace (s)
15
10
5
0
a
Pre-intervention
Post-intervention


g)
TUG with a verbal task (s)
15
10
5
0
a
Pre-intervention
Post-intervention
h)
TUG with a motor task (s)
15
10
5
0
a
ab
Pre-intervention
Post-intervention
i)
TUG with verbal and motor tasks (s)
15
10
5
0
a
ab
a
Pre-intervention
Post-intervention
j)
6MWT (m)
800
600
400
200
0
Pre-intervention
Post-intervention
LSRE
HSRE
CG
k)
Right knee extensors (kgf)
30
20
10
0
a
bc
Pre-intervention
Post-intervention
l)
Left knee extensors (kgf)
30
20
10
0
Pre-intervention
Post-intervention


m)
Right hip flexor (kgf)
20
15
10
5
0
a
b
Pre-intervention
Post-intervention
p)
Left ankle extensors (kgf)
15
10
5
0
a
b
Pre-intervention
Post-intervention
LSRE
HSRE
CG
n)
Left hip flexor (kgf)
20
15
10
5
0
a
b
Pre-intervention
Post-intervention
q)
Sit-to-stand (s)
15
10
5
0
a
a
a
Pre-intervention
Post-intervention
o)
Right ankle extensors (kgf)
15
10
5
0
a
b
Pre-intervention
Post-intervention
r)
Sit-to-stand (w)
80
60
40
20
0
a
ab
Pre-intervention
Post-intervention

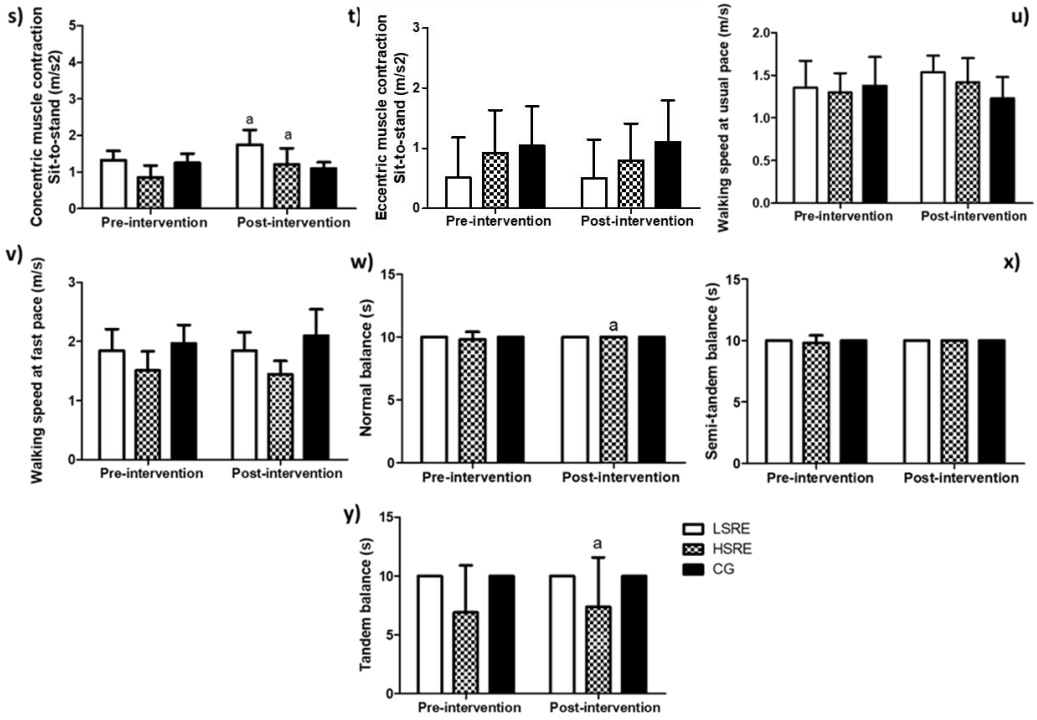
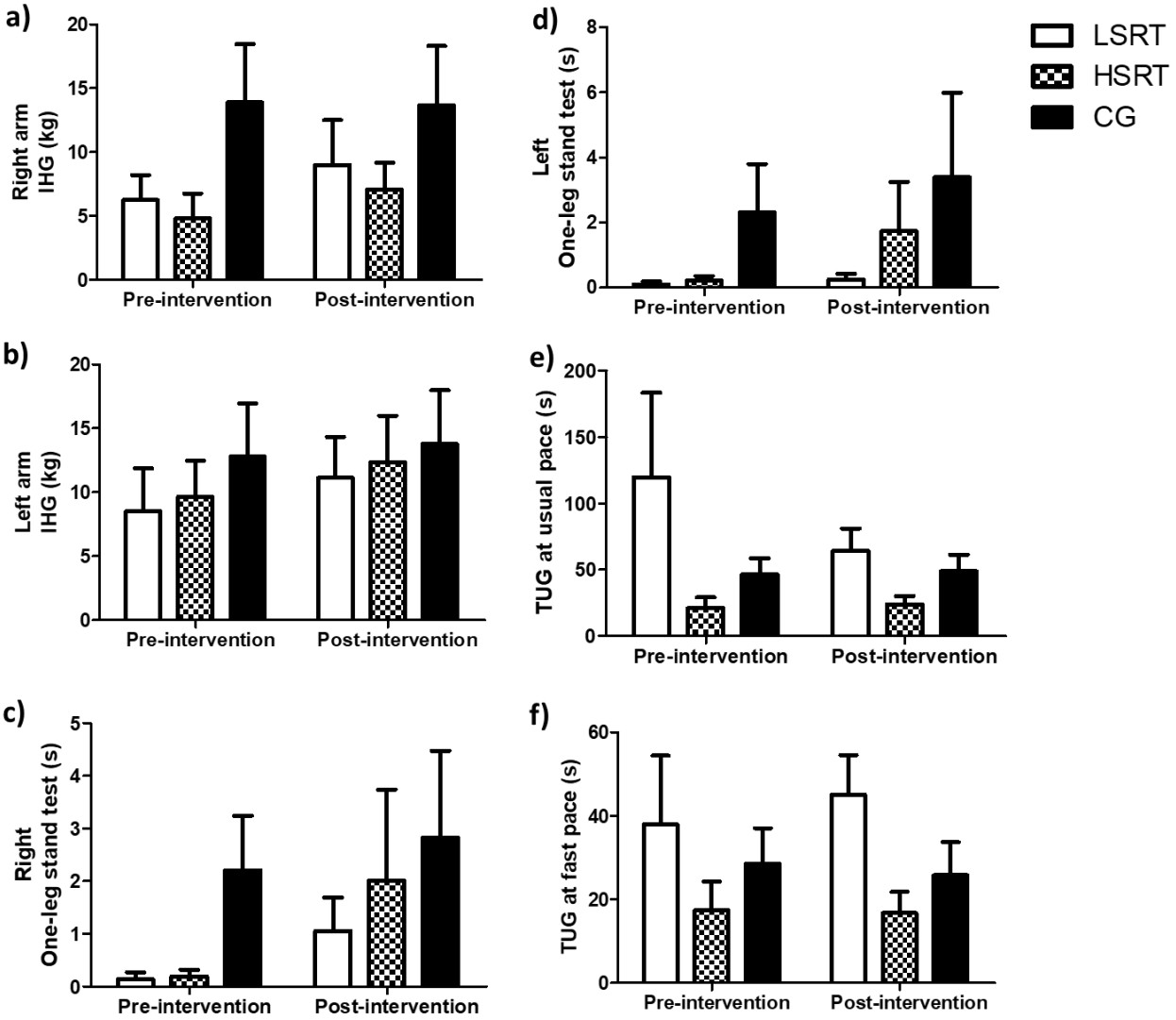
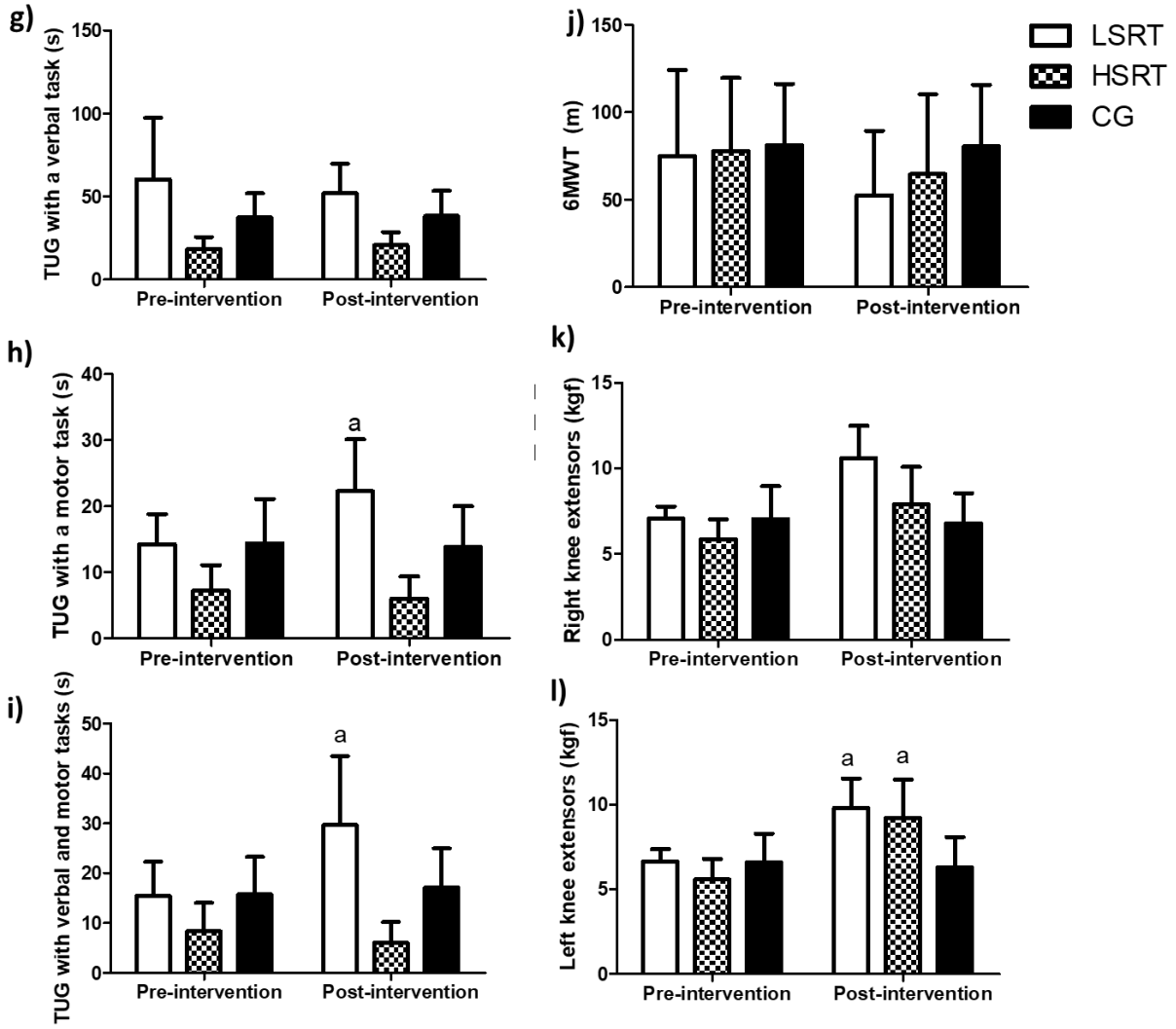
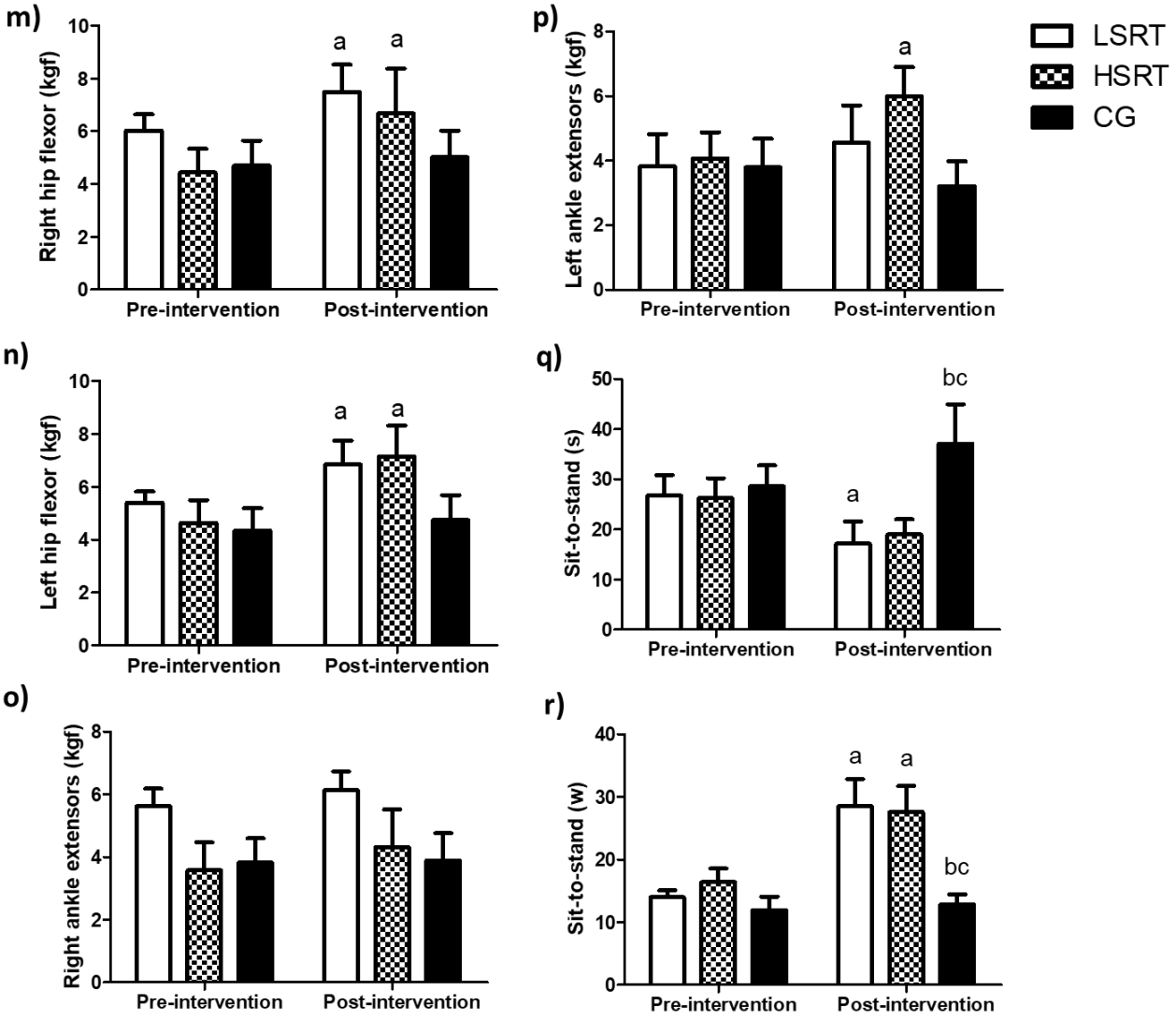


Figure 13. Effects of RT on physical performance in prefrail older adults. LSRT= Low-speed resistance training; HSRT= High-speed resistance training; CG= Control group. 6MWT= 6-minute walking test; IHG= Isometric handgrip strength; TUG= Timed "Up and Go"; WS= Walking speed; aP<0.05 vs Pre-intervention; bP<0.05 vs LSRT; cP<0.05 vs HSRT.

RT caused fewer improvements in frail in comparison to prefrail. Power (P<0.01) in the sit-to-stand test, muscle strength of the left knee extensors (P=0.01) and right (P=0.001) left (P=0.001) hip flexors were both improved after LSRT and HSRT. Particularly, exclusive improvements in TUG associated with a motor task (P=0.01), TUG associated with motor and verbal tasks (P=0.01), and time in the sit-to-stand test (P=0.01) were found in LSRT, while only HSRT improved muscle strength of the left ankle extensors (P=0.001) and the velocity of the muscle concentric contraction in the sit-to-stand test (P=0.01). Exercise groups showed higher performance (P=0.001) and power (P=0.001) in the sit-to-stand tests in comparison to CG. There were no significant differences among exercise groups.


a)
Right arm IHG (kg)
20
15
10
5
0
Pre-intervention
Post-intervention
b)
Left arm IHG (kg)
20
15
10
5
0
Pre-intervention
Post-intervention
c)
Right One-leg stand test (s)
5
4
3
2
1
0
Pre-intervention
Post-intervention
d)
Left One-leg stand test (s)
8
6
4
2
0
Pre-intervention
Post-intervention
e)
TUG at usual pace (s)
200
150
100
50
0
Pre-intervention
Post-intervention
f)
TUG at fast pace (s)
60
40
20
0
Pre-intervention
Post-intervention
LSRT
HSRT
CG


g)
TUG with a verbal task (s)
150
100
50
0
Pre-intervention
Post-intervention
j)
6MWT (m)
150
100
50
0
Pre-intervention
Post-intervention
LSRT
HSRT
CG
h)
TUG with a motor task (s)
40
30
20
10
0
a
Pre-intervention
Post-intervention
k)
Right knee extensors (kgf)
15
10
5
0
Pre-intervention
Post-intervention
i)
TUG with verbal and motor tasks (s)
50
40
30
20
10
0
a
Pre-intervention
Post-intervention
l)
Left knee extensors (kgf)
15
10
5
0
a
a
Pre-intervention
Post-intervention


m)
Right hip flexor (kgf)
10
8
6
4
2
0
a
a
Pre-intervention
Post-intervention
p)
Left ankle extensors (kgf)
8
6
4
2
0
a
Pre-intervention
Post-intervention
LSRT
HSRT
CG
n)
Left hip flexor (kgf)
10
8
6
4
2
0
a
a
Pre-intervention
Post-intervention
q)
Sit-to-stand (s)
50
40
30
20
10
0
a
bc
Pre-intervention
Post-intervention
o)
Right ankle extensors (kgf)
8
6
4
2
0
Pre-intervention
Post-intervention
r)
Sit-to-stand (w)
40
30
20
10
0
a
a
bc
Pre-intervention
Post-intervention

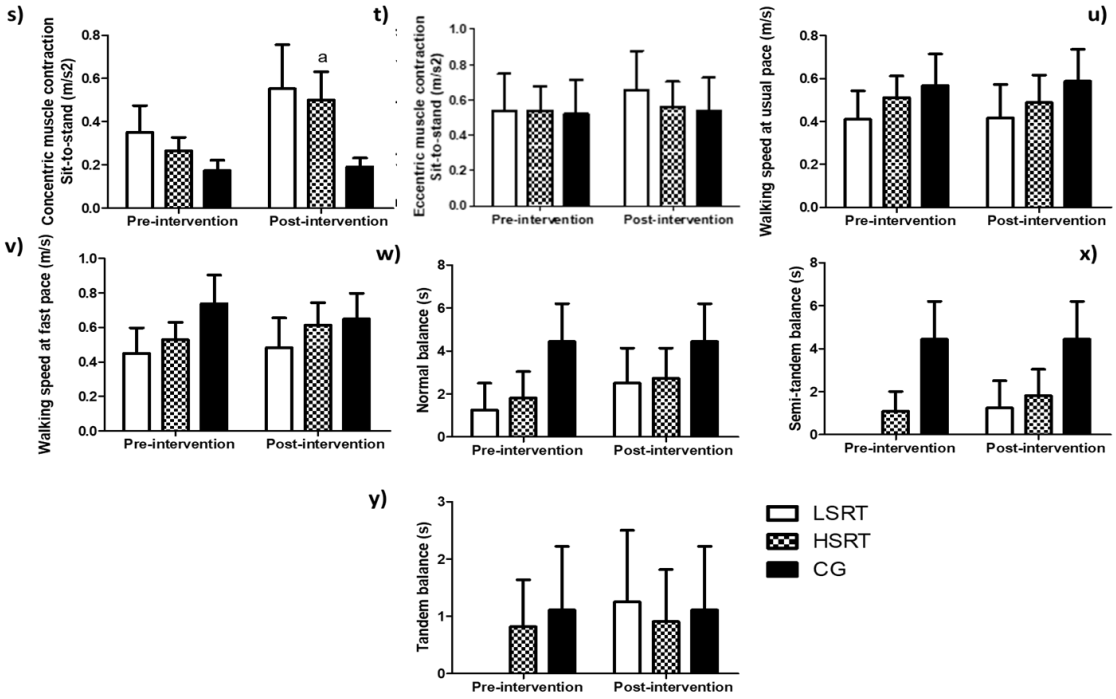


Figure 14. Effects of RT on physical performance in frail older adults. LSRT= Low-speed resistance training; HSRT= High-speed resistance training; CG= Control group. 6MWT= 6-minute walking test; IHG= Isometric handgrip strength; TUG= Timed "Up and Go"; WS= Walking speed; aP<0.05 vs Pre-intervention; bP<0.05 vs LSRT; cP<0.05 vs HSRT.

Fourteen participants, six in the HSRT, four in the LSRT, and four in the CG, performed the sit-to-stand test with mobility aids or researchers' help at baseline. On the other hand, four participants in the LSRT and three in the HSRT no longer needed help after exercise protocols.

Cognitive parameters

The effects of RT on cognitive parameters are shown in Figures 15-22. There were no within- and between-group differences on MEEM, CDT, and STROOP. On the other hand, higher verbal learning was observed after both LSRT and HSRT when compared to CG.

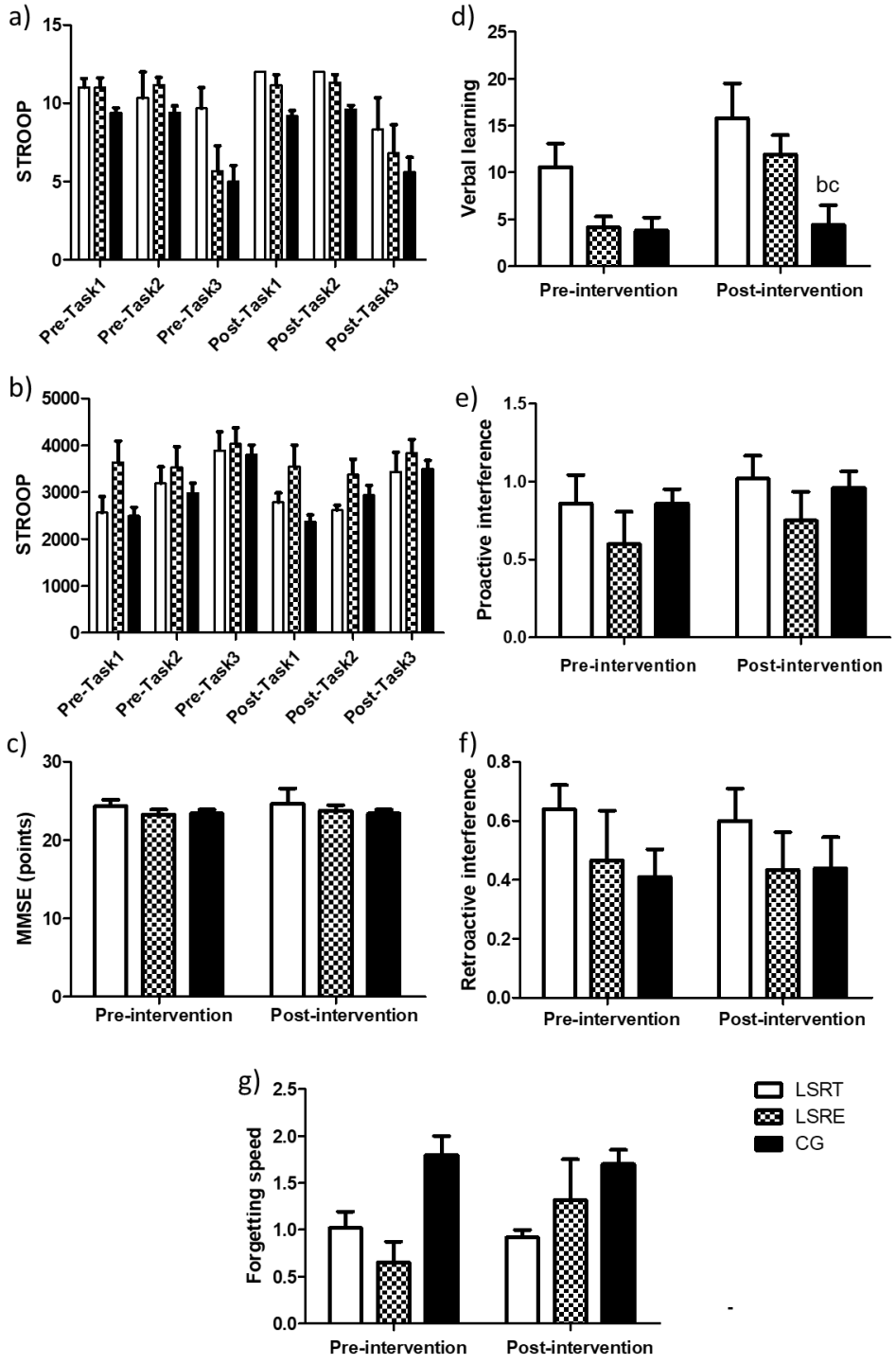


Figure 15. Effects of RT on cognitive parameters in prefrail older adults. LSRT= Low-speed resistance training; HSRT= High-speed resistance training; CG= Control group; MMSE= Mini-mental state examination; bP<0.05 vs LSRT; cP<0.05 vs HSRT.

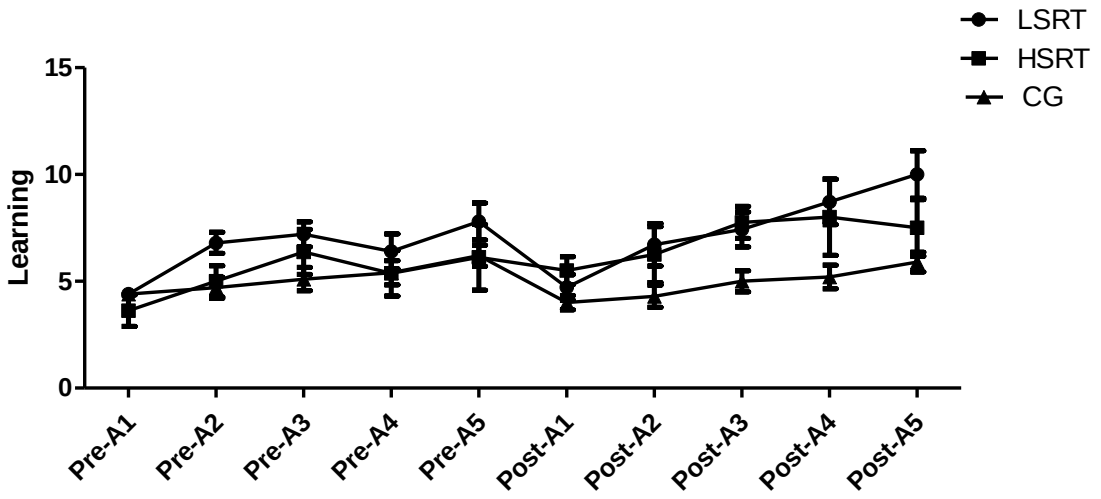


Figure 16. Effects of RT on RAVLT performance in prefrail older adults. LSRT= Low-speed resistance training; HSRT= High-speed resistance training; CG= Control group.

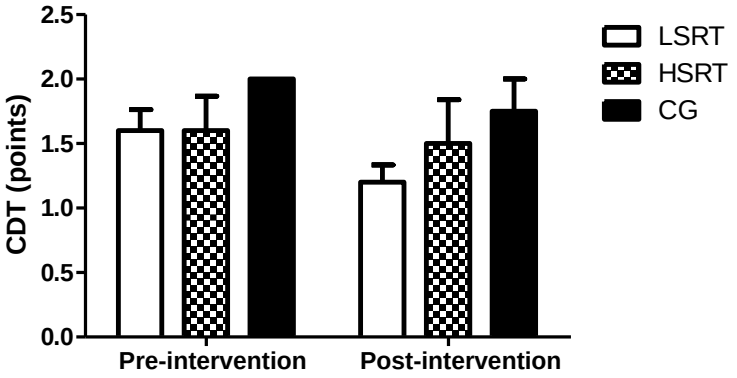
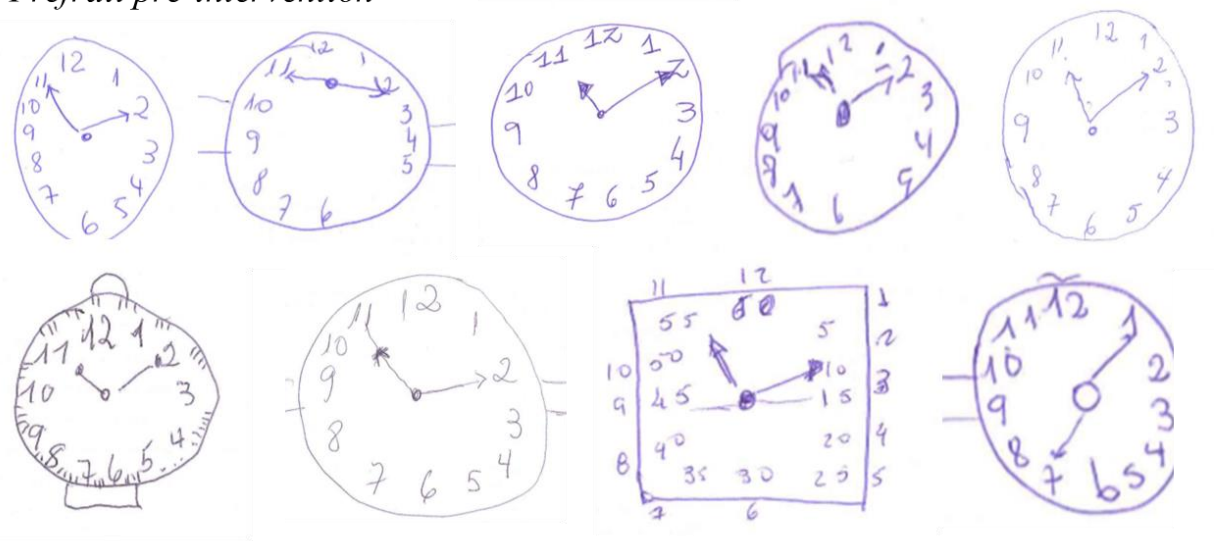


Figure 17. Effects of RT on Clock Drawing Tests (CDT) performance in prefrail older adults. LSRT= Low-speed resistance training; HSRT= High-speed resistance training; CG= Control group.

Prefrail pre-intervention



Prefrail post-intervention

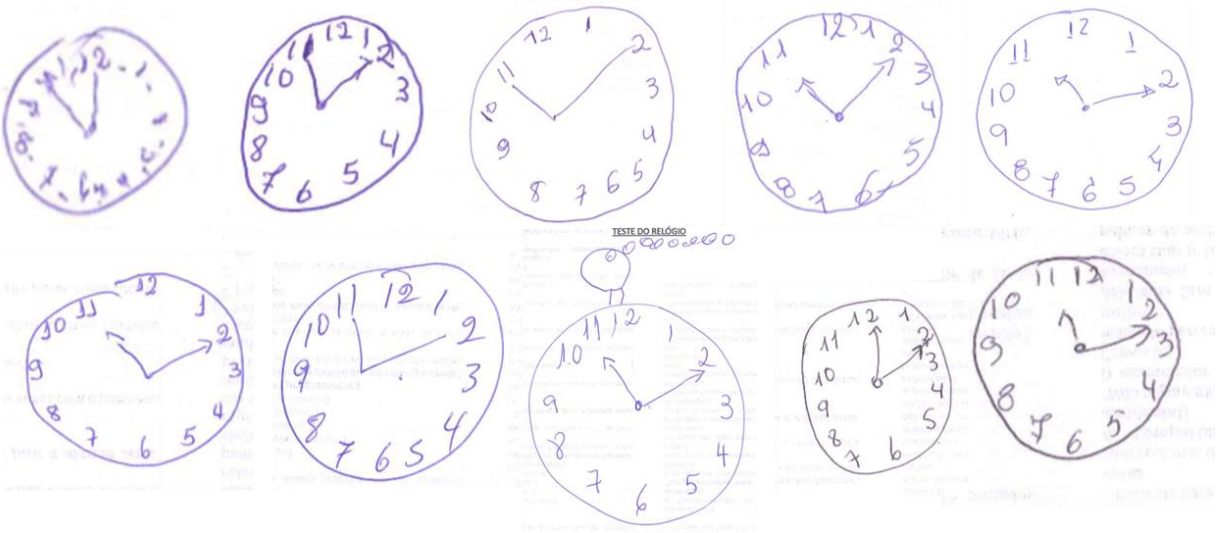


Figure 18. Examples of CDT tests in prefrail participants. In frail, no significant within- and between-group differences were observed on MEEM and STROOP performances. However, RAVLT performance (P=0.01) was significantly improved after HSRT.

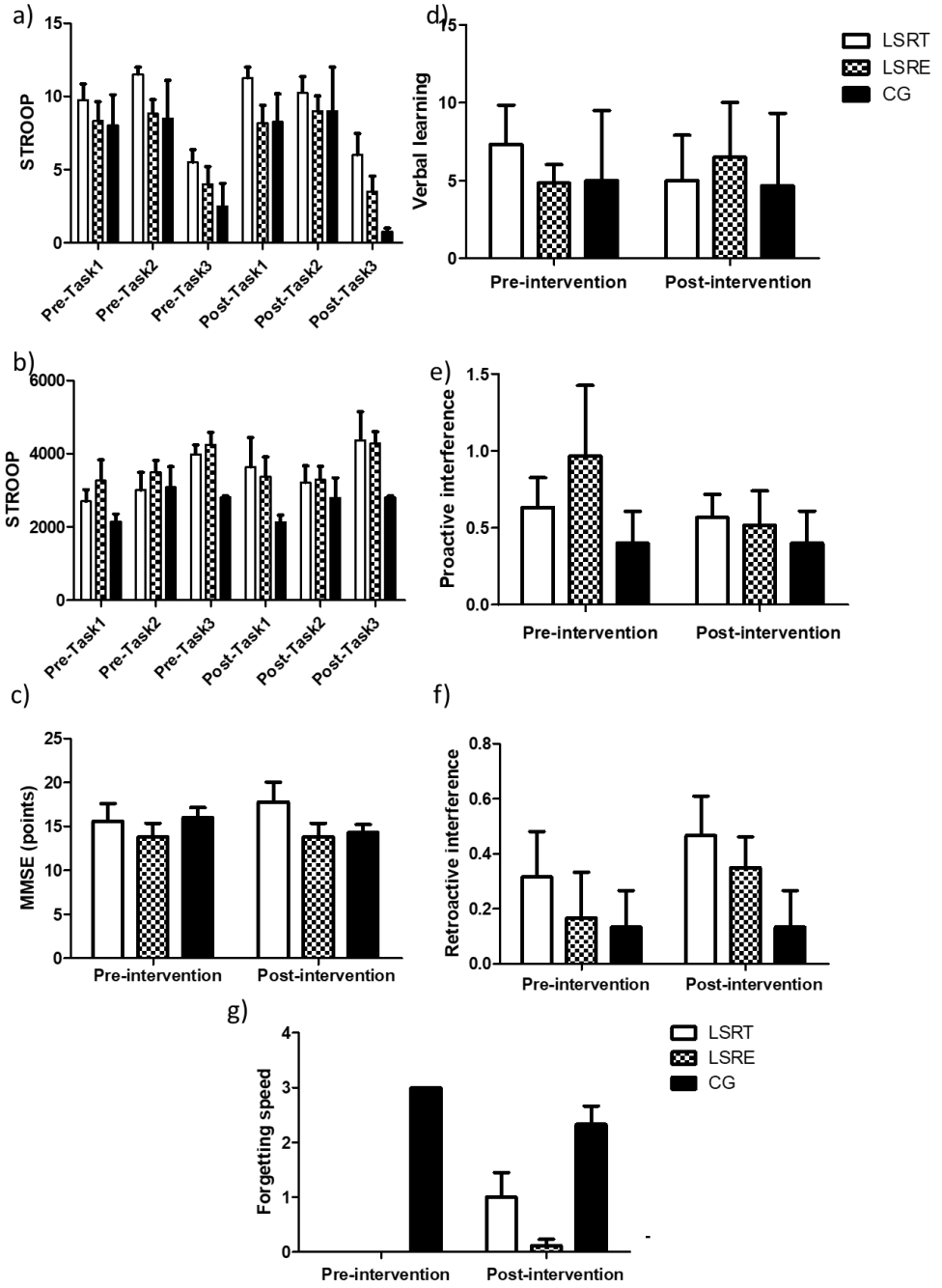


Figure 19. Effects of RT on cognitive parameters in frail older adults. LSRT= Low-speed resistance training; HSRT= High-speed resistance training; CG= Control group; MMSE= Mini-mental state examination.

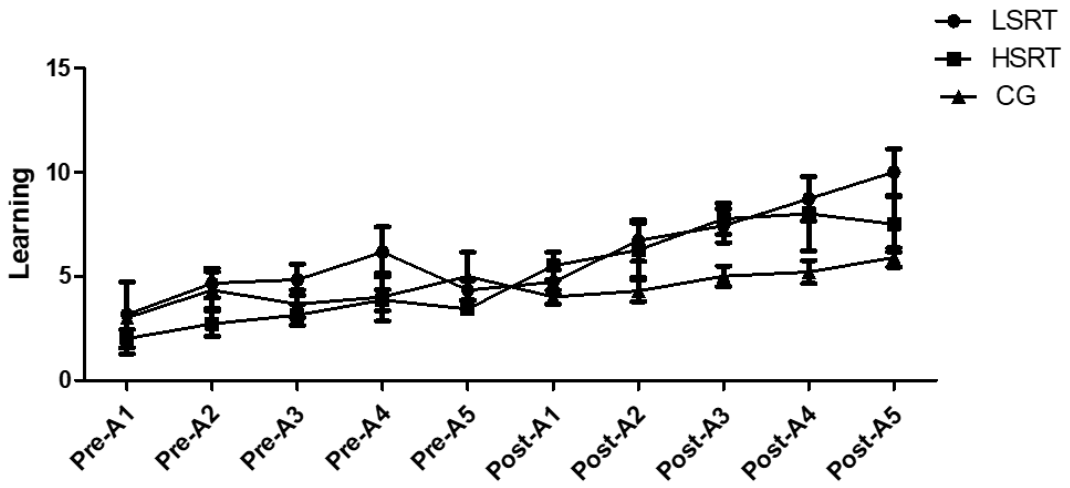


Figure 20. Effects of RT on RAVLT performance in frail older adults. LSRT= Low-speed resistance training; HSRT= High-speed resistance training; CG= Control group.

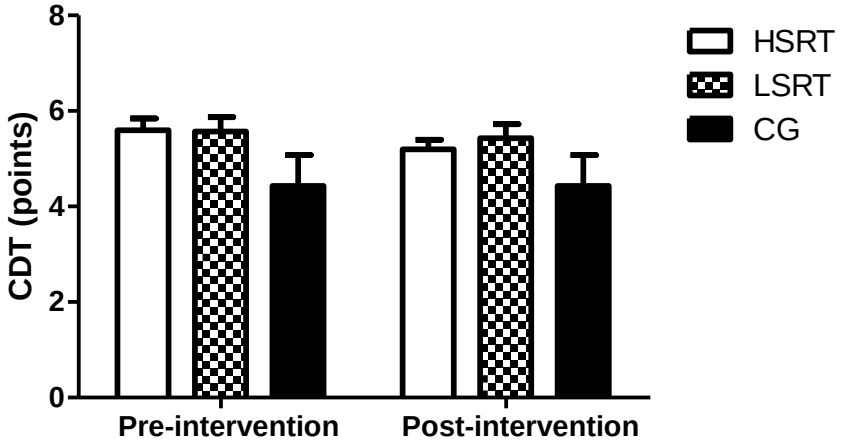
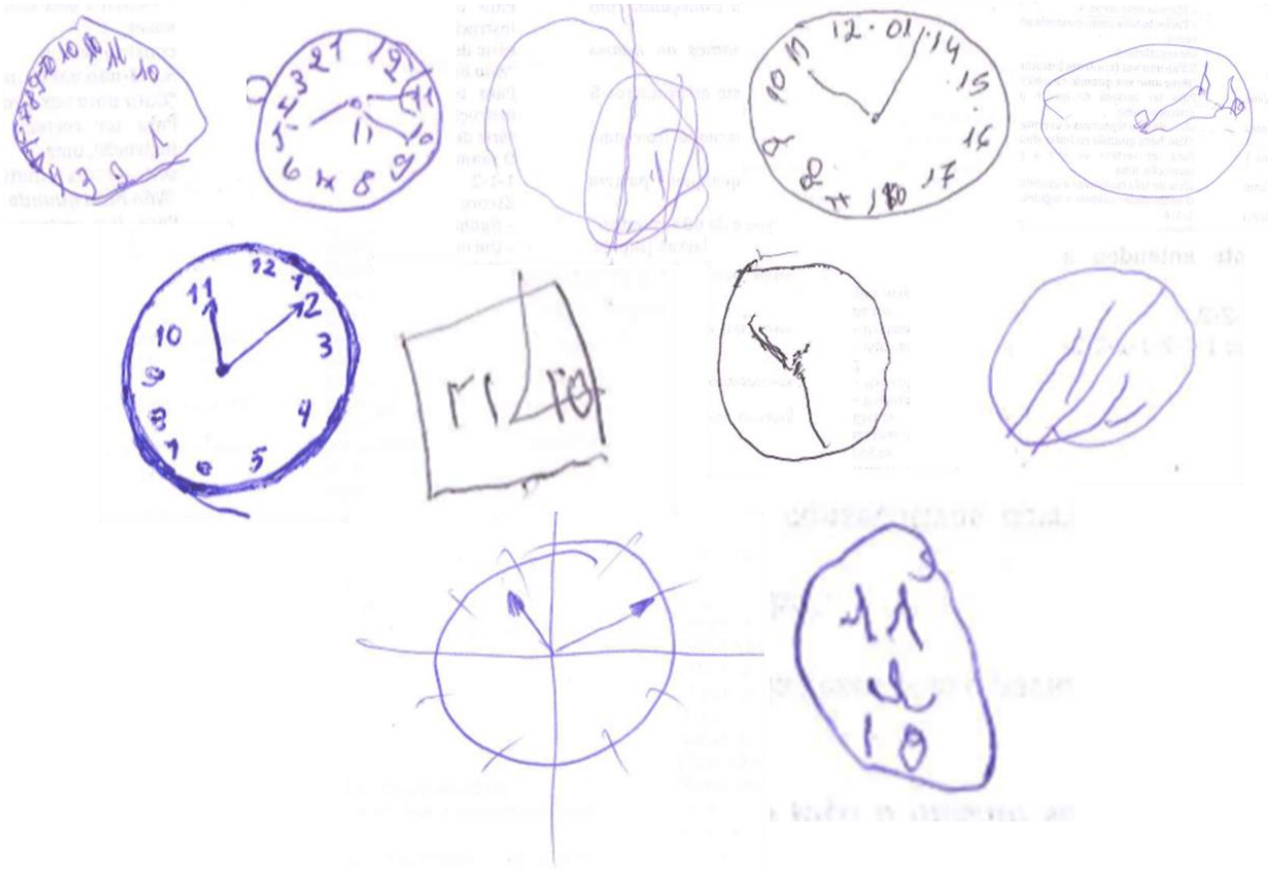


Figure 21. Effects of RT on Clock Drawing Tests (CDT) performance in frail older adults. LSRT= Low-speed resistance training; HSRT= High-speed resistance training; CG= Control group.

Frail pre-intervention



Frail post-intervention

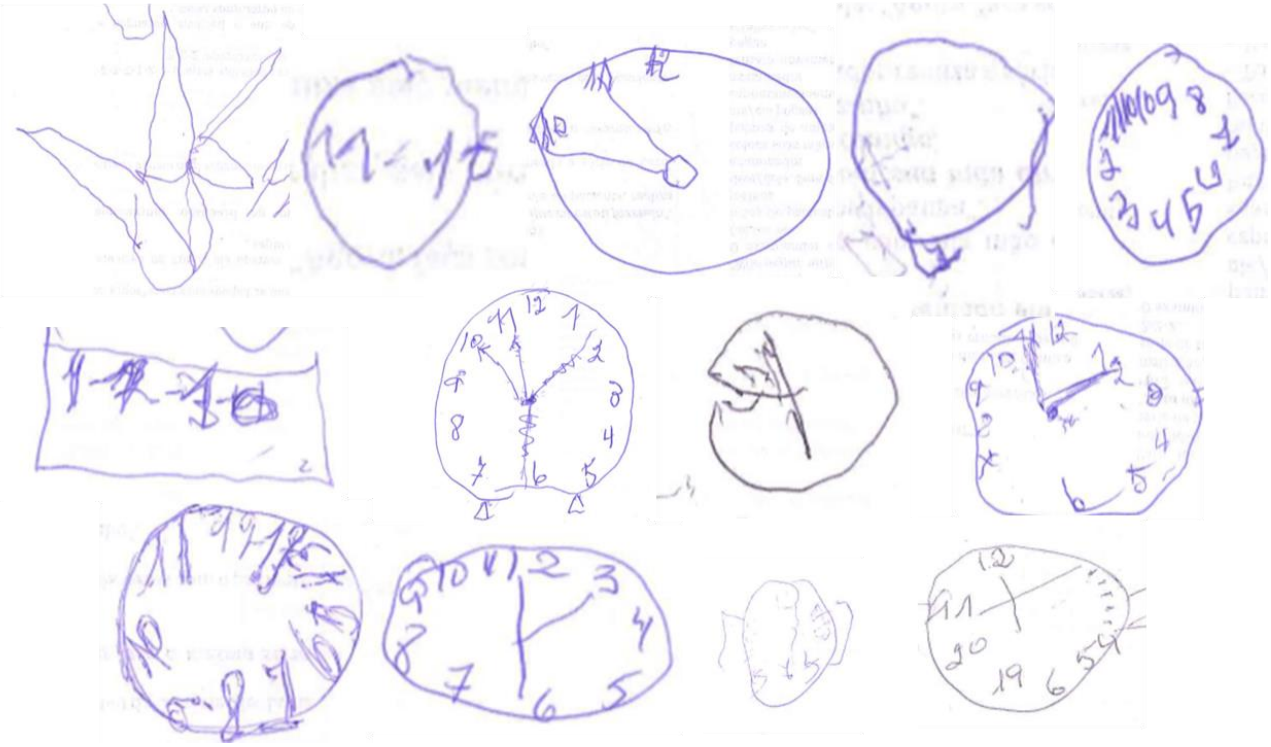


Figure 22. Examples of CDT tests in frail participants.

Blood pressure and heart rate

The effects of RT on blood pressure and heart rate are shown in Figure 23. There were no within- and between-group differences on blood pressure and heart rate in response to any intervention in prefrail and frail.

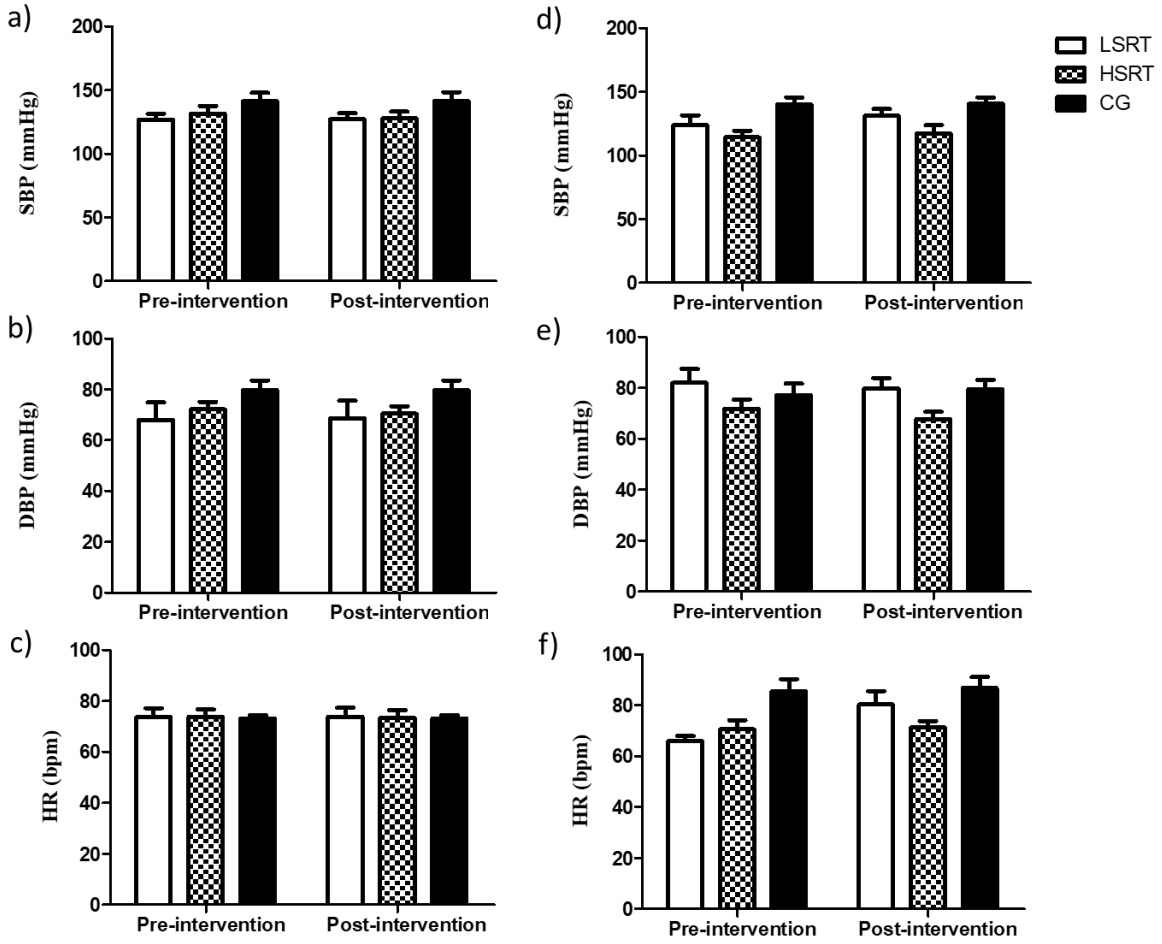


Figure 23. Effects of RT on blood pressure in prefrail (a, b, c) and frail (d, e, f) older adults. LSRT= Low-speed resistance training; HSRT= High-speed resistance training; CG= Control group; SBP= Systolic blood pressure; DBP= Diastolic blood pressure; HR= Heart rate.

DISCUSSION

The main findings of the present study (Table 2) indicate that RT reversed frailty status and improved physical function in prefrail and frail older adults. Nevertheless, different improvements were observed among the groups in response to LSRT and HSRT. In addition, prefrail older adults showed higher RAVLT performance after both RT protocols in comparison to CG. Finally, no changes in blood pressure and heart rate were observed in any group.

Table X. Effects of RT on frailty status, physical performance, cognitive function, and blood pressure and heart rate of prefrail and frail people.

	Prefrail			Frail		
Variable	LSRT	HSRT	CG	LSRT	HSRT	CG
Frailty status						
Weakness	↑	↔	↔	↑	↔	↔
Slow walking speed	↑	↑	↔	↔	↔	↔
Unintentional weight loss	↔	↔	↔	↑	↑	↔
Exhaustion	↑	↑	↔	↑	↑	↔
Low activity level	↔	↔	↔	↑	↑	↔
Physical performance						
Upper-limb muscle strength	↔	↔	↔	↔	↔	↔
Lower-limb muscle strength	↑↑	↑	↔	↑↑	↑	↔
Lower-limb muscle power	↑↑	↑	↔	↑	↑	↔
Mobility	↑	↑↑	↔	↔	↔	↔
Dual-task	↑	↑↑	↔	↑	↑	↔
Balance	↓	↑	↔	↔	↔	↔
Cognitive function						
Overaal	↔	↔	↔	↔	↔	↔
RAVLT	↑	↑	↔	↔	↔	↔
STROOP	↔	↔	↔	↔	↔	↔
Hemodynamic parameters						
SBP	↔	↔	↔	↔	↔	↔
DBP	↔	↔	↔	↔	↔	↔
HR	↔	↔	↔	↔	↔	↔

LSRT= Low-speed resistance training; HSRT= High-speed resistance training; CG= Control group; SBP= Systolic blood pressure; DBP= Diastolic blood pressure; HR= Heart rate; ↑= Improved vs Pre-intervention; ↑↑= Improved vs Pre-intervention and CG and/or experimental group; ↓= Reduced; ↔= Unchanged.

Effects of RT on frailty status

RT reversed frailty status in both prefrail and frail older adults. In prefrail, 54.5% of prefrail participants returned to robust condition after LSRT, while 18.1% became robust after HSRT. Changes in frailty status occurred in response to improvements in weakness, slowness, and self-reported exhaustion. Similar findings were observed in frail, given that LSRT reversed frail to prefrail in 62.5% of the cases and to robust in 12.5%, while 45.4% became prefrail and 9.0% robust after HSRT. However, frailty reversion occurred based on changes in weight loss, sedentary behavior and exhaustion complaints.

Our findings are supporting by prior investigations that observed that exercise training could reverse frail status in prefrail and frail older adults (71–77). However, most studies combined RT with other types of exercise or other health interventions (75), limiting inferences regarding the impact of RT alone on frailty status (78).

This information seems to be important since some studies have reported low adherence to multicomponent exercise training programs, mainly in institutionalized frail older adults (74,76), which might occur due to the fact the frail patients cannot support very-long exercise sessions (79). In addition, aerobic and gait exercises are not feasible and probably hard to prescribe in frail nursing home residents due to the high prevalence of mobility limitations and the need for help to transfer from a place to another found in this population (80).

On the other hand, RT programs may be fully performed with individuals sitting in bed or in a chair without the need for transferring or walking, prioritizing some muscle groups, using body weight, free weights or elastic bands (17,24).

Most studies investigating RT have focused on frailty components and only a small number of evidence reported its effects on frailty status (71,81). In one of the few studies addressing this topic, Giné-Garriga et al. (71) found that a 12-week RT program composed by exercises that mimic activities of daily living (ADL) performed at moderate-to-high intensity reversed frailty in community-dwelling older adults. However, although these findings brought promising perspectives for the management of frailty by RT, the lack of important information about the RT protocol (e.g., familiarization, cadence) and the inclusion of balance training restrict its clinical reproducibility.

Our findings have high clinical applicability by demonstrating that 16-week lower-limb LSRT and HSRT programs considerably reversed frailty status in prefrail and frail older adults, possibly reducing the risk of negative health outcomes in these people (6–10).

Notably, improvements in frailty criteria in response to RT occurred according to frailty status, so that weakness, slowness, and exhaustion were increased in prefrail, and weight

loss, sedentary behavior, and exhaustion were improved in frail. Although surprising, similar results were found in the LIFE-P study (72), in which frailty reversion in frail people by exercise training was not associated with improvements on slowness and weakness, but physical activity levels.

A possible explanation for these findings is based on the direct and indirect effects of RT on frailty components. As prefrail individuals show more preserved physical function in comparison to frail counterparts, improvements on weakness (IHG) and slowness (WS) are easier to reach the threshold for detecting frailty. In contrast, some frail participants of the present study showed IHG scores next to zero and the time taken to perform WS higher than sixty seconds.

In this context, improvements in physical function may have reduced perceived fatigue (82), motivating frail patients to increase physical activity levels. Regarding weight loss, muscle hypertrophy is a well-established product of RT (83,84) and it is possible to suggest that our exercise programs reduced weight loss by modulating muscle mass.

Effects of RT on the physical function of prefrail and frail older adults

- Effects of RT on muscle strength and power of prefrail and frail older adults

In the present study, we observed that LSRT and HSRT improved lower-limb muscle strength (i.e., knee extensors, hip flexors, ankle extensors) and power (i.e., time and power in the sit-to-stand) in prefrail and frail older adults. Nevertheless, greater improvements were observed in LSRT when compared to HSRT and CG.

These findings are in concordance with previous original articles (22,73,85–87) and systematic reviews (81) that found improved physical function in prefrail and frail older adults after LSRT (73,85,86) and HSRT (85,87,88) programs. However, just a few studies compared the effects of LSRT and HSRT in prefrail and, for the best of our knowledge, there are no investigations in frail people.

In contrast to the present study, Zech et al. (86) and Drey et al. (85) observed that 12 weeks of LSRT and HSRT similarly improved SPPB performance and had no effect on lower-limb muscle power in prefrail community-dwelling older adults. It is likely that these results are based on the fact that exercise intensity was controlled based on the rating of perceived exertion (RPE) method and physical exercises were performed in a *Bodyspider* machine, in which individuals had to perform single-leg exercises, likely leading to inadequate perceptions of exertion due to instability. This view was reinforced by Lopez et al. (89), who

proposed that frail people may show a reduced capacity to exercising based on effort perception, affecting exercise prescription, resulting in limited gains.

Several mechanisms may potentially explain why LSRT elicited greater improvements in lower limb muscle strength and power in comparison to HSRT, including the time under tension (TUT), range of motion (ROM), the prevalence of comorbidities, and cognitive status.

TUT refers to the time spent performing muscular contractions (90). Results from a systematic review and meta-analysis suggested that TUT has a strong effect on strength gains by healthy older adults in response to RT (83), with large effects being observed for muscular contractions that lasted on average 6 s (83). These premises are supported by original investigations that found larger hypertrophy (91–93) and greater isometric muscle strength (91) after RT performed with slow movements (~7 s) in comparison to very-speed RT (~2 s) (92,93).

According to the size principle of Henneman et al. (94), motoneuron and motor units (MU) are recruited from smallest to largest. In the light of RT, this means that type II muscle fibers, those more associated with force generation and muscle hypertrophy (95), are primarily recruited in response to the exercise intensity and the velocity of muscle contractions (96). However, some designs of RT performed at low-to-moderate intensity may reduce the supply of oxygen and metabolic substrates to the muscle (91), leading to the accumulation of products of cellular metabolism, including lactate, H^+, inorganic phosphate (Pi), and ADP (92,93), reducing force development, and stimulating progressive recruitment of additional MU (97).

In this context, the long total contraction time performed by LSRT (~5 s vs ~3 s in HSRT) may have caused greater improvements on muscle strength by creating a more challenging environment, inducing the recruitment of large MU and type II muscle fibers, resulting in superior neuromuscular adaptations.

Alternatively, TUT has been associated with increased myofibrillar protein synthesis and phosphorylation of anabolic signaling proteins (i.e., p70S6K, 4EBP1, and p90RSK) (98), likely inducing muscle hypertrophy (99). However, skeletal muscle mass was not measured in the present study.

In relation to the higher muscle power observed in LSRT, force plays a key role in power production (96,100), so that improvements on muscle strength serve as the main driver for the ability to express high power outputs (100).

Another possible explanation for the inferior improvements in muscle strength and power found after HSRT is based on the range of motion (ROM), given many frail participants

used wheelchairs and showed a clinical diagnosis of lower limb osteoarthritis. Indeed, the length-tension curve relationship states that exercises performed at optimal muscle length evokes greater myosin and actin interaction, and so strength (101). On the other hand, exercises performed at partial ROM commonly produce less neuromuscular adaptations, which are restricted to the specific ROM in which the trained occurred (102).

Considering that sit-to-stand performance involves the total extension of the knee and hip joints, older adults with joint limitations may not have exercised in the full ROM and completely improved their muscle strength and power. Sit-to-stand performance may also has been influenced by the prevalence and severity of comorbidities such as femoral fracture and stroke, given that participants' performance in these conditions is practically based on one leg.

According to Cadore and Izquierdo (39), the prescription of HSRT in older adults with disabilities should take into consideration other factors than the variables of RT, such as emotional aspects of the patient, physical and emotional environment, and the structure of the instructions. Regarding the latter, further attention from HSRT participants is needed to keep high the velocity of concentric muscle contractions and researchers have recommended avoiding complex oral instructions (39).

Although participants of the present study were cognitively able to understand exercise and testing instructions, HSRT sessions were closely monitored, and our HSRT protocol was composed by a few repetitions in an attempt to maintain participants' concentration, the possibility that HSRT was not performed with the maximal power output cannot be ruled out.

- *Effects of RT on mobility, dual-task performance, and balance in prefrail and frail older adults*

The main motivation for the prescription of HSRT to older adults is based on the fact that this type of RT could elicit greater improvements in mobility when compared to LSRT (24,39,40,42,103). These assumptions are supported by the observation that lower limb muscle power was significantly associated with physical and mobility tests, such as SPPB (30,104), gait speed (30,104), chair rise time (29), stair climb time (29,30,104), and various domains of disability (28,105) in health and mobility-limited older adults; and that, when compared to muscle strength, muscle power may be a better predictor of general mobility (28–30).

Researchers have also considered the coupling body of evidence that directly compared the effects of HSRT and LSRT on functional capacity. Bean et al. (33) reported similar improvements in SPPB in older adults after non-equalized 16-week LSRT and HSRT programs. Nevertheless, the superior effects of HSRT were observed when participants were

categorized according to baseline mobility limitations (33). Miszko et al. (31), Botataro et al. (106), and Ramírez-Campillo et al. (34) found that HSRT program caused greater improvements in physical performance tests comparison with LSRT, while Lopes et al. (35) observed exclusive improvements in sit-to-stand and TUG performances after HSRT.

Although systematic review and metanalyses (37,38) support the abovementioned data, authors found a wide confidence interval among studies, which indicate that the effects of both LSRT and HSRT are still compatible with a clinically non-relevant difference. In addition, most studies were based on physically healthy older adults, short-term RT protocols, and expensive exercise machines, limiting extrapolations for prefrail and frail older adults.

In this context, findings of the present study are unique and add to the current knowledge by indicating that HSRT is more effective to improve TUG performance in comparison to LSRT in prefrail older adults. A question that remains from these findings, then, is "how HSRT produced greater improvements in TUG performance than LSRT in the absence of superior improvements in muscle strength and power?"

A likely explanation is that muscle power was improved in other muscle actions than those assessed in the present study. TUG involves the interaction among several body movements, including sit-to-stand transition, walking, turn and stand-to-sit transition (107). Besides muscle power and strength of the knee and hip extensors to sit-to-stand (108), TUG performance might require muscle power of the ankle flexors and extensors to stride velocity (29) and fast response to perturbations to turn (109).

Despite the significant similar improvements in muscle power, mobility remained unchanged in frail participants after LSRT and HSRT. These results should be interpreted cautiously, given that most participants of the current study needed researchers' help or were not able to perform mobility tests at baseline, causing a wide variability in the results. Indeed, although no significant within-group differences were observed in WS and TUG, seven participants became independent in the performance of mobility tests after RT protocols. This phenomenon might also have influenced frailty status and indicates that long-term RT protocols seem to be necessary to reverse physical dysfunction in institutionalized frail older adults.

Notably, improvements in muscle power may also account for the observed differences in balance in prefrail (30). However, it is worth mentioning that all participants in the LSRT and CG achieved the highest performance in normal and tandem tests in both pre- and post-intervention periods, while one participant in the HSRT could not perform the test for 10 s at baseline and showed improvements in response to RT. In fact, one-leg stand performance supports the hypothesis that any exercise protocol was effective to improve balance.

Another important finding is that prefrail HSRT participants showed better performance on TUG with verbal, motor, and both tasks in comparison to those in the LSRT, while LSRT was most effective to increase dual-task performance in frail. These results suggest that the effects of RT on dual-task performance are dependent on frail status.

Effects of RT on cognitive function, blood pressure and heart rate of prefrail and frail older adults

Although a number of studies have been published in the last years, there is still no consensus on the effects of RT on the cognitive function of older adults (Coelho-Junior et al., 2019, article 13) and only a few studies have examined prefrail and frail people. Cardalda et al. (87) and Yoon et al. (110) observed improved overall cognitive function in frail older adults. This view was expanded by Van de Rest et al. (45), who found increased digit span, attention, and working memory performances in prefrail and frail older adults after a 24-week LSRT program. To the best of our knowledge, only Yoon et al. (111) compared the effects of HSRT and LSRT, and results demonstrated similar improvements in overall cognitive function after both protocols of RT.

The current study contributes to the growing literature by indicating that RT might improve verbal memory in community-dwelling prefrail older adults, regardless of the velocity of muscle contraction. However, our findings differed from prior investigations since we did not observe significant changes in overall cognition, middle-term memory, inhibitory capacity, and attention in prefrail and frail older adults.

Different results might be partially attributed to differences in sample characteristics, given that some studies (45,112,113) combined prefrail and frail participants, cognitive status (e.g., MCI) (87,112–114), mobility (mobility-limited vs able to walk) (87,112,113), methods used for cognitive outcome measures (45,87,113,115), and designs of the RT programs (45,87,113,115).

Healthy and older adults with mild cognitive impairment (MCI), for example, showed different patterns of electrical brain activation after RT (114), which may have impacted cognitive adaptations (Coelho-Junior et al., 2019, article 13). Furthermore, the limited mobility of our sample likely influenced physical activity levels and may have a role in our results (116). Still, findings from Cardada et al. (87) should be carefully interpreted since exercise intensity was not controlled.

Notably, the present findings also differed from prior investigations on the acute effects of RT on cognitive function (Coelho-Junior et al., 2019, article 14), in which low-speed

and high-speed resistance exercise acutely improved RAVLT, but not STROOP performance in frail older adults.

Taken as a whole, the present study indicates that LSRT and HSRT may similarly improve verbal memory in community-dwelling prefrail older adults. On the other hand, these RT protocols were not able to increase many cognitive domains in frail older adults, suggesting that more studies testing different designs of exercise are still necessary.

Regarding blood pressure, researchers (117–122) have argued that frail patients may need further attention in the management of cardiovascular risk factors, although observational studies (Coelho-Junior et al., 2019; article 11), systematic reviews and meta-analysis (123) and large randomized clinical trials have not supported this hypothesis (124).

Our findings refute the hypothesis that RT may reduce blood pressure levels and heart rate in prefrail and frail older adults. A possible explanation for these results may be the fact frail patients show multiple cardiac and vascular abnormalities (e.g., left ventricular hypertrophy, worse systolic function, increased arterial stiffness) (6,125), cardiac autonomic (126) and endothelial (127) dysfunctions, while RT is not enough to reverse these abnormalities and consequently improve blood pressure and heart rate.

Indeed, most evidence on the effects of RT on blood pressure has investigated robust community-dwelling older adults (128–132) and no prior studies included prefrail or frail participants.

Practical Applications

Current RT protocols were first thought to improve lower-limb muscle strength, power and mobility, and possibly frailty status, of prefrail and frail older adults that have no access to exercise machines or gyms. The main muscles responsible for get up and walk were selected and worked during the exercise sessions, and findings certainly support the importance of incorporating functional exercises when designing an intervention aiming to improve physical function in older adults (71). Although one may argue that exercise for gluteus and abdomen could offer additional improvements, frail participants complained of exhaustion during a pilot study using more than four exercises.

Two main features of the current RT protocols should be highlighted. First, its low cost, given that the price of all the equipment was around R$ 700,00 and seems feasible to public health programs aim to improve health in older adults. Second, the short duration of exercise sessions, which lasted approximately 25 minutes. Nevertheless, it is important to

mention that RT sessions were performed individually in frail and in groups of 3-4 participants in prefrail to ensure the effectiveness of exercise programs.

There is limited research indicating the minimal clinically important difference (MCID) for the physical performance tests used in the present study. However, when data are interpreted in the light of sarcopenia cutoffs (133), it is possible to observe the prefrail participants already had good physical performance before the intervention, while improvements in the physical function of frail participants did not reach non-sarcopenia status, although values have increased substantially.

In this context, (ex) prefrail participants would take part in more structured exercise training programs (e.g., multicomponent exercise programs [MCEP]) in an attempt to improve other physical functions than muscle strength and power, such as cardiorespiratory capacity and balance. Such an approach could collaborate to an overall enhancement of health status concomitant with a reduction in the risk for many health-related negative outcomes.

On the other hand, (ex) frail are still improving essential physical capacities and the inclusion of other types of exercise at this moment does not seem to be a good strategy, so that they could perform HSRT and LSRT for some more time until reestablishing enough mobility to perform aerobic exercises, for example. Nevertheless, since ROM limitations could have restricted the effects of exercise interventions, participants could benefit from flexibility training programs.

Another practical aspect of the current study is that the reversion of frailty was also influenced by the nursing home environment. Indeed, when frail participants showed minimal ability and resistance to walking few steps, the board of the institution and the chief physiotherapist were contacted, and I explained the importance to improve patients' physical activity levels. A non-structured walking program was created in which frail participants walked for some time with the assistance of nursing students.

It is worth mentioning that an affinity loop was created between researcher and participants. Long conversations about many subjects before or after exercise sessions were common and undoubtedly influenced dropout rates and the successes of the protocol.

Finally, the question that remains is "What is the best RT protocol to improve the frail status and health-related parameters associated with frailty in prefrail and frail older adults?" Taking into consideration all limitations of the present study (please, see below), both exercise programs seem to be important in these populations improving different domains and reversing frailty status. As was abovementioned, the next step would be combining LSRT and HSRT with other exercise interventions. However, future studies investigating RT protocols

based on LSRT and HSRT, as classically proposed by professor's Häkkinen group (134), would be welcome to expand the current findings.

Limitations

The present study is not free of limitations. First, participants' randomization was stratified by age, BMI, and sit-to-stand performance and non-significant differences among the groups at baseline may have impacted significant differences post-intervention. Second, participants were not screened for dementia since they were only required to understanding exercise commands. Third, the current findings are prevalently based on prefrail and frail older women and extrapolations should be carefully performed. Forth, although LSRT and HSRT had no effects on blood pressure, researchers observed that frailty was associated with higher systolic and diastolic pressures measured by ambulatory blood pressure monitoring, but not office blood pressure (117). Fifth, the lack of changes in cognitive function may have occurred in function of the short period, since periods of intervention shorter than 12 months may not be enough to detect changes on cognitive parameters, as proposed by Vellas et al. (135). Sixth, our sample size and inclusion criteria limited further analysis (e.g., respondents and nonrespondents) (136,137). Seventh, the possible mechanisms underlying the effects of RT on physical function were not investigated. Eight, prefrail and frail older adults were recruited from different settings. Finally, additional covariables (e.g., high inflammatory status (138)) that could influence the current results were not controlled.

CONCLUSION

Findings of the present study indicate that both LSRT and HSRT reversed frailty status and improved physical performance in prefrail and frail older adults. However, different patterns of improvement were observed among RT protocols. Regarding frailty status, LSRT seemed to be more effective in reverse prefrailty and frailty when compared to HSRT. Greater improvements in muscle strength and power were also observed after LSRT, while HSRT caused greater improvements in mobility and dual-task performance. Finally, RT programs similarly improved verbal memory in prefrail.

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ARTICLE 13

Can resistance training improve cognitive function in older adults? A systematic review and meta-analysis

Abstract

Objective: To investigate the impact of resistance training (RT) on cognitive function in older adults with and without dementia by conducting a systematic review of experimental studies. **Design:** We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. **Data sources:** We performed a literature search with no restriction on publication year in MEDLINE, Embase, CINAHL, SPORTDiscus, and AgeLine from inception up to August 2019. **Eligibility criteria:** Experimental studies investigating the impact of RT on cognitive function in people aged 60 years or older with or without dementia. **Results:** We included 18 studies, of which 11 investigated non-demented community-dwelling older adults, four investigated older adults with mild-cognitive impairment, and three investigated prefrail and frail older adults. RT significantly improved overall cognitive function in demented older adults (SMD= 1.02; 95% CI= 0.22 to 1.82, P=0.01; χ^2= 11.47, df= 3, P= 0.009, I^2= 74%) and short-term memory in cognitively intact older adults (MD= -0.15; 95% CI= -0.23 to -0.08, P<0.0001; I^2 = 0%, χ2= 3.97, df = 6, P = 0.68). **Conclusion:** Cognition is significantly improved by RT in older adults. However, different adaptations are observed according to cognitive levels. In fact, overall cognitive function is only improved in cognitively healthy individuals, while amelioration of short-term memory was exclusively found in demented older adults. These findings encourage the use of RT as a tool to preserve mental health in the older population.

Keywords: Physical exercise; Strength training; Dementia; Frailty.

Introduction

Cognition may be understood as the expression of brain activity by which mind interacts with the world [1]. Over the life course, the human brain undergoes extensive structural and functional changes. To simplify, cognitive function expands from the gestational period until adulthood, and prevalently declines past the age of 60 [2]. Age-related diseases accelerate the rate of neuronal dysfunction and cognitive decline, which in a growing share of the older population becomes severe enough to compromise social engagement. This phenomenon has gained widespread attention owing to the profound clinical and socioeconomic impact of cognitive impairment. Indeed, recent reports of the World Health Organization (WHO) [3] alert that the maintenance of mental health should be prioritize in older adults in the attempt to preserve the individual's autonomy and avoid the genesis of chronic degenerative diseases.

In this context, accumulating evidence indicates that physical activity (PA), any bodily movement that results in energy expenditure above resting levels [4], may positively affect cognitive function in older adults and individuals with mild cognitive impairment (MCI) [5], thereby reducing the risk of dementia [6]. Based on these premises, researchers have argued that exercise training, a structured form of physical activity that has as objective the improvement or maintenance of physical fitness [4], could elicit greater benefits in comparison to PA and consequently be used as a tool for the preservation of mental health in older adults [7].

Resistance training (RT) is a type of exercise training that involves performing muscle contractions against an applied force and has been suggested as a first line therapy to counteract the effects of aging on the neuromuscular system [8,9]. Regarding cognition, systematic reviews and meta-analyses of randomized clinical trials have found improved cognitive performance in RT-trained older adults [10,11]. However, investigations are old [12], included individuals aged <60 years [10,11], did not involve pooled analyses [10], and restricted the sample to demented older adults [12], thereby limiting conclusions.

To fill this gap in knowledge, the present systematic review and meta-analysis aimed at investigating the effects of RT on cognitive function in demented and non-demented older adults.

Materials and Methods

We conducted a systematic review and meta-analysis of interventional studies to quantify the effects of RT on cognitive function in older adults. The study was fully performed by investigators and no librarian was part of the team. This study complies with the criteria of the Primary Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [13] and Cochrane Handbook for Systematic Reviews and Interventions [14]. All data are available in the Open Science Framework at https:// doi 10.17605/OSF.IO/MVW4J

Eligibility criteria

The inclusion criteria of the present study consisted of: (a) experimental studies that investigated the chronic effects of RT in humans; (b) age of participants ≥60 years; (c) assessment of at least one cognitive domain via validated questionnaires and tests; (d) presence of a control group; € published studies (English, Italian, Portuguese, and Spanish languages). Studies that investigated demented and non-demented older adults were considered. To be included in the meta-analysis, in addition to the aforementioned inclusion criteria, investigations had to provide: (f) pre-post mean and standard deviation (SD) of each intervention arm. We excluded observational and quasi-experimental studies, acute interventions, or any investigation that combined RT with other interventions (e.g., aerobic exercise). Studies that evaluated cognition based on sub-domains of scales were also excluded.

Search strategy and selection criteria

Studies published on or before August 2019 were retrieved by two investigators (HJCJ, EM) from the following five electronic databases: (1) MEDLINE (PubMed interface) (2) Embase (EBSCO interface), (3) CINAHL (EBSCO interface), (4) SPORTDiscus (EBSCO interface), and (5) AgeLine (EBSCO interface). Reference lists for reviews (Supplementary File [SF] 1) and retrieved articles for additional studies were checked and citation searches in key articles were performed on Google Scholar and ResearchGate for additional reports. Initially, a search strategy was designed using keywords, MeSH terms, and free text words such as resistance training, cognitive function, older adults. Additionally, keywords and subject headings were exhaustively combined using Boolean operators. The complete search strategy used for the PubMed is shown in SF2. Only eligible full texts in English, Italian, Portuguese or Spanish languages were considered for review.

Data extraction and quality assessment

Titles and abstracts of retrieved articles were screened for eligibility by two researchers (HJCJ, EM). If an abstract did not provide enough information for evaluation, the full-text was retrieved. Disagreements were solved by a third reviewer (MCU). Reviewers were not blinded to authors, institutions, or manuscript journals. Data extraction was independently performed by two reviews (HJCJ, EM) using a standardized coding form. Disagreements were solved by a third reviewer (MCU). Coded variables included methodological quality and the characteristics of the studies. The quality of reporting for each study was performed by two researchers (HJCJ, EM) using the Critical Appraisal Skills Programme (CASP) criteria for clinical trials [15]. The agreement rate for quality assessment between reviewers was κ=0.99.

Statistical analysis

The meta-analysis was conducted using Revman V.5. Effect sizes (ESs) were measured using mean and SD. Where SDs were not available from trial authors, they were calculated from t-values, confidence intervals or standard errors, where reported in articles (SF3). In addition, if a study included more than one cognitive test, or had more sub-domains in one test, all results were extracted. Pooled ES for: a) overall cognitive function, b) short-term memory, and c) concentration and attention was calculated based on standard mean difference (SMD), given that different tools were used to measure these cognitive domains. Mean difference (MD) was used when short-term memory was assessed with the digit span test of the Wechsler Adult Intelligence Scale III (WAIS III). Due to the different characteristics of the included studies, a random-effect model was used to calculate the pooled ES. Funnel plots were used to evaluate publication bias. Heterogeneity across studies was tested using the Q-statistics, while the I^2 index was used to assess inconsistency [14]. In addition, the I^2 index was classified as might not be important (0-40%), may represent moderate heterogeneity (30-60%), may represent substantial heterogeneity (50-90%), and represents considerable heterogeneity (75-100%) [14]. Forest plots were used to illustrate summary statistics and the variation (heterogeneity) across studies.

Results

Literature search

Of the 2490 registers recovered from electronic databases and hand search, 2440 records were excluded based on duplicate data, title or abstract. Fifty studies were fully

reviewed and assessed for eligibility and 32 were excluded (SF4). Finally, 18 studies met the inclusion criteria (Figure 1).

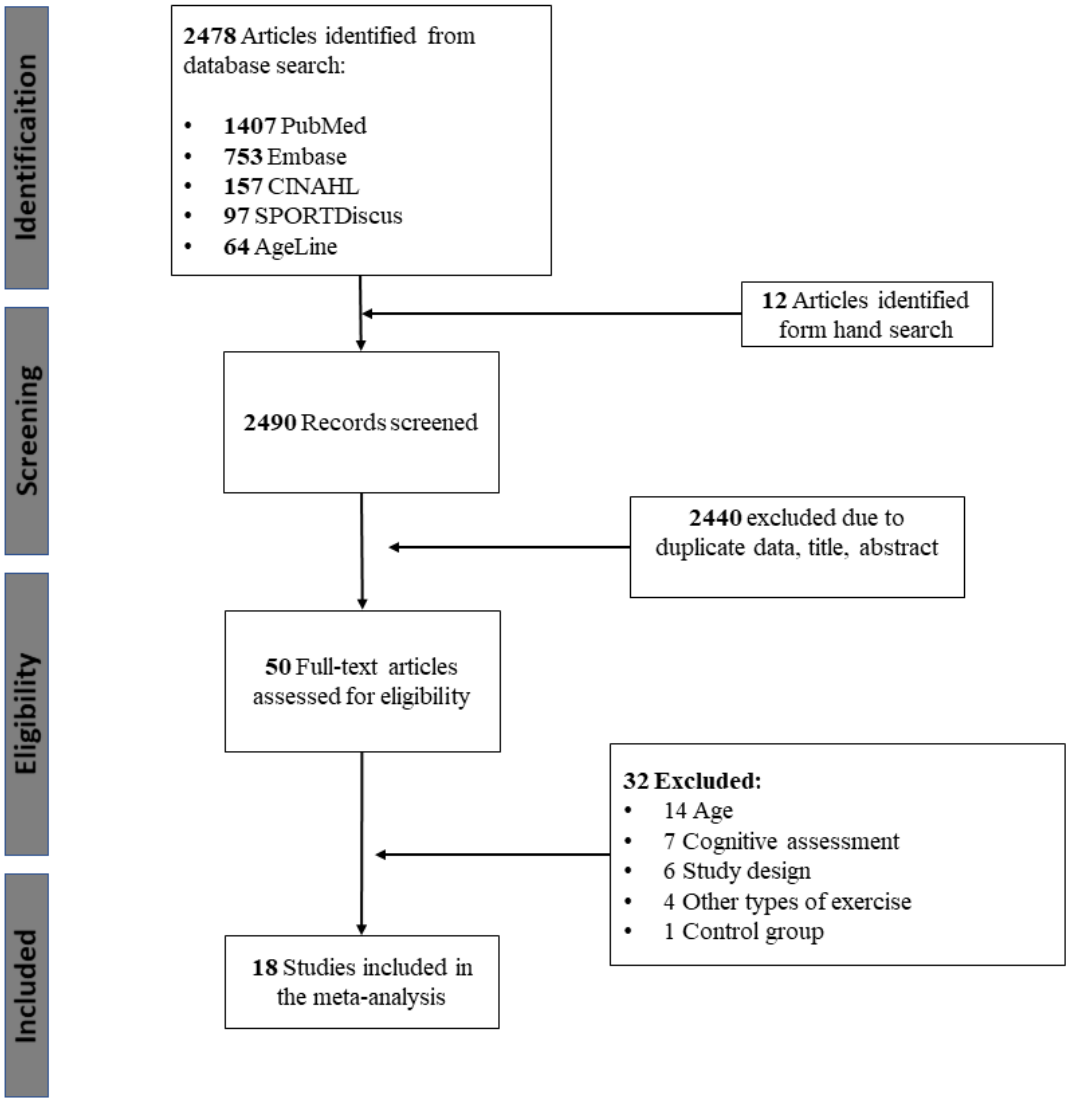

Figure 1. Flowchart of the study.

Characteristics of included studies

Table 1 provides a general description of included studies. Overall, community-dwelling older adults from 10 different countries (Armenia, Brazil, Canada, Ireland, Korea, Netherland, Spain, Switzerland, Taiwan, and the United States of America) were investigated between 1998 and 2019. Eleven studies (61.1%) investigated non-demented community-dwelling older adults [16–22], four studies (22.2%) investigated older adults with MCI [21,23–25], three studies (16.6%) investigated prefrail and frail older adults [26–28], while older adults with memory complains [29] (5.6%) were investigated in one study. Mean ages ranged from

65.3 to 84.8 years. RT protocols included traditional RT (TRT) [16,19,29–33,20–27], high-speed RT (HSRT) [24,28], circuit RT [18], and respiratory RT [17]. Sessions of exercise were performed once [33], twice [21,24,27,32,33], and third [16,17,31,18,19,22,25,26,28–30] weekly using 2-4 sets at low-to-moderate [16,18,22,31], moderate [32], moderate-to-high [24,25,28], and high intensities [21,23,24,30,31,33] for six to 36 weeks. Cognitive outcomes included overall cognitive function [16,18,21,25,26,29,30], short-term memory [17,19,31,33,20–23,25,27–29], long-term memory [31], attention and concentration [21,23,27,28,31,33], set-shifting [17,23,33], spatial awareness [32], reaction time [27,32], and verbal fluency [27,30].

Table 1. Main characteristics of the included studies.

Study	Country	Sample	Age	Intervention duration	Resistance training protocol	Control group	Cognitive outcomes
Ansai et al., 2015	Brazil	Community-dwelling older adults	82.4	16 weeks	3d/week; 3 sets of 10-12RM; 2s for CON and 2s for the ECC	No intervention	Overall cognitive function, verbal fluency
Busse et al., 2008	Brazil	Older adults with memory impairment	72.2	36 weeks	3d/week; 3 sets of 8-12 reps; 3s for CON and 6s for the ECC	—	Overall cognitive function, short-term memory
Cardalda et al., 2019	Spain	Frail older adults with MCI	84.8	12 weeks	3d/week; 2-3 sets of 10-15 reps	Social activities	Overall cognitive function
Cassilhas et al., 2007	Brazil	Community-dwelling older adults	~68.0	24 weeks	3d/week; 2 sets of 8 reps at 50% 1RM	Stretching	Short-term memory, long-term memory, attention and concentration
Cassilhas et al., 2007	Brazil	Community-dwelling older adults	~68.0	24 weeks	3d/week; 2 sets of 8 reps at 80% 1RM	Stretching	Short-term memory
Ferreira et al., 2015	Brazil	Community-dwelling older adults	~67.0	24 weeks	3d/week; 7 sets of breathing exercises and inspiratory muscle training	Social activities	Short-term memory, set-shifting
Fragala et al., 2014	Brazil	Community-dwelling older adults	70.6	6 weeks	2d/week; 3 sets of 10-15 repetitions at moderate intensity	—	Spatial Awareness, reaction time

Hong et al., 2018	Korea	Community-dwelling older adults	75.5	12 weeks	2d/week; Resistance exercise at 15 RM	No intervention	Overall cognitive function, short-term memory, attention and concentration
Hong et al., 2018	Korea	Older adults with MCI	75.5	12 weeks	2d/week; Resistance exercise at 15 RM	No intervention	Overall cognitive function, short-term memory, attention and concentration
Lachman et al., 2006	USA	Community-dwelling older adults with disabilities	60-94	24 weeks	3d/week; Resitance exercise with elastic bands	No intervention	Short-term memory
Liu-Ambrose et al., 2010	Canada	Community-dwelling older women	69.6	24 weeks	1d/week; 2 sets of 7RM	Balance, core, and streching exercises	Short-term memory, attention and concentration, set-shifting
Liu-Ambrose et al., 2010	Canada	Community-dwelling older women	69.6	24 weeks	2d/week; 2 sets of 7RM	Balance, core, and streching exercises	Short-term memory, attention and concentration, set-shifting
Nagamatsu et al., 2013	Canada	Older adults with MCI	~75.0	24 weeks	1-2d/week; 2 sets of 7RM	Balance, core, and streching exercises	Short-term memory, attention and concentration, set-shifting

Perrig-Chiello et al., 1998	Switzerland	Community-dwelling older adults	73.2	8 weeks	1d/week; 8 resistance exercises	—	Short-term memory
Tsai et al., 2019	Taiwan	Older adults with MCI	~65.3	16 weeks	3d/ week; 3 sets of 10 reps at 75% 1RM	Stretching	Overall cognitive function, short-term memory
Timmons et al., 2017	Ireland	Community-dwelling older adults	69.3	12 weeks	3d/week; 6 exercise circuit at 60% 1RM	—	Overall cognitive function
Smolarek et al., 2016	Brazil	Community-dwelling older adults	65.8	12 weeks	3d/week; 3 sets of 10 reps at 60-70% 1RM	No intervention	Overall cognitive function
Petrosyan, 2013	Armenia	Community-dwelling older men	66.7	12 weeks	3d/week; 2 sets of 6-8 reps at 50-60% 1RM	No intervention	Short-term memory
de Rest et al., 2014	Netherlands	Prefrail and frial older adults	~79.0	24 weeks	2d/week; 3-4 sets of 8-15 reps at 50-75% 1RM	—	Short-term memory, attention and concentration, reaction time, verbal fluency
Yoon et al., 2017	Korea	Older adults with MCI	~76.3	12 weeks	2d/week; 2-3 sets of 8-10 reps at hard intensity; 2s for CON and 2s for the ECC	Stretching	Overall cognitive function
Yoon et al., 2017	Korea	Older adults with MCI	~76.3	12 weeks	2d/week; 2-3 sets of 12-15 reps at somewhat hard intensity; As quick as possible for CON and 2s for the ECC	Stretching	Overall cognitive function

Yoon et al., 2018	Korea	Prefrail and frial older adults	~73.0	16 weeks	3d/ week; 2-3 sets of 12-15 reps at somewhat hard intensity; As quick as possible for CON and 2s for the ECC	—	Short-term memory, attention and concentration

CON= Concentric; ECC= Eccentric; MCI= Mild cognitive impairment; RM= Repetition maximum; USA= United States of America

Quality assessment

The overall score of quality assessment of cross-sectional and longitudinal studies is shown in Table 2. Detailed quality assessment is available in SF5. All studies reported the item required by the CASP criteria in relation to the focus (item 1), equivalences in treatments (item 6), external validity (item 9), and advantages of benefits (item 11). No studies blinded participants or health workers (item 4). However, 55.6% did not consider a measure of overall cognitive function (item 10) [17,19–23,27,31–33], 33.3% failed to clearly report whether individuals were analyzed according to the intention-to-treat method (item 3)[18,19,28,31–33], 16.6% investigated individuals who were not similar in the main variables at baseline (item 5) [22], and 5.6% did not clarify if participants were allocated to treatments randomly (item 2) [22].

Table 2. Study quality.

	Item No								
Study	**1**	**2**	**3**	**4**	**5**	**6**	**9**	**10**	**11**
Ansai et al., 2015	Y	Y	Y	N	Y	Y	Y	Y	Y
Busse et al., 2008	Y	Y	Y	N	N	Y	Y	Y	Y
Cardalda et al., 2019	Y	Y	Y	N	Y	Y	Y	Y	Y
Cassilhas et al., 2007	Y	Y	CT	N	Y	Y	Y	N	Y
Ferreira et al., 2015	Y	Y	Y	N	Y	Y	Y	N	Y
Fragala et al., 2014	Y	Y	CT	N	Y	Y	Y	N	Y
Hong et al., 2018	Y	Y	Y	N	Y	Y	Y	N	Y
Lachman et al., 2006	Y	Y	CT	N	Y	Y	Y	N	Y
Liu-Ambrose et al., 2010	Y	Y	Y	N	Y	Y	Y	N	Y
Nagamatsu et al., 2012	Y	Y	CT	N	Y	Y	Y	N	Y
Perrig-Chiello et al., 1998	Y	Y	Y	N	Y	Y	Y	N	Y
Tsai et al., 2019	Y	Y	Y	N	Y	Y	Y	Y	Y
Timmons et al., 2017	Y	Y	CT	N	Y	Y	Y	Y	Y
Smolarek et al., 2016	Y	Y	Y	N	Y	Y	Y	Y	Y
Petrosyan, 2013	Y	CT	Y	N	CT	Y	Y	N	Y
de Rest et al., 2014	Y	Y	Y	N	Y	Y	Y	N	Y
Yoon et al., 2017	Y	Y	Y	N	Y	Y	Y	Y	Y
Yoon et al., 2018	Y	Y	CT	N	Y	Y	Y	Y	Y

1. Did the trial address a clearly focused issue?; **2.** Was the assignment of patients to treatments randomised?; **3.** Were all of the patients who entered the trial properly accounted for at its conclusion?; **4.** Were patients, health workers and study personnel 'blind' to treatment?; **5.** Were the groups similar at the start of the trial; **6.** Aside from the experimental intervention, were the groups treated equally?; **9.** Can the results be applied to the local population, or in your context?; **10.** Were all clinically important outcomes considered?; **11.** Are the benefits worth the harms and costs?; CT= Can't tell; N= No; Y= Yes.

Effects of resistance training on cognitive function

- Overall cognitive function

Nine studies (five with non-demented and four with demented participants) investigated the effects of RT on overall cognitive function (Figure 2). Overall cognitive function was measured using the Montreal Cognitive Assessment (MoCA) in five studies [16,18,21,24,30], the Mini Mental State Examination (MMSE) in three studies [24–26], and the Cambridge Cognitive Examination (CAMCOG) in one study [29]. Yoon et al. [24] assessed overall cognitive function using both MMSE and MoCA and pooled analyses were performed accordingly. Results indicated a significant ES (SMD= 0.65; 95% CI= 0.24 to 1.07, P=0.002) for the effects of RT using MMSE from Yoon et al. [24] in the combined sample. Substantial heterogeneity (χ^2= 22.45, df= 8, P= 0.004, I^2= 64%) was found across studies. When the sample size was stratified according to diagnosis of dementia, the effects of RT remained significant in demented (SMD= 1.02; 95% CI= 0.22 to 1.82, P=0.01; χ^2= 11.47, df= 3, P= 0.009, I^2= 74%), but not in non-demented older adults (SMD= 0.41; 95% CI= -0.02 to 0.84, P=0.06; χ^2= 7.59, df= 4, P= 0.11, I^2= 47%). Yoon et al. [24] included two intervention groups: TRT and HSRT, and further analyses were performed accordingly. Results were no longer significant when TRT was removed (SMD= 1.00; 95% CI= -0.09 to 2.10, P=0.07) from the pooled analysis and heterogeneity increased from "may represent substantial heterogeneity" (I^2=74%) to "considerable heterogeneity" (I^2=81%, χ^2= 10.62, df= 2, P= 0.005). On the other hand, the exclusion of HSRT reduced ES (SMD= 0.62; 95% CI= 0.17 to 1.08, P=0.007), although it remained significant, and reduced heterogeneity classification from "may represent substantial heterogeneity" to "might not be important" (χ^2= 2.40, df= 2, P= 0.30, I^2= 17%).

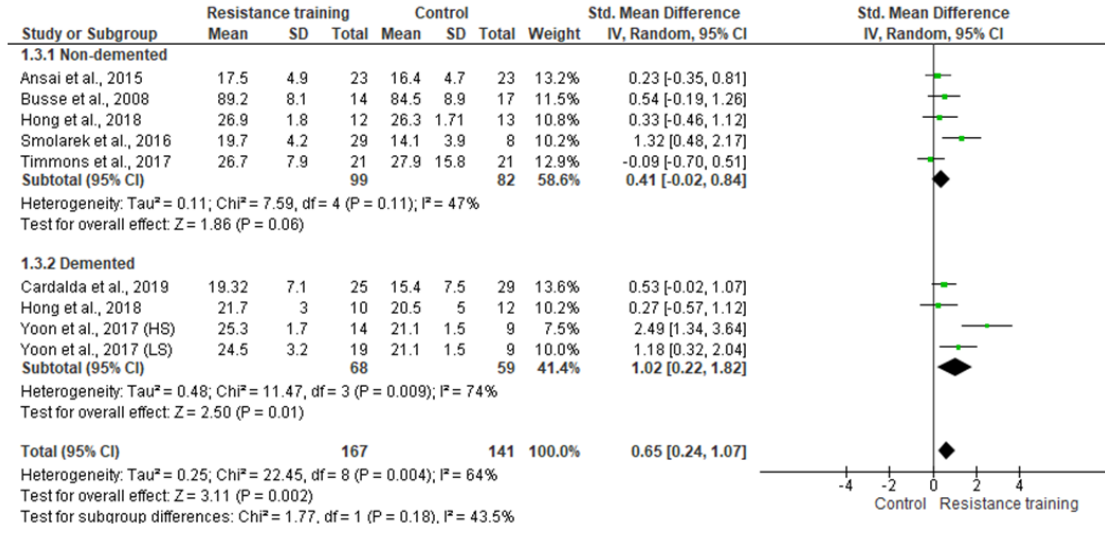

Figure 2. Standard mean difference of the effects of RT on overall cognitive function in non-demented and demented older adults.

When pooled analysis was performed using MoCA from Yoon et al. [24], the effects of RT on cognitive function were no longer significant in the non-demented sample (SMD= 0.68; 95% CI= -0.07 to 1.44, P=0.01; χ^2= 10.86, df= 3, P= 0.01, I^2= 72%) (SF6).

- *Short-term memory*

Short-term memory was assessed using immediate and delayed free recall in three studies [20,22,27] and Rey 15-Item Memory Test in two studies [21,28]. A non-significant pooled ES was found in the whole sample (SMD= 0.19; 95% CI= -0.06 to 0.45, P=0.14; χ^2= 2.30, df= 6, P= 0.89, I^2= 0%) and in the non-demented subset (SMD= 0.18; 95% CI= -0.11 to 0.48, P=0.23; χ^2= 0.49, df= 4, P= 0.49, I^2= 0%) (SF7).

Other four studies [17,21,31,33] assessed short-term memory using the digit span test. Overall ES indicated a significant effect of RT on digit span in the whole sample (MD= -0.15; 95% CI= -0.23 to -0.08, P<0.0001; I^2= 0%, χ^2= 3.97, df= 6, P= 0.68) and in the non-demented subset (MD= -0.15; 95% CI= -0.23 to -0.08, P<0.0001; I^2= 0%, $\chi 2$= 3.84, df= 5, P= 0.57) (Figure 3).

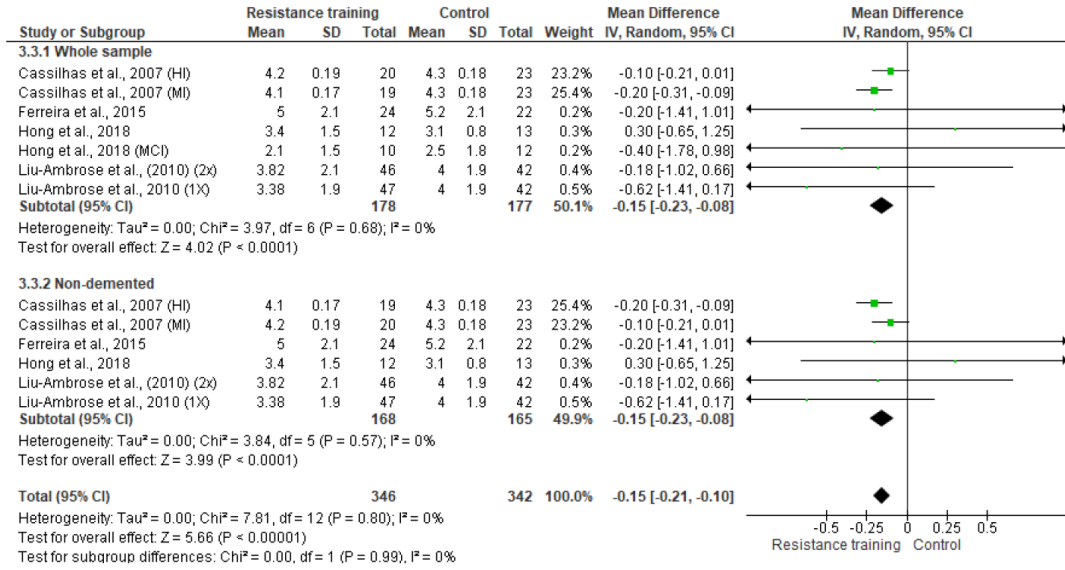

Figure 3. Mean difference of the effects of RT on digit span performance in the whole and non-demented samples.

- *Concentration and attention*

Concentration and attention were assessed using the Stroop test in three studies [21,27,33] and the Toulouse-Pieron's concentration attention test in one study [31]. No significant pooled ES were found for the overall (SMD= -0.01; 95% CI= -0.29 to 0.27, P=0.94; I^2= 43%, χ^2= 10.46, df= 6, P= 0.11) and non-demented samples (SMD= 0.01; 95% CI= -0.31 to 0.33, P= 0.95; I^2= 51%, χ^2= 10.28, df = 5, P= 0.07) (Figure 4).

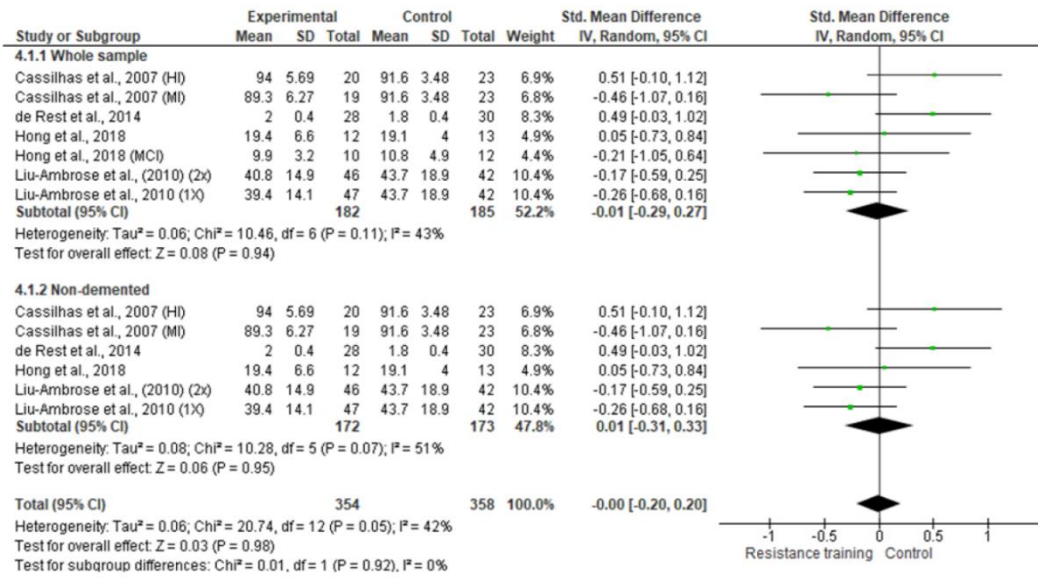

Figure 4. Standard mean difference of the effects of RT on concentration and attention in the whole and non-demented samples.

Discussion

The main findings of the present study indicate that RT improved overall cognitive function in demented, but not in non-demented older adults, while short-term memory, assessed by the digit span of the WAIS III, was only significantly increased in non-demented older adults. No effects of RT were observed for the concentration and attention domain.

These results are in line with prior systematic reviews, which found that aerobic exercise improved overall cognitive function in demented older adults [12,34]. However, no other investigations reported improved overall cognitive function in older adults in response to RT. Our findings have substantial clinical relevance since MMSE and MoCA are routinely used in clinics and research for cognitive screening [35,36] and low scores in these tests are associated with numerous negative health-related outcomes, such as sedentary lifestyle, insomnia, loneliness, and dementia [37–40].

Notably, RT did not improve overall cognitive function in cognitively healthy older adults, while short-term memory was significantly increased in this population, but not in demented older adults. Although we are unable to explain the underlying mechanisms, these findings may indicate that different brain regions are affected by RT according to the progression of dementia. This proposition is supported by Hong et al. [21], who found an exclusive increase in alpha waves of the electroencephalogram (EEG) in demented older adults after 12 weeks of RT. However, there is a lack of empirical evidence comparing the underlying neural mechanisms elicited by RT in older adults with different cognitive levels.

Regarding short-term memory, prior studies observed that hormonal levels (i.e., insulin-like growth factor-1 [IGF-1]) [41], EEG pattern (i.e., theta wave) [21], and brain morphology (i.e., brain volume) [33] were changed in parallel to improvements in short-term memory after RT in non-demented older adult. These adaptations may explain, at least partially, the findings of the present study.

It is important to mention that our quality assessment analysis identified a lack of important information, such as if enrollees were treated according to the intention to treat method, the inclusion of other measures in addition to hypothesis tests, and if all clinically important outcomes were considered. Particularly, the P-value may not sufficiently represent significance, ES, and clinical relevance of results, and the use of additional analyses is encouraged [42,43]. In addition, the absence of evaluation of global cognitive function limits the extrapolation of findings to public health program, given the prognostic value of this parameter.

Future studies aimed at investigating the effects of RT on cognition in older adults should include evaluation of overall cognitive function to provide evidence for guidelines on exercise and mental health. These findings may be further explored through follow-up designs, which can identify if maintaining or improving overall cognitive function in demented older adults with RT may prevent the development of dementia. Although many cognitive domains were investigated, only few studies reported similar data to be included in the meta-analysis. In fact, improvements in overall cognitive function in demented older adults may not be explained by short-term memory or concentration and attention, suggesting that other cognitive domains may be improved after RT. Therefore, researchers should consider using already investigated tools to assess cognitive domains to facilitate comparisons among studies.

Finally, a reduced ES was found when TRT of Yoon et al. [24] was removed, which may indicate that HSRT has limited impact on cognitive function. On the other hand, findings from quasi-experimental studies [44] and samples composed by young to middle age adults [44,45] suggest a positive impact of RT on cognition. However, the lack of evidence limited possible comparisons among TRT and HSRT. Thus, more studies investigating RT modalities other than TRT should be performed to allow comparisons among interventions.

Conclusion

Cognition is significantly improved after RT in older adults. However, different adaptations are observed according to cognitive levels. In fact, overall

cognitive function is only improved in cognitively healthy individuals, while amelioration of short-term memory was exclusively found in demented older adults. These findings encourage the use of RT as a tool to preserve mental health in the older population.

Acknowledgments

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Supplementary material 1

List of SRMA

Brunt, A., Albines, D., & Hopkins-Rosseel, D. (2019). The Effectiveness of Exercise on Cognitive Performance in Individuals with Known Vascular Disease: A Systematic Review. Journal of clinical medicine, 8(3), 294.

de Asteasu, M. L. S., Martinez-Velilla, N., Zambom-Ferraresi, F., Casas-Herrero, A., & Izquierdo, M. (2017). Role of physical exercise on cognitive function in healthy older adults: a systematic review of randomized clinical trials. Ageing research reviews, 37, 117-134.

Gates, N., Singh, M. A. F., Sachdev, P. S., & Valenzuela, M. (2013). The effect of exercise training on cognitive function in older adults with mild cognitive impairment: a meta-analysis of randomized controlled trials. The American Journal of Geriatric Psychiatry, 21(11), 1086-1097.

Gomes-Osman, J., Cabral, D. F., Morris, T. P., McInerney, K., Cahalin, L. P., Rundek, T., ... & Pascual-Leone, A. (2018). Exercise for cognitive brain health in aging: a systematic review for an evaluation of dose. Neurology: clinical practice, 8(3), 257-265.

Guitar, N. A., Connelly, D. M., Nagamatsu, L. S., Orange, J. B., & Muir-Hunter, S. W. (2018). The effects of physical exercise on executive function in community-dwelling

older adults living with Alzheimer's-type dementia: a systematic review. Ageing research reviews.

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Kelly, M. E., Loughrey, D., Lawlor, B. A., Robertson, I. H., Walsh, C., & Brennan, S. (2014). The impact of exercise on the cognitive functioning of healthy older adults: a systematic review and meta-analysis. Ageing research reviews, 16, 12-31.

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Van Uffelen, J. G., Paw, M. J. C. A., Hopman-Rock, M., & van Mechelen, W. (2008). The effects of exercise on cognition in older adults with and without cognitive decline: a systematic review. Clinical Journal of Sport Medicine, 18(6), 486-500.

Supplementary material 2

SEARCH ON PUBMED

Patients

Aged [MESH]

Frail elderly [MESH]

Older adults

Intervention

Plyometric exercise [MESH]

Resistance Training [MESH]

Circuit resistance training

High-velocity resistance training

Power training

Strength training

Weight-bearing training

Weight-lifting training

Outcomes

cognition [MESH]

cognitive function

executive function

problem solving

memory

attention

language

visual perception

BOOLEAN OPERATORS

AND, OR

COMBINATIONS

1- Plyometric exercise [MESH] AND Aged [MESH] AND cognition [MESH]

2- Resistance Training [MESH] AND Aged [MESH] AND cognition [MESH]

3- Resistance Training [MESH][tw] AND Aged [MESH] AND cognition [MESH]

4- Resistance Training AND Aged [MESH] AND cognition [MESH]

5- Resistance Training AND Aged [MESH] AND cognition

6- Circuit resistance training AND Aged [MESH] AND cognition [MESH]

7- Circuit resistance training [tw] AND Aged [MESH] AND cognition [MESH]

8- High-velocity resistance training [tw] AND Aged [MESH] AND cognition [MESH]

9- Power training AND Aged [MESH] AND cognition [MESH]

10- Power training [tw] AND Aged [MESH] AND cognition [MESH]

11- Strength training [tw] AND Aged [MESH] AND cognition [MESH]

12- Weight-bearing training AND Aged [MESH] AND cognition [MESH]

13- Weight-bearing training [tw] AND Aged [MESH] AND cognition [MESH]

14- Weight-lifting training AND Aged [MESH] AND cognition [MESH]

15- Weight-lifting training [tw] AND Aged [MESH] AND cognition [MESH]

16- Plyometric exercise [MESH] AND Frail elderly [MESH] AND cognition

17- Resistance Training [MESH] AND Frail elderly [MESH] AND cognition [MESH]

18- Resistance Training [MESH] AND Frail elderly [MESH] AND cognition [MESH]

19- Resistance Training [MESH] AND Frail elderly [MESH] AND cognition

20- Resistance Training [MESH][tw] AND Frail elderly [MESH] AND cognition

21- Resistance Training AND Frail elderly [MESH] AND cognition

22- Circuit resistance training AND Frail elderly [MESH] AND cognition [MESH]

23- Circuit resistance training AND Frail elderly [MESH] AND cognition

24- High-velocity resistance training AND Frail elderly [MESH] AND cognition [MESH]

25- High-velocity resistance training AND Frail elderly [MESH] AND cognition

26- Power training AND Frail elderly [MESH] AND cognition [MESH]

27- Strength training AND Frail elderly [MESH] AND cognition [MESH]

28- Strength training [tw] AND Frail elderly [MESH] AND cognition [MESH]
29- Weight-bearing training AND Frail elderly [MESH] AND cognition [MESH]
30- Weight-lifting training AND Frail elderly [MESH] AND cognition [MESH]
31- Plyometric exercise [MESH] AND older adults AND cognition [MESH]
32- Resistance Training [MESH] AND older adults AND cognition [MESH]
33- Resistance Training [MESH][tw] AND older adults AND cognition [MESH]
34- Resistance Training [tw] AND older adults AND cognition [MESH]
35- Circuit resistance training AND older adults AND cognition [MESH]
36- High-velocity resistance training AND older adults AND cognition [MESH]
37- Power training AND older adults AND cognition [MESH]
38- Strength training AND older adults AND cognition [MESH]
39- Strength training [tw] AND older adults AND cognition [MESH]
40- Weight-bearing training AND older adults AND cognition [MESH]
41- Weight-lifting training AND older adults AND cognition [MESH]
42- Plyometric exercise AND Aged [MESH] AND (cognition [tw] OR cognitive function [tw] OR executive function [tw] OR problem solving [tw] OR memory [tw] OR attention [tw] OR language [tw] OR visual perception [tw])
43- Resistance Training AND Aged [MESH] AND (cognition [tw] OR cognitive function [tw] OR executive function [tw] OR problem solving [tw] OR memory [tw] OR attention [tw] OR language [tw] OR visual perception [tw])
44- Resistance Training [tw] AND Aged [MESH] AND (cognition [tw] OR cognitive function [tw] OR executive function [tw] OR problem solving [tw] OR memory [tw] OR attention [tw] OR language [tw] OR visual perception [tw])
45- Circuit resistance training AND Aged [MESH] AND (cognition [tw] OR cognitive function [tw] OR executive function [tw] OR problem solving [tw] OR memory [tw] OR attention [tw] OR language [tw] OR visual perception [tw])
46- High-velocity resistance training AND Aged [MESH] AND (cognition [tw] OR cognitive function [tw] OR executive function [tw] OR problem solving [tw] OR memory [tw] OR attention [tw] OR language [tw] OR visual perception [tw])

47- Power training AND Aged [MESH] AND (cognition [tw] OR cognitive function [tw] OR executive function [tw] OR problem solving [tw] OR memory [tw] OR attention [tw] OR language [tw] OR visual perception [tw])

48- Power training [tw] AND Aged [MESH] AND (cognition [tw] OR cognitive function [tw] OR executive function [tw] OR problem solving [tw] OR memory [tw] OR attention [tw] OR language [tw] OR visual perception [tw])

49- Strength training AND Aged [MESH] AND (cognition [tw] OR cognitive function [tw] OR executive function [tw] OR problem solving [tw] OR memory [tw] OR attention [tw] OR language [tw] OR visual perception [tw])

50- Strength training [tw] AND Aged [MESH] AND (cognition [tw] OR cognitive function [tw] OR executive function [tw] OR problem solving [tw] OR memory [tw] OR attention [tw] OR language [tw] OR visual perception [tw])

51- Weight-bearing training AND Aged [MESH] AND (cognition [tw] OR cognitive function [tw] OR executive function [tw] OR problem solving [tw] OR memory [tw] OR attention [tw] OR language [tw] OR visual perception [tw])

52- Weight-bearing training [tw] AND Aged [MESH] AND (cognition [tw] OR cognitive function [tw] OR executive function [tw] OR problem solving [tw] OR memory [tw] OR attention [tw] OR language [tw] OR visual perception [tw])

53- Weight-lifting training AND Aged [MESH] AND (cognition [tw] OR cognitive function [tw] OR executive function [tw] OR problem solving [tw] OR memory [tw] OR attention [tw] OR language [tw] OR visual perception [tw])

54- Weight-lifting training [tw] AND Aged [MESH] AND (cognition [tw] OR cognitive function [tw] OR executive function [tw] OR problem solving [tw] OR memory [tw] OR attention [tw] OR language [tw] OR visual perception [tw])

55- Plyometric exercise AND older adults AND (cognition [tw] OR cognitive function [tw] OR executive function [tw] OR problem solving [tw] OR memory [tw] OR attention [tw] OR language [tw] OR visual perception [tw])

56- Resistance Training AND older adults AND (cognition [tw] OR cognitive function [tw] OR executive function [tw] OR problem solving [tw] OR memory [tw] OR attention [tw] OR language [tw] OR visual perception [tw])

57- Circuit resistance training AND older adults AND (cognition [tw] OR cognitive function [tw] OR executive function [tw] OR problem solving [tw] OR memory [tw] OR attention [tw] OR language [tw] OR visual perception [tw])

58- High-velocity resistance training AND older adults AND (cognition [tw] OR cognitive function [tw] OR executive function [tw] OR problem solving [tw] OR memory [tw] OR attention [tw] OR language [tw] OR visual perception [tw])

59- Strength training AND older adults AND (cognition [tw] OR cognitive function [tw] OR executive function [tw] OR problem solving [tw] OR memory [tw] OR attention [tw] OR language [tw] OR visual perception [tw])

60- Strength training [tw] AND older adults AND (cognition [tw] OR cognitive function [tw] OR executive function [tw] OR problem solving [tw] OR memory [tw] OR attention [tw] OR language [tw] OR visual perception [tw])

61- Weight-bearing training AND older adults AND (cognition [tw] OR cognitive function [tw] OR executive function [tw] OR problem solving [tw] OR memory [tw] OR attention [tw] OR language [tw] OR visual perception [tw])

62- Weight-bearing training [tw] AND older adults AND (cognition [tw] OR cognitive function [tw] OR executive function [tw] OR problem solving [tw] OR memory [tw] OR attention [tw] OR language [tw] OR visual perception [tw])

63- Weight-lifting training AND older adults AND (cognition [tw] OR cognitive function [tw] OR executive function [tw] OR problem solving [tw] OR memory [tw] OR attention [tw] OR language [tw] OR visual perception [tw])

64- Weight-lifting training [tw] AND older adults AND (cognition [tw] OR cognitive function [tw] OR executive function [tw] OR problem solving [tw] OR memory [tw] OR attention [tw] OR language [tw] OR visual perception [tw])

65- (Plyometric exercise [MESH] OR Resistance Training [MESH] OR Circuit resistance training OR High-velocity resistance training OR Power training OR Strength training OR Weight-bearing training OR Weight-lifting training) AND (Aged [MESH] OR Frail elderly [MESH] OR Older adults) AND (cognition [MESH] OR cognitive function OR executive function OR problem solving OR memory OR attention OR language OR visual perception);

66- (Plyometric exercise [MESH][tw] OR Resistance Training [MESH][tw] OR Circuit resistance training [tw] OR High-velocity resistance training [tw] OR Power training [tw] OR Strength training Weight-bearing training [tw] OR Weight-lifting training [tw]) AND (Aged [MESH] OR Frail elderly [MESH] OR Older adults) AND (cognition [MESH] OR cognitive function OR executive function OR problem solving OR memory OR attention OR language OR visual perception).

Supplementary material 3

CI in SD

		Upper CI	Lower CI	N	Estimate. SD	T value for a 95% CI
Timmons et al., 2017	Intervention	8,7	5,1	21	7,9	2,1
	Control	6,2	-1	21	15,8	2,1
Ferreira et al., 2015	Intervention	5,8	4,8	24	2,4	2,1
	Control	5,5	4,5	22	2,3	2,1

Mean

		%change	*Baseline*	Δ	*Final*
MocA					
Timmons et al., 2017	Intervention	2,7	26,0	0,70	26,7
	Control	3,2	27,0	0,86	27,9
A-Rey Figure					
Cassilhas et al., 2007	High intensity	8,31	10,1	0,84	10,9
	Moderate intensity	8,38	11,3	0,94	12,2
	Control	5,17	9,2	0,48	9,7
WAIS-III					
Cassilhas et al., 2007	High intensity	-0,10	4,3	0,00	4,2
	Moderate intensity	-0,12	4,1	0,00	4,1
	Control	-0,14	4,3	-0,01	4,3

WSM-R					
Cassilhas et al., 2007	High intensity	0,95	4,1	0,04	4,1
	Moderate intensity	0,97	4,5	0,04	4,5
	Control	0	4,4	0,00	4,4
Stroop					
Cassilhas et al., 2007	High intensity	6,90	87,1		94,0
	Moderate intensity	4,85	84,47		89,3
	Control	6,67	84,9		91,6

CONVERTION

Supplementary material 4

Excluded

Aged <60 years old

1- Anderson-Hanley, C., Nimon, J. P., & Westen, S. C. (2010). Cognitive health benefits of strengthening exercise for community-dwelling older adults. Journal of Clinical and Experimental Neuropsychology, 32(9), 996-1001.

2- Cherup, N., Roberson, K., Potiaumpai, M., Widdowson, K., Jaghab, A. M., Chowdhari, S., ... & Signorile, J. (2018). Improvements in cognition and associations with measures of aerobic fitness and muscular power following structured exercise. Experimental gerontology, 112, 76-87.

3- Coetsee, C., & Terblanche, E. (2017). The effect of three different exercise training modalities on cognitive and physical function in a healthy older population. European Review of Aging and Physical Activity, 14(1), 13.

4- David, F. J., Robichaud, J. A., Leurgans, S. E., Poon, C., Kohrt, W. M., Goldman, J. G., ... & Corcos, D. M. (2015). Exercise improves cognition in Parkinson's disease: The PRET-PD randomized, clinical trial. Movement Disorders, 30(12), 1657-1663.

5- Fernandez-Gonzalo, R., Fernandez-Gonzalo, S., Turon, M., Prieto, C., Tesch, P. A., & del Carmen García-Carreira, M. (2016). Muscle, functional and cognitive adaptations after flywheel resistance training in stroke patients: a pilot randomized controlled trial. Journal of neuroengineering and rehabilitation, 13(1), 37.

6- Iuliano, E., di Cagno, A., Aquino, G., Fiorilli, G., Mignogna, P., Calcagno, G., & Di Costanzo, A. (2015). Effects of different types of physical activity on the cognitive functions and attention in older people: A randomized controlled study. Experimental gerontology, 70, 105-110.

7- Iuliano, E., Fiorilli, G., Aquino, G., Di Costanzo, A., Calcagno, G., & di Cagno, A. (2017). Twelve-week exercise influences memory complaint but not memory performance in older adults: A randomized controlled study. Journal of aging and physical activity, 25(4), 612-620.

8- Kimura, K., Obuchi, S., Arai, T., Nagasawa, H., Shiba, Y., Watanabe, S., & Kojima, M. (2010). The influence of short-term strength training on health-related quality of life and executive cognitive function. Journal of physiological anthropology, 29(3), 95-101.

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10- Mavros, Y., Gates, N., Wilson, G. C., Jain, N., Meiklejohn, J., Brodaty, H., ... & Baker, M. K. (2017). Mediation of cognitive function improvements by strength gains after resistance training in older adults with mild cognitive impairment: outcomes

of the study of mental and resistance training. Journal of the American Geriatrics Society, 65(3), 550-559.

11- Silva-Batista, C., Corcos, D. M., Roschel, H., Kanegusuku, H., Gobbi, L. T., Piemonte, M. E., ... & Ugrinowitsch, C. (2016). Resistance Training with Instability for Patients with Parkinson's Disease. Medicine and science in sports and exercise, 48(9), 1678-1687.

12- Singh, M. A. F., Gates, N., Saigal, N., Wilson, G. C., Meiklejohn, J., Brodaty, H., ... & Baker, M. K. (2014). The Study of Mental and Resistance Training (SMART) study—resistance training and/or cognitive training in mild cognitive impairment: a randomized, double-blind, double-sham controlled trial. Journal of the American Medical Directors Association, 15(12), 873-880.

13- Strassnig, M. T., Signorile, J. F., Potiaumpai, M., Romero, M. A., Gonzalez, C., Czaja, S., & Harvey, P. D. (2015). High velocity circuit resistance training improves cognition, psychiatric symptoms and neuromuscular performance in overweight outpatients with severe mental illness. Psychiatry research, 229(1-2), 295-301.

14- Teixeira, R. B., Marins, J. C. B., Amorim, P. R. S., Teoldo, I., Cupeiro, R., Andrade, M. O. C. D., ... & Lima, L. M. (2019). Evaluating the effects of exercise on cognitive function in hypertensive and diabetic patients using the mental test and training system. The World Journal of Biological Psychiatry, 20(3), 209-218.

Lack of cognitive assessment

15- Bolandzadeh, N., Tam, R., Handy, T. C., Nagamatsu, L. S., Hsu, C. L., Davis, J. C., ... & Liu-Ambrose, T. (2015). Resistance training and white matter lesion progression in older women: Exploratory analysis of a 12-month randomized controlled trial. Journal of the American Geriatrics Society, 63(10), 2052-2060.

16- Chang, M., Ramel, A., Jonsson, P. V., Thorsdottir, I., & Geirsdottir, O. G. (2019). The effect of cognitive function on mobility improvement among community-living older adults: A 12-week resistance exercise intervention study. Aging, Neuropsychology, and Cognition, 1-12.

17- Davis, J. C., Bryan, S., Marra, C. A., Sharma, D., Chan, A., Beattie, B. L., ... & Liu-Ambrose, T. (2013). An economic evaluation of resistance training and aerobic training versus balance and toning exercises in older adults with mild cognitive impairment. PLoS One, 8(5), e63031.

18- Özkaya, G. Y., Aydin, H., Toraman, F. N., Kizilay, F., Özdemir, Ö., & Cetinkaya, V. (2005). Effect of strength and endurance training on cognition in older people. Journal of sports science & medicine, 4(3), 300.

19- Liu-Ambrose, T., Nagamatsu, L. S., Voss, M. W., Khan, K. M., & Handy, T. C. (2012). Resistance training and functional plasticity of the aging brain: a 12-month randomized controlled trial. Neurobiology of aging, 33(8), 1690-1698.

20- Ten Brinke, L. F., Bolandzadeh, N., Nagamatsu, L. S., Hsu, C. L., Davis, J. C., Miran-Khan, K., & Liu-Ambrose, T. (2015). Aerobic exercise increases hippocampal volume in older women with probable mild cognitive impairment: a 6-month randomised controlled trial. Br J Sports Med, 49(4), 248-254.

21- Tsutsumi, T., Don, B. M., Zaichkowsky, L. D., & Delizonna, L. L. (1997). Physical fitness and psychological benefits of strength training in community dwelling older adults. Applied human science, 16(6), 257-266.

Lack of a control group

22- Forte, R., Boreham, C. A., Leite, J. C., De Vito, G., Brennan, L., Gibney, E. R., & Pesce, C. (2013). Enhancing cognitive functioning in the elderly: multicomponent vs resistance training. Clinical interventions in aging, 8, 19.

Included other types of exercise than RT

23- da Silveira Langoni, C., de Lima Resende, T., Barcellos, A. B., Cecchele, B., Knob, M. S., do Nascimento Silva, T., ... & Schwanke, C. H. A. (2019). Effect of exercise on cognition, conditioning, muscle endurance, and balance in older adults with mild cognitive impairment: a randomized controlled trial. Journal of Geriatric Physical Therapy, 42(2), E15-E22.

24- Ruiz, J. R., Gil-Bea, F., Bustamante-Ara, N., Rodríguez-Romo, G., Fiuza-Luces, C., Serra-Rexach, J. A., ... & Lucia, A. (2015). Resistance training does not have an effect on cognition or related serum biomarkers in nonagenarians: a randomized controlled trial. International journal of sports medicine, 36(01), 54-60.

25- Ponce-Bravo, H., Ponce, C., Feriche, B., & Padial, P. (2015). Influence of two different exercise programs on physical fitness and cognitive performance in active older adults: Functional resistance-band exercises vs. recreational oriented exercises. Journal of sports science & medicine, 14(4), 716.

26- Molloy, D. W., McLaughlin, J. S., RICHARDSON, L. D., & Crilly, R. G. (1988). The effects of a three-month exercise programme on neuropsychological function in elderly institutionalized women: a randomized controlled trial. Age and Ageing, 17(5), 303-310.

Study design/Poster

27- Chan, K. N., Chen, Y., Lit, Y., Massaband, P., Kiratli, J., Rabkin, R., & Myers, J. N. (2019). A randomized controlled trial of exercise to prevent muscle mass and functional loss in elderly hemodialysis patients: Rationale, study design, and baseline sample. Contemporary clinical trials communications, 15, 100365.

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facilities: evaluation of the applicability with focus on cognitive function. Physical therapy, 86(4), 489-498.

31- N., Fallah, C.L., Hsu, N., Bolandzadeh, B.L., Beattie, P., Graf, T.-A., Liu. (2012). Refining exercise prescription to promote executive functions in older adults using multistate transition modeling. Alzheimer's and Dementia, 8(4). P100

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Figure captions/Supplementary material

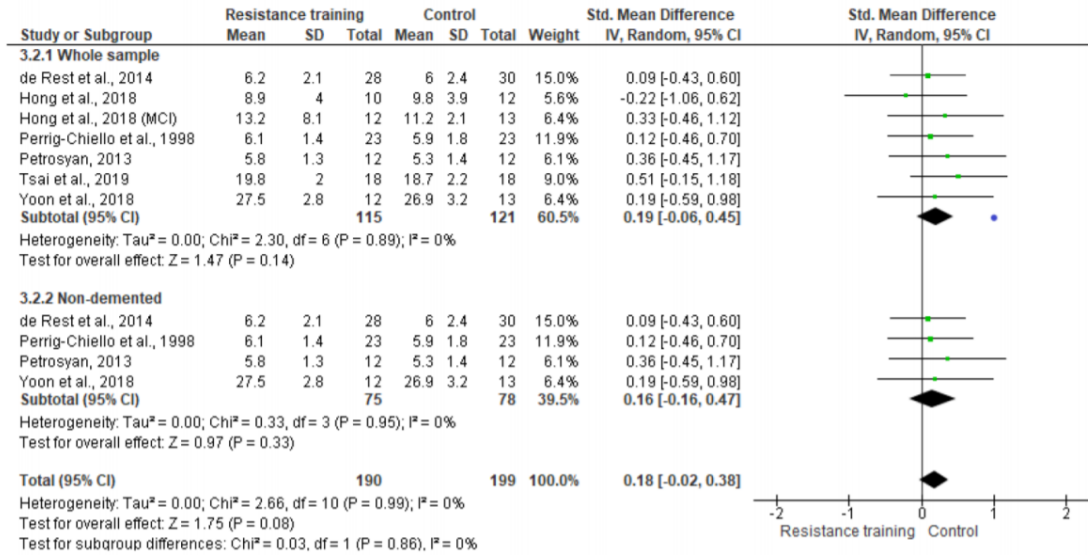

Figure S6. Standard mean difference of the effects of RT on overall cognitive function in non-demented and demented older adults based on MoCA.

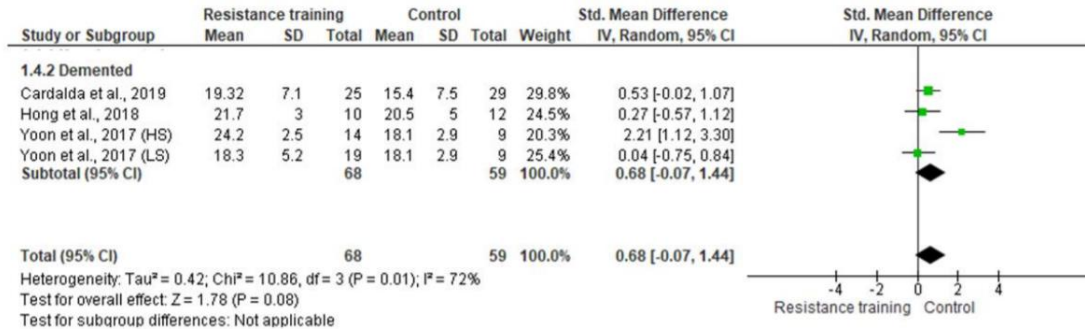

Figure S7. Standard mean difference of the effects of RT on short-term memory in demented older adults.

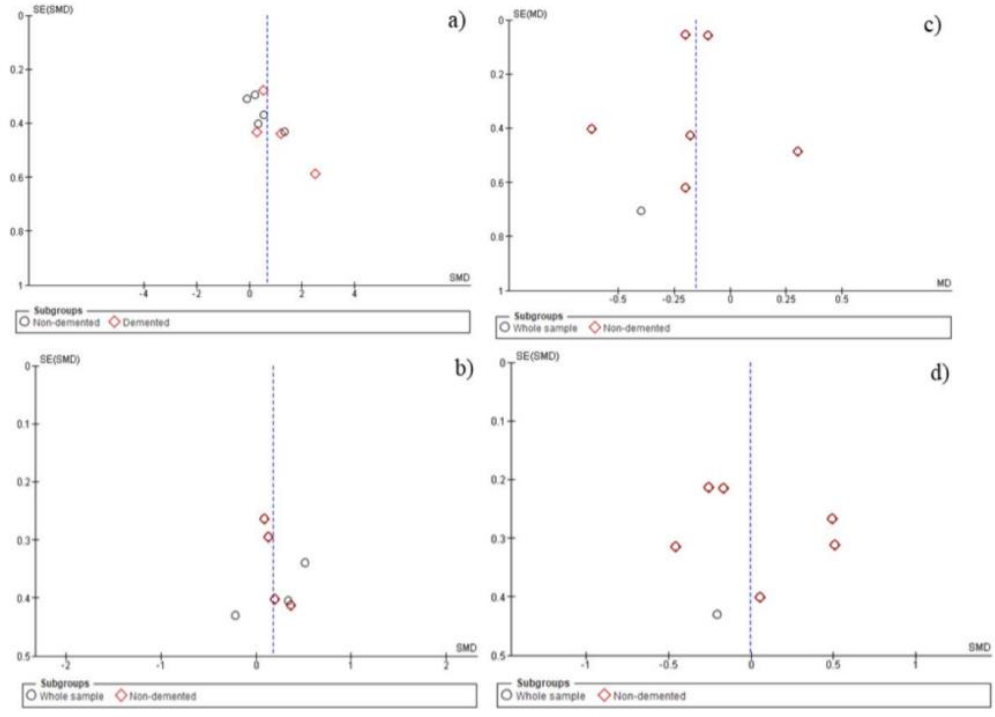

Figure SF8. **Funnel plots**: a) RT on overall cognitive function, b) RT on short-term memory, c) RT on digit span performance, and d) RT on concentration and attention. Funnel plots shows distributions of the SMD and SD in relation to standard error in the funnel plots were symmetrical, suggesting a low probability of study bias.

Compliance with Ethical Standards

Disclosure of potential conflicts of interest

Author HJCJ, Author EM, Author MCS, and Author MCU declare that they have no conflict of interest.

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Article 14

Acute Effects of Low- and High-Speed Resistance Exercise on the Cognitive Function of Institutionalized Frail Older Adults

Abstract

Aim: The present study aimed to investigate the acute effects of low-speed resistance exercise (LSRE) and high-speed resistance exercise (HSRE) on the cognitive function of frail older adults. **Material and methods:** This was a randomized crossover study. Eighteen institutionalized frail older women randomly performed LSRE, HSRE, and a control session (CS). Cognitive function was recorded before, over 1 h, and 24 h after the end of the experimental session. Exercise sessions were performed using 4 exercises for lower limbs. Particularly, LSRE was composed of 4 sets of 8-10 repetitions at 70%-75% of 1-repetition maximum (1RM). The concentric and eccentric phases were carried out for 2-s. For HSRE, exercises were performed 8 times (sets) with 3-5 repetitions at 70%-75% of 1RM. The concentric phase was performed as fast as possible and the eccentric phase was carried out for 2-s. **Results**: Both LSRE (P=0.01) and HSRE (P=0.001) increased VL scores IA the exercise session, but only LSRE (P=0.01) remained significant higher at 1h. At 24h, VL was significantly higher in CS in comparison to rest (P=0.001) and HSRE (P=0.01). No changes were observed in FS, IR, and DR in response to any session and no other differences were observed between-group. Regarding STROOP, no significant effects of strength and power exercises were observed on the number of correct answers, while it was significantly reduced at 1h during the incongruent stimulus in CS. **Conclusion:** Our findings indicate that both power and strength exercises acutely increased VL, an indicative of verbal immediate memory, in frail older women. However, a different pattern was observed among the groups, given that VL remained improved during 1h after the LSRE, while it was only increased IA the HSRE. No acute effects of exercise were observed on STROOP performance. Nevertheless, the number of correct answers was significantly reduced in the CS during the incongruent stimulus.

INTRODUCTION

The roman aphorism *mens sana in corpore sano* acknowledges the well-recognized positive effects of physical exercise on brain function. This concept seems to be particularly important in older adults, give the age-related decline in cognitive function (1). Specifically, observational studies have found that frail older people are at higher risk for cognitive decline (2,3), which may indicate that exercise therapy may be an important tool in the management of frail patients.

Low-Speed Resistance Exercise (LSRE), a type of exercise in which muscles work or hold against an applied force at low to moderate velocity, has been considered the first-line therapy to prevent age-related neuromuscular decline (4). Regarding cognition, an increasing number of evidence has found that an acute session of RE may cause transient improvements in cognitive function. However, most findings are based in clinical and non-clinical populations of older adults (5,6) and the few available studies are restricted to working memory (5–8).

Hsieh et al. (5) found improved working memory 10 min following a session of LSRE in non-demented older men. Similarly, Naderi et al. (6) observed improved working memory in older women and men who performed RE at 40% 1RM and 70% 1RM.

Notably, researchers (9) have argued that high-speed resistance exercise (HSRE), a type of resistance exercise in which muscle contractions are performed as fast as possible, should be included in resistance training programs for older adults that aim to improve physical function, given that some aspects of the neuromuscular function seem to be more dependent of high-speed muscle actions than on those performed with low speed (10,11). However, the effects of HSRE on the cognitive function are still unknown.

Based on these premises, the present study investigated the acute effects of LSRE and HSRE on the cognitive function of frail older adults.

MATERIALS AND METHODS

This is a randomized cross-over study that investigated the acute effects of two types of resistance exercise on cognitive parameters of non-demented frail older women. The protocol was approved by the Research Ethics Committee of the University of Campinas (UNICAMP, Campinas, Brazil). All study procedures were conducted in compliance with the Declaration of Helsinki and the Resolution 196/96 of the National Health Council.

Participants

Institutionalized older women (aged 72 to 99 years) were recruited from a public nursing home located in eastern region of São Paulo State, in southern Brazil. Individuals were eligible if they: a) aged 60 years or over; b) were frail according to Fried's criteria(12); c) possessed sufficient physical and cognitive abilities to perform all exercises required by the protocol; and d) had a physician authorization to participate. Exclusion criteria included having participated in a structured physical exercise training program in the past six months, uncorrected visual deficit, color blindness, prescription of hormone replacement therapy and/or psychotropic drugs, any unstable cardiovascular event (e.g., myocardial infarction) or complication in the past 6 months, and dementia according to the Mini-mental Mental State Examination (MMSE) scores adjusted by educational level (13,14).

Enrollers were randomized by an independent researcher using a computer-generated list of random numbers into low-speed resistance exercise (LSRE), high-speed resistance exercise (HSRE), and control session (CS).

All experiments were performed in the rehabilitation unit of the nursing home. Food consumption was maintained constant during the previous 48 h and enrollers consumed a standard breakfast 60–90 min before the being of the experimental sessions. Experimental sessions were separated by one week.

Ten repetition maximum test (10RM)

Participants were familiarized with resistance exercises used in the present study prior to the ten-repetition maximum test (10RM). 10RM tests was performed in following three exercises: squat on the chair (until 90° knee flexion), seated unilateral hip flexion, and seated unilateral knee extension. Before the tests, enrollers performed a brief specific warm-up using light loads. Afterward, the 10RM load was determined up to 5 attempts, with a 3-minute interval between the attempts. The resistance was increased according to the capacity of the volunteer to perform more than one successful repetition maximum with the proper technique. The test was completed when participants were unable to perform more than 10 repetitions using proper technique (15). All trials were performed with participants using the full range of motion. Subsequently, the one-maximum repetition (1RM) was calculated based on the following formula:

a) 1RM= (10RM/ (1.0278 -[0.0278 × 10])) (16).

Experimental sessions

Exercise sessions were performed in the mornings (08:00 am–12:00 am) under the supervision of at least two fitness instructors. After a brief warm-up, participants performed the following exercises using an adjustable weight vest and ankle weights (DOMYOS®, Shangai, China) : 1st) squat on the chair (until 90° knee flexion), 2nd) seated unilateral hip flexion, 3rd) seated unilateral knee extension, and 4th) bilateral calf raise. The total volume (sets x repetitions x load= ~ 172032000 sets * reps* kg) was equalized among the exercise sessions. However, LSRE and HSRE were designed according to the peculiarities of each type of resistance exercise (17). During LSRE, participants performed 4 sets of 8-10 repetitions at 70%-75% of 1RM. The concentric and eccentric phases should be carried out for 2-s. For HSRE, exercises were performed 8 times (sets) with 3-5 repetitions at 70%-75% of 1RM. The concentric phase was performed as fast as possible and the eccentric phase was carried out for 2-s. Bilateral calf raise was performed with the load of unilateral knee extension. A researcher was responsible for monitoring and ensuring that the velocity of muscle

contraction was according to the protocol. Particularly, verbal encouragement was provided in the HSRE. During CS, participants remained seated in a comfortable chair for approximately 30 min.

Cognitive function

All cognitive tests were performed before (rest), immediately after (IA), 1h and 24h after the end of the exercise session face-to-face in a private silent room by a trained researcher, and a familiarization trial was provided before testing.

Rey's Auditory Verbal Learning Test (RALVT)

RALVT is a neuropsychological tool widely for testing episodic memory (18–21) and its scores have been strongly associated with the atrophy of medial temporal lobe structures (e.g., hippocampus) responsible for memory formation and maintenance after learning (20). In addition, RALVT is useful to distinguish patients with and without dementia (18) and normative data according to gender and age have been provided to young, middle-aged and older adults (21,22) and patients with stroke, epilepsy, and neoplasm (19). The test consists in read aloud two lists (A and B) of 15 substantives each (with a 1-s interval between each word). At the beginning of the test, the list A was read five consecutive times by a researcher. Then, participants were requested to recall as many words was possible after each trial (A1-A5). The list B, interference list, with new 15 substantives was read after A5 and words were retrieved (B1). Finally, participants were asked to recall the words from list A immediately after the interference list (A6, immediate recall) and after a delay of 20 minutes (A7, delayed recall), without listen the list A again (22). Eight different lists (4 lists A and 4 lists B) were provided in each session to avoid learning effects. Seven summary scores were used to the assess episodic memory, delayed memory, verbal learning, susceptibility to interference (22):

a) Verbal learning (VL) score= ΣA1-A5 – (5 * A1);
b) VL curve= A1, A2, A3, A4, A5;
c) Forgetting speed (FS)= A7-A6;

d) Immediate recall (IR)= The sum of correct words retrieved in A6;

e) Delayed recall (DR)= The sum of correct words retrivied in A7.

Stroop test

A computerized version of the Stroop test (TESTINPACS^{TM}) was used to provide reaction time (ms) and the number of correct words in each stimulus (control, congruent, incongruent) (23,24). To the test, participants remained seated in front of a 17-inch color monitor. The distance between the participant and the monitor was chosen according to participants' vision needs. Stroop was divided into three phases. In the first phase, control stimulus, the monitor exhibited a rectangle painted in green, yellow, blue, or red. Two possible responses, corresponding or not to the color of the rectangle, were exhibited at the lower corners of the monitor, and participants were requested to tell the color corresponding to the rectangle. The second phase was called congruent stimulus and consisted in stimulus (i.e., name of a color) and responses (i.e., name of two colors, one corresponding to the first color and the other not) exhibited as words in white. The correct answer was telling which colors match. The third phase, incongruent stimulus, is called Stroop effect and consisted of four colors exhibited is an incompatible color. The participants were requested to tell the color corresponding to the letters and inhibit the response for the identity of the disclosed word. A total of 36 stimuli (12 attempts each phase) were randomly provided and the time was registered in milliseconds. After the participants' response, a researcher was responsible to immediately press the corresponding key (← or →). This protocol was established after a pilot study in which we observed that participants of the present study took too long or were not able to return the hand to the initial position, if they had to take it off, even if the keyboard was composed only by two keys.

Statistical analysis

Normality of data was tested using the Kormonov-Smirnov test. Intragroup and intergroup comparisons in the different periods for RALVT and Stroop variables were performed using two-way analysis of variance (ANOVA) followed by Dunnett's

post-hoc test. The level of significance was 5% ($P < 0.05$) and all procedures were performed using Graphpad PRISM software (CA, USA).

RESULTS

Eighteen subjects were recruited for the present study and fifteen accepted to be evaluated for inclusion criteria. Of these, four had dementia according to MMSE scores and one left the study after the 10RM test, leaving a total ten older women. The main characteristics of the studied sample are shown in Table 1. Participants completed all experimental sessions.

Table 1. Main characteristics of study participants

Variables	n= 10
Age, years	86.2 ± 10.2
BMI, kg/m²	23.5 ± 1.3
Period of institutionalization, years	1.0 ± 0.0
MMSE, points	16.4 ± 4.4
Comorbidities (%)	
Hypertension	80
Osteoarthritis	60
Stroke	20
Diabetes	20

Data are presented as mean ± SD and %. BMI= Body mass index; MMSE= Mini mental state examination.

The acute effects of resistance exercise on RAVLT are shown in Figures 1 and 2. The point-by-point analysis indicated that VL increased linearly from A1 to A5 IA the HSRE session (Figure 1; $F=12.12$; $P<0.001$). A significantly higher A5 was observed at rest ($P=0.01$), IA ($P=0.001$), and 1h after exercise ($P=0.001$) in LSRE. However, A4 was only improved 1h after the LSRE (Figure 1, $P<0.001$). Figure 2a shows the overall VL scores. Increased VL scores were observed IA both HSRE ($P=0.001$) and LSRE ($P=0.01$) than in CS, but only LSRE ($P=0.01$) remained significant

higher at 1h. At 24h, VL was significantly higher in CS in comparison to rest (P=0.001) and HSRE (P=0.01). No changes were observed in FS, IR, and DR in response to any session and no other differences were observed between-group.

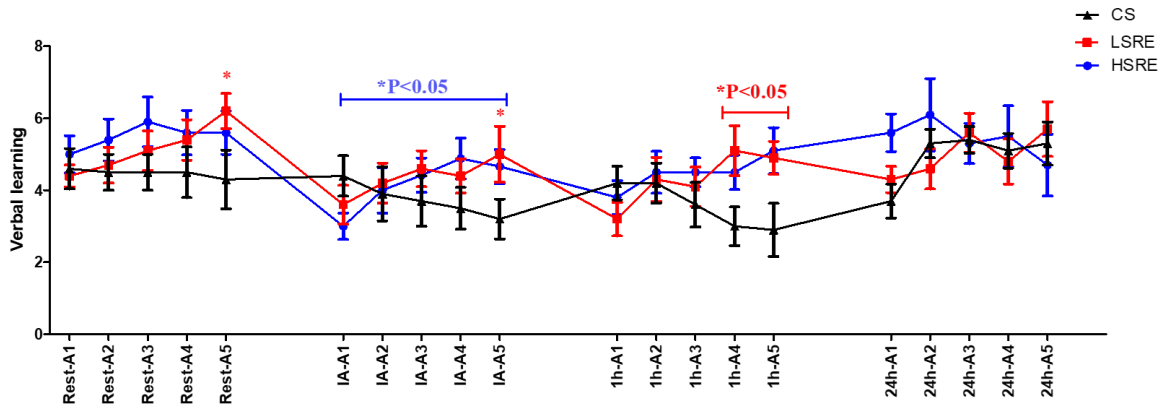

Figure 1. Point-by-point RALVT analysis. CS= Control session, LSRE= Low-speed resistance exercise; HSRE= High-speed resistance exercise. *P<0.05 vs A1.

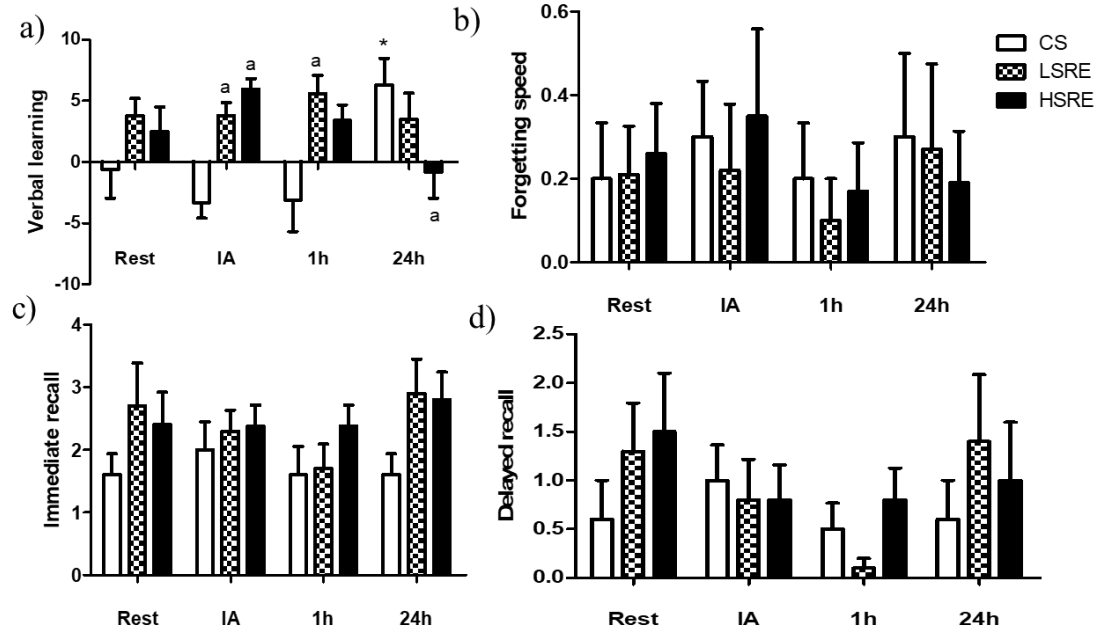

Figure 2. RALVT score. CS= Control session, LSRE= Low-speed resistance exercise; HSRE= High-speed resistance exercise; IA= Immediately after. *P<0.05 vs A1; aP<0.05 vs CS; bP<0.05 vs LSRE.

The acute effects of resistance exercise on STROOP performance are shown in Figures 3 and 4. No significant effects of strength and power exercises were

observed on the number of correct answers (Figure 3b and 3c), while it was significantly reduced at 1h during the incongruent stimulus in CS (Figure 3a). No changes were observed in reaction time (Figure 4) and no other differences were observed between-group.

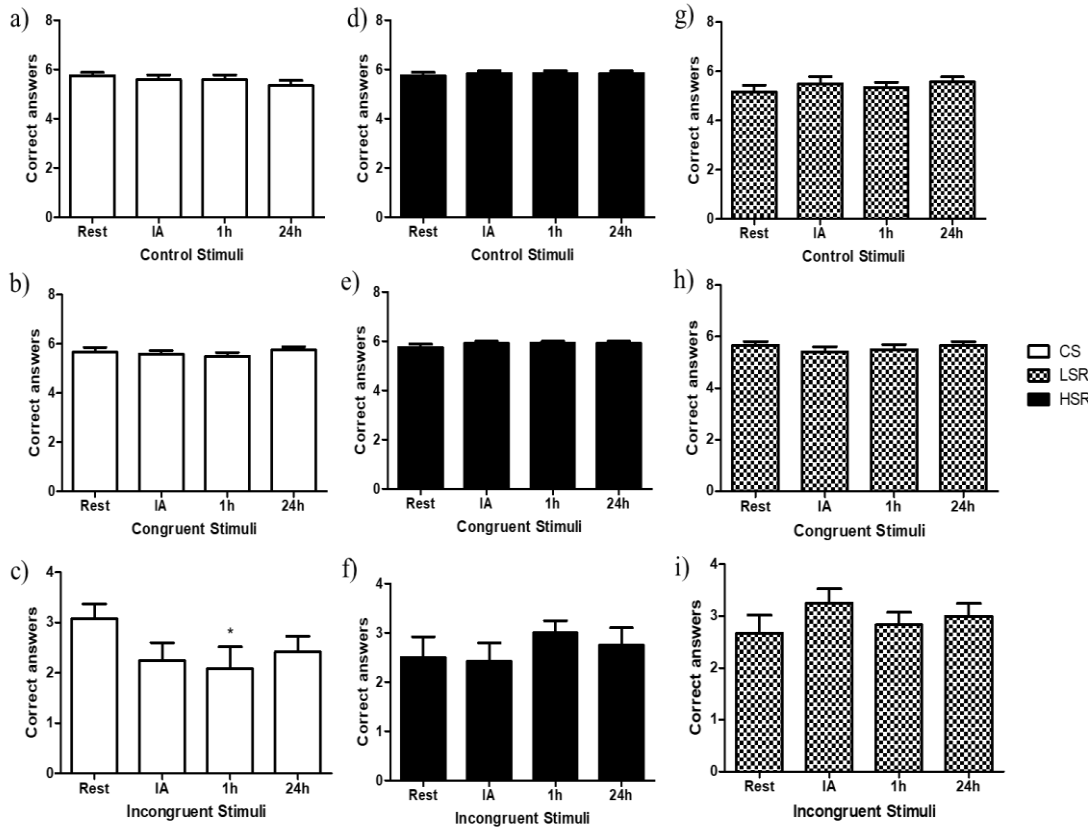

Figure 3. Correct answers on Stroop test. CS= Control session, LSRE= Low-speed resistance xercise; HSRE= High-speed resistance exercise; IA= Immediately after. *P<0.05 vs A1; aP<0.05 vs CS; bP<0.05 vs LSRE.

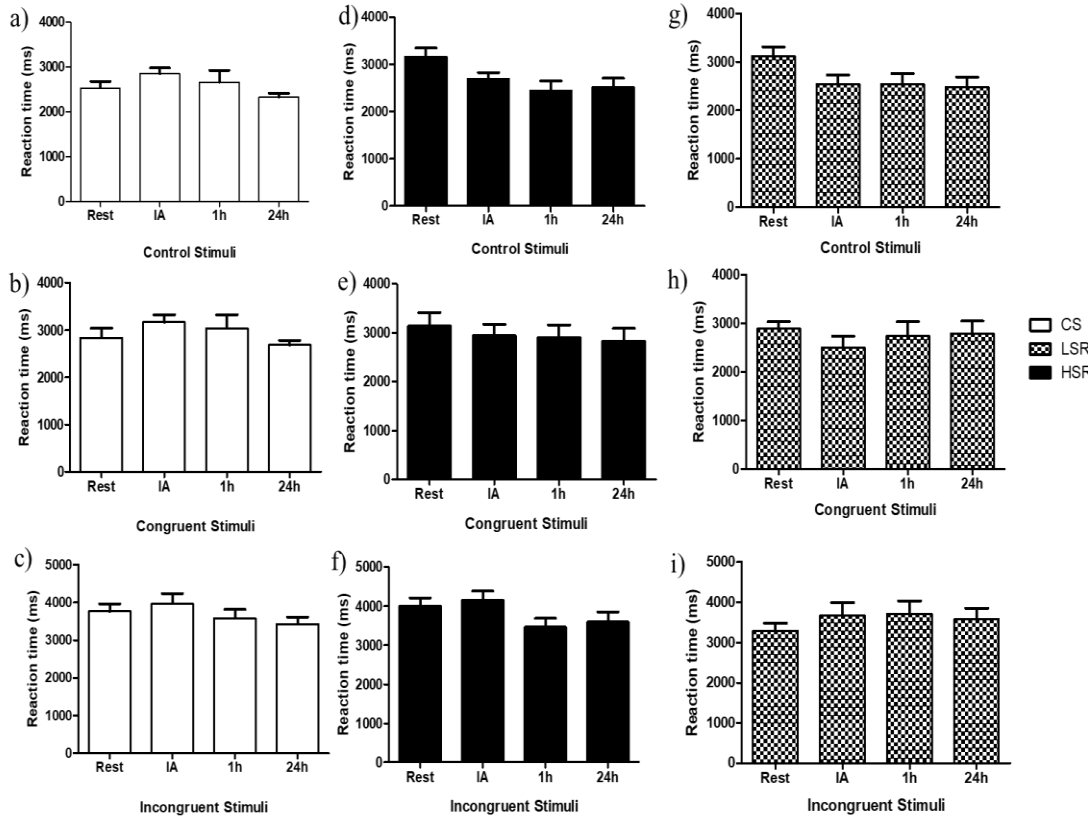

Figure 4. Reaction time on Stroop test. CS= Control session, LSRE= Low-speed resistance exercise; HSRE= High-speed resistance exercise; IA= Immediately after.

DISCUSSION

The main findings of the present study indicate that both power and strength exercises acutely increased VL, an indicative of verbal immediate memory, in frail older women. However, a different pattern was observed among the groups, given that VL remained improved during 1h after the LSRE, while it was only increased IA the HSRE. No acute effects of exercise were observed on STROOP performance. Nevertheless, the number of correct answers was significantly reduced in the CS during the incongruent stimulus.

There is still a lack of evidence on the acute effects of resistance exercise on the individual's capacity to store and subsequent retrieve information, and the few available studies are restricted to working memory (5–8). In older adults, Hsieh et al. (5) found improved working memory 10 min following a session of LSRE in non-

demented older men. Similarly, Naderi et al. (6) observed improved working memory in older women and men who performed LSRE at 40% 1RM and 70% 1RM.

In this context, our results provide a prima facie case for the differential effects of LSRE and HSRE on verbal memory in frail older women. Notably, LSRE elicited longer learning improvements in comparison to HSRE, although results seem to be greater IA HSRE than in LSRE. Taken together, these findings add to the existing literature indicating that the velocity of muscle contraction influences cognitive function in response to resistance exercise.

Although is beyond the scope of this study to explain the possible bio-physiological mechanisms underlying the improved verbal memory performance found following an acute bout of LSRE and HSRE, the contraction time could be a plausible explanation for our findings, given that the duration of muscle contractions during each set was about ~40 s in LSRE and ~ 12.5 s in HSRE, which might have caused different neuroendocrine responses (25).

Insulin-like growth factor-1 (IGF-1), for example, is acutely increased in response to LSRE in older adults (26) and systemic IGF-1 levels are significantly associated with verbal memory and hippocampal perfusion and volume (27). In addition, acute improvements in IGF-1 levels in brain areas strongly associated with memory formation (e.g., hippocampus, cortex) (28) and seem to be critically involved in exercise-induced improvements in neuronal activation and cell proliferation (28,29).

On the other hand, endocrine responses to HSRE are commonly lower in comparison to LSRE (25), which might indicate that other mechanisms may be associated with acute HSRE-induced transitory cognitive gains. Nitric oxide (NO) may be a possible candidate for improved verbal memory after HSRE, given that NO was improved after acute HSRE in older women (30) and infusion of NO precursor, L-arginine, improved learning and memory, as well as increased the length of cortical capillaries in rats (31,32), while NO inhibition by L-NAME inhibited cognitive improvements (31,32).

Nevertheless, these speculations cover only some of the myriad of mechanisms that can be responsible for the acute effects of resistance exercise on cognition and future studies are required to better explore this issue.

Notably, VL performance was significantly reduced 24 after HSRE session and significant increased after CS. Audiffrenn (33) proposed an inverted-U shaped curve to explain the relationship between exercise intensity and cognitive improvements in response to an acute session of exercise, so that low- and high-intensity exercise sessions are expected to induce low transitory cognitive improvements, while greater changes may be observed after moderate-intensity exercise.

One possible reason why this phenomenon was not observed in the current study may be that frail participants have high baseline cortisol levels (34). Although HSRE was performed at moderate-to-high intensity, frail patients may have reduced resiliency to physical stress, causing exaggerated hypercortisolemia during recovery and causing transient reduction in memory performance (35).

The effects of resistance exercise on Stroop performance remain equivocal. In accordance with the present study, Alves et al. (36), Dunsky et al. (37) and Tsai et al. (26) did not observe improvements in Stroop performance post-LSRE in middle-aged and older adults with mild-cognitive impairment. On the hand, Johnson et al. (38) found increased performance on the incongruent stimulus up to 1h post-resistance exercise. These findings are supported by a recent systematic review and meta-analysis that a unique session of LSRE may induce moderate improvements on inhibitory control (8).

These abovementioned findings are hard to reconcile, but a possible explanation for these divergent results may be fact that Johnson et al. (38) used a circuit-based resistance exercise, which has a significant aerobic component (39). In addition, differences on age and healthy status may also collaborated with the findings of the present study since healthy adults were investigated by Johnson et al (38) and Wilke et al. (8), while frail older women took part of the present study.

There are some limitations to mention in addition to the lack of mechanisms. First, our findings are limited to frail older adults and should be carefully extrapolated to non-institutionalized robust older adults. Second, our sample size was only composed by women. Third, reaction time was based on the researcher's velocity response to participants stimulus.

CONCLUSION

Our findings indicate that both power and strength exercises acutely increased VL, an indicative of verbal immediate memory, in frail older women. However, a different pattern was observed among the groups, given that VL remained improved during 1h after the LSRE, while it was only increased IA the HSRE. No acute effects of exercise were observed on STROOP performance. Nevertheless, the number of correct answers was significantly reduced in the CS during the incongruent stimulus.

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ARTICLE 15

Acute Effects of Low- and High-Speed Resistance Exercise on Hemodynamic Parameters of Institutionalized Frail Older Adults

Abstract

Aim: The present study aimed to investigate the acute effects of low-speed resistance exercise (LSRE) and high-speed resistance exercise (HSRE) on the hemodynamic parameters of frail older adults. **Material and methods:** This was a randomized crossover study. Sixteen institutionalized frail older adults (81.0 ± 9.2 years, 23.2 ± 2.1 kg/m²) randomly performed LSRE, HSRE, and a control session (CS). Blood pressure was recorded before, over 1 h, and 24 h after the end of the experimental session. Exercise sessions were performed using 4 exercises for lower limbs. Particularly, LSRE was composed of 4 sets of 8-10 repetitions at 70%-75% of 1-repetition maximum (1RM). The concentric and eccentric phases were carried out for 2-s. For HSRE, exercises were performed 8 times (sets) with 3-5 repetitions at 70%-75% of 1RM. The concentric phase was performed as fast as possible and the eccentric phase was carried out for 2-s. **Results**: Both LSRE and HSRE caused post-exercise hypotension. Notably, a longer reduction was observed in LSRE (over 1 hour) in comparison to HSRE (~20 min) and an exclusive reduction in mean arterial pressure were observed after LSRE. **Conclusion:** Our findings suggest that resistance exercise caused post-exercise hypotension, regardless of the velocity of concentric muscle contraction. However, a longer reduction in systolic blood pressure and an exclusive decrease in mean arterial pressure were observed after LSRE.

Key words: Power training, Resistance training, Blood pressure, Hypertension, Elderly

Introduction

Frailty is a highly prevalent condition among older adults and is defined as a potentially reversible state of increased vulnerability to negative health-related outcomes [1]. Although the progression of frailty is commonly associated with physical and cognitive deterioration [2,3], cardiovascular diseases are highly prevalent among this population [4] and frequently lead to hospitalization due to inappropriate care [5].

In this sense, a recent report of the European Society of Hypertension-European Union Geriatric Medicine Society (ESHEUGMS) Working Group proposed that special attention should be given in the antihypertensive treatment of frail older [6]. However, no guidelines or algorithms for the management of cardiovascular diseases in frail are available [4].

Notably, many evidence [7–11] has supported the importance of exercise training as a non-pharmacological therapy to reduce blood pressure in older adults with different diagnosis, consequently reducing the cardiovascular risk in this population [12].

However, the benefits of physical exercise on blood pressure are not exclusively found after training programs since an unique session of exercise may induce post-exercise hypotension (PEH), a phenomenon characterized by reduced blood pressure values to levels below to those reported either prior to exercise or on a control session [13]. PEH may occur up to 24 hours [14] and collaborates to lower cardiovascular risk during the performance of activities of daily living [15,16], besides predicting responders and non-responders to exercise therapy [17,18].

A substantial body of evidence indicates that PEH may occur in response to different types of exercise, including low-speed resistance exercise (LSRE) [19–22], a type of exercise in which muscles work or hold against an applied force at low to moderate velocity. These observations are clinically important because resistance exercise is a well-stablished therapy to counteract the age-associated neuromuscular and osteoarticular deterioration [23]. Nevertheless, researchers [24,25] have argued that high-speed resistance exercise (HSRE), a type of resistance exercise in which muscle contractions are performed as fast as possible, should be included in resistance training

programs for older adults that aim to improve physical function, given that some aspects of the neuromuscular function seem to be more dependent of high-speed muscle actions than on those performed with low speed [26,27]. However, the effects of HSRE on hemodynamic parameters of older adults have been poorly explored.

Indeed, just a few studies have investigated the effects of HSRE on blood pressure. Though, existing studies were based on healthy older women [28,29], blood pressure measured only immediately after the session of exercise [30], and not equalized exercise protocols [28].

Therefore, the present study aimed at investigating the acute effects of LSRE and HSRE on hemodynamic parameters of institutionalized frail older adults. Our hypothesis is that HRSE may elicit longer and greater PEH than LSRE.

Material and methods

This is a randomized crossover study that investigated the acute effects of two different types of resistance exercise on hemodynamic parameters of frail older adults. The protocol was approved by the Research Ethics Committee of the University of Campinas (UNICAMP, Campinas, Brazil). All study procedures were conducted in compliance with the Declaration of Helsinki and the Resolution 196/96 of the National Health Council.

Institutionalized older adults (aged 72 to 99 years) were recruited from a public nursing home located in eastern region of São Paulo State, in southern Brazil. Individuals were eligible if they: a) aged 60 years or over; b) were frail according to Fried's criteria [31]; c) possessed sufficient physical and cognitive abilities to perform all exercises required by the protocol; and d) had a physician authorization to participate. Exclusion criteria included having participated in a structured physical exercise training program in the past six months, prescription of hormone replacement therapy and/or psychotropic drugs, and any unstable cardiovascular event (e.g., myocardial infarction) or complication in the past 6 months.

Enrollers were randomized by an independent researcher using a computer-generated list of random numbers into low-speed resistance exercise (LSRE), high-speed resistance exercise (HSRE), and control session (CS).

The experimental design of the current study is shown in Figure 1. All experiments were performed in the rehabilitation unit of the nursing home. Food consumption was maintained constant during the previous 48 h and enrollers consumed a standard breakfast 60–90 min before the being of the experimental sessions. Experimental sessions were separated by one week.

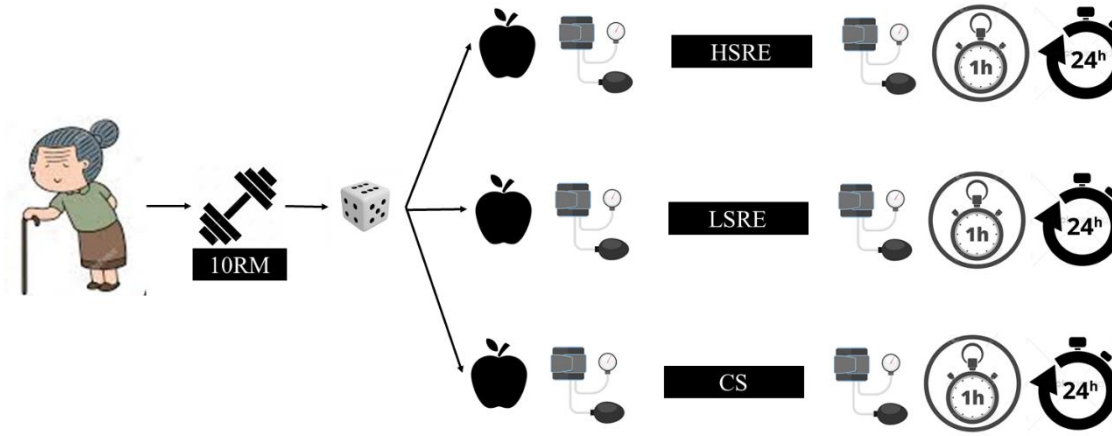

Figure 1. Experimental design of the present study. 10RM= 10-repetition maximum test; CS= Control session; HSRE= High-speed resistance exercise; LSRE= Low-speed resistance exercise.

Ten repetition maximum test (10RM)

Participants were familiarized with resistance exercises used in the present study prior to the 10-repetition maximum test (10RM). 10RM tests was performed in following three exercises: squat on the chair (until 90° knee flexion), seated unilateral hip flexion, and seated unilateral knee extension. Before the tests, individuals performed a brief specific warm-up using light loads. Afterward, the 10RM load was determined up to 5 attempts, with a 3-minute interval between the attempts. The resistance was increased according to the capacity of the volunteer to perform more than one successful repetition maximum with the proper technique. The test was completed when participants were unable to perform more than 10 repetitions using

proper technique [32]. All trials were performed with participants using the full range of motion. Subsequently, the one- repetition maximum (1RM) was calculated based on the following formula:

a) 1RM= (10RM/ (1.0278 -[0.0278 × 10])) [33].

Experimental sessions

Exercise sessions were performed in the mornings (08:00 am–12:00 am) under the supervision of at least two fitness instructors. After a brief warm-up, participants performed the following exercises using an adjustable weight vest and ankle weights (DOMYOS®, Shangai, China) : 1st) squat on the chair (until 90° knee flexion), 2nd) seated unilateral hip flexion, 3rd) seated unilateral knee extension, and 4th) bilateral calf raise. The total volume (sets x repetitions x load= ~ 172032000 sets * reps* kg) was equalized among the exercise sessions. However, LSRE and HSRE were designed according to the peculiarities of each type of resistance exercise [23]. During LSRE, participants performed 4 sets of 8-10 repetitions at 70%-75% of 1RM. The concentric and eccentric phases should be carried out for 2-s. For HSRE, exercises were performed 8 times (sets) with 3-5 repetitions at 70%-75% of 1RM. The concentric phase was performed as fast as possible and the eccentric phase was carried out for 2-s. Bilateral calf raise was performed with the load of unilateral knee extension. A researcher was responsible for monitoring and ensuring that the velocity of muscle contraction was according to the protocol. Particularly, verbal encouragement was provided in the HSRE. During CS, participants remained seated in a comfortable chair for approximately 30 min.

Hemodynamic parameters

Hemodynamic parameters were measured accordingly to the VII Joint National Committee of High Blood Pressure (JNC7) [34]. The baseline blood pressure of each session was based on the mean values measured in three consecutive visits. Participants remained seated in a comfortable chair in a room with artificial light for baseline and post-exercise blood pressure measurements. The hemodynamic parameters

were blindly measured in the left arm using an automated oscilometric equipment (BP 3BT0A, Microlife AG, Widnau, Switzerland) [35] and were recorded immediately after (IA) (0 minute), and 10, 20, 30, 50, and 60 minutes, as well as 24 h after the exercise completion. At the end of each measurement, the equipment provided systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR). Mean arterial pressure (MAP) was determined based on the formula:
b) (SBP + [2*DBP])/3).

Statistical analysis

Normality of data was tested using the *Kormonov-Smirnov* test. Intragroup and intergroup comparisons in the different periods (i.e., baseline, 10', 20', 30', 50', 60' and 24h after the end of each session) for SBP, DBP, HR, and MAP were performed using two-way analysis of variance (ANOVA) followed by Dunnett's post-hoc test. The level of significance was 5% ($P < 0.05$) and all procedures were performed using Graphpad PRISM software (CA, USA).

Results

Twenty-two subjects were recruited for the present study and twenty accepted to be evaluated for inclusion criteria. Of these, two had a clinical diagnosis of psychiatric diseases and two left the study after the 10RM test, leaving a total sixteen older adults. The main characteristics of the studied sample are shown in Table 1. Participants completed all experimental sessions.

Table 1. Main characteristics of study participants.

Variables	n= 16
Age, years	81.0 ± 9.2
BMI, kg/m²	23.2 ± 2.1
Male, %	37.5
Period of institutionalization, years	2.2 ± 3.4
Hemodynamic parameters	
SBP, mmHg	128.8 ± 19.8
DBP, mmHg	77.4 ± 12.2
MAP, mmHg	77.4 ± 12.2
HP, bpm	76.8 ± 12.1
Comorbidities (%)	
Hypertension	87.5
Osteoarthritis	37.5
Stroke	37.5
Diabetes	10.0
Low-back pain	6.25
Parkinson's disease	6.25
Drug class (%)	
ACE inhibitor	75.0
Diuretic	31.2
ANG II receptor antagonista	25.0
Proton-pump inhibitor	31.2
Antihyperglycemic	12.5
Alpha and beta-blockers	6.2
Nonsteroidal anti-inflammatory drug	6.2

Data are presented in mean ± SD and %. BMI= Body mass index; SBP= Systolic blood pressure; DBP= Diastolic blood pressure;MAP= Mean arterial pressure; HR= Heart rate; ACE= Angiotensin converting enzyme; ANG= Angiotensin

Hemodynamic parameters are shown on Figure 2 and Table 2. Both LSRE and HSRE caused systolic PEH (Figure 2a). However, different patters were observed among the sessions. SBP was significantly reduced at 30 and 50 min after HSRE and over the entire period after LSRE. Lower SBP were found at 10, 30, and 50 min in HSRE and at 20 in LSRE when compared to CS. MAP was only significantly reduced after LSRE at 10, 20, and 30 min (Figure 2d). In addition, lower MAP at 20 min was observed in LSRE in comparison to CS. No significant changes were observed in DBP and HR for any session and no differences were observed between the exercise groups (Figure 2b and 2d).

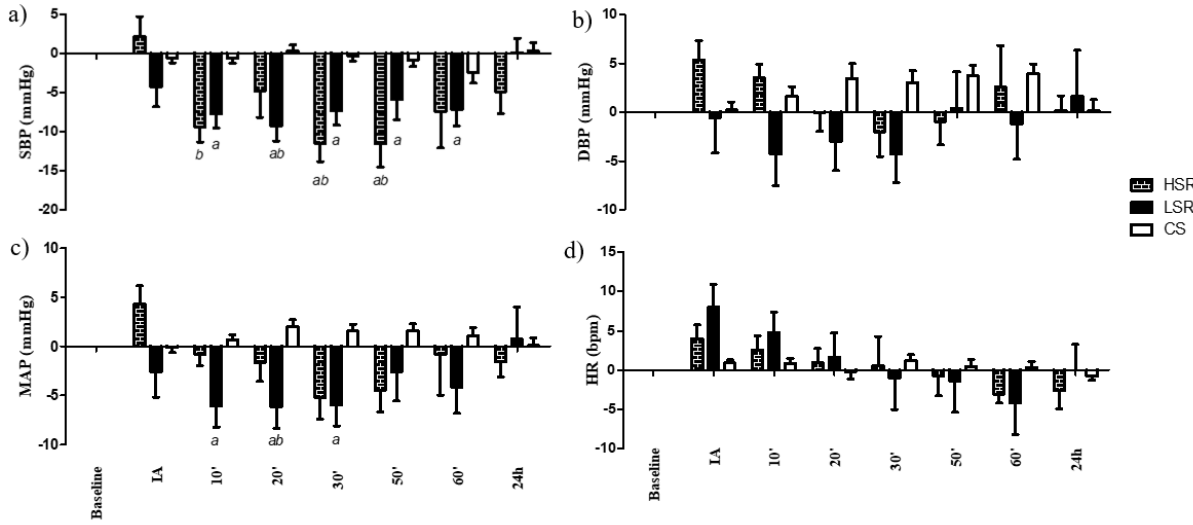

Figure 2. Hemodynamic parameters in experimental sessions. CS= Control session; DBP= Diastolic blood pressure; HR= Heart rate; HSRE= High-speed resistance exercise; LSRE= Low-speed resistance exercise; MAP= Mean arterial pressure; SBP= Systolic blood pressure.

Table 2. Hemodynamic parameters on experimental sessions.

Variable		CS	LSRE	HSRE
SBP	Baseline	124.4 ± 17.8	126.3 ± 19.1	126.1 ± 17.9
	IA	123.6 ± 17.7 (-0.5, -0.7)	120.8 ± 21.8 (-4.2, -5.5)a	128.3 ± 21.5 (1.5, 2.1)
	10'	123.6 ± 17.8 (-0.5, -0.7)	116.3 ± 17.6 (-7.6, -10.0)a	116.8 ± 17.8 (-7.3, -9.3)b

	20'	124.8 ± 17.7 (0.3, 0.3)	113.7 ± 12.5 (-9.2, -12.6)ab	121.4 ± 17.6 (-3.2, -4.7)
	30'	123.9 ± 16.7 (-0.2, -0.5)	116.1 ± 13.3 (-7.3, -10.1)a	114.6 ± 16.4 (-8.8, -11.5)ab
	50'	123.3 ± 17.2 (-0.8, -1.1)	117.7 ± 13.7 (-5.8, -8.6)a	114.6 ± 16.4 (-8.5, -11.5)ab
	60'	121.9 ± 20.7 (-2.3, -2.5)	116.4 ± 15.0 (-7.1, -9.8)a	118.8 ± 12.8 (-4.3, -7.3)
	24h	124.9 ± 19.0 (0.3, 0.5)	125.4 ± 13.0 (0.1, -0.9)	121.3 ± 14.2 (-3.3, -4.8)
	Baseline	78.1 ± 20.8	77.7 ± 18.7	74.7 ± 11.1
	IA	78.2 ± 20.7 (0.2, 0.1)	75.5 ± 11.9 (-0.5, -2.1)	80.1 ± 11.8 (7.7, 5.3)
	10'	79.7 ± 22.9 (1.6, 1.6)	72.5 ± 9.8 (-4.2, -5.1)	78.2 ± 10.1 (5.2, 3.5)
	20'	81.1 ± 23.4 (3.4, 3.0)	73.6 ± 9.8 (-3.0, -4.1)	74.6 ± 9.4 (0.6, -0.0)
DBP	30'	80.7 ± 23.1 (3.0, 2.6)	72.6 ± 9.6 (-4.2, -5.1)	72.7 ± 8.7 (-1.5, 2.0)
	50'	81.2 ± 22.8 (3.7, 3.1)	76.1 ± 12.7 (0.3, -1.6)	73.8 ± 11.2 (-0.5, -0.9)
	60'	81.5 ± 23.2 (3.9, 3.3)	74.6 ± 8.9 (-1.1, -3.1)	77.3 ± 15.6 (4.9, 2.5)
	24h	78.3 ± 21.6 (0.1, 0.2)	76.7 ± 11.5 (1.6, 3.0)	74.8 ± 12.7 (0.1, 0.1)
	Baseline	93.5 ± 17.4	93.9 ± 17.7	91.8 ± 12.5
	IA	93.3 ± 17.1 (-0.1, -0.1)	90.6 ± 14.0 (-2.5, -3.3)	96.1 ± 14.1 (4.7, 4.2)
	10'	94.3 ± 19.1 (0.6, 0.8)	87.1 ± 10.6 (-6.0, -6.8)a	91.0 ± 11.5 (-0.6, -0.7)
	20'	95.6 ± 19.6 (2.0, 2.1)	86.9 ± 9.9 (-6.1, -6.9)ab	90.2 ± 10.8 (-1.2, -1.6)
MAP	30'	95.1 ± 18.9 (1.5, 1.5)	87.1 ± 10.2 (-5.9, -6.8)a	86.7 ± 9.5 (-4.9, -5.1)
	50'	95.2 ± 19.2 (1.6, 1.7)	89.9 ± 11.1 (-2.5, -3.9)	87.4 ± 10.5 (-4.2, -4.4)
	60'	94.9 ± 20.4 (1.0, 1.4)	88.5 ± 9.6 (-4.1, -5.3)	91.1 ± 13.3 (0.7, -0.7)
	24h	93.8 ± 19.2 (0.0, 0.3)	92.9 ± 10.4 (0.7, -0.9)	90.3 ± 11.7 (-1.4, -1.5)
	Baseline	77.5 ± 13.6	73.6 ± 13.3	75.2 ± 12.7
	IA	78.1 ± 13.1 (0.9, 0.6)	79.5 ± 16.9 (7.9, 5.8)	79.2 ± 12.1 (5.9, 4.0)
	10'	78.2 ± 14.3 (0.8, 0.7)	77.0 ± 14.9 (4.7, 3.3)	77.8 ± 12.3 (3.9, 2.5)
	20'	77.5 ± 14.5 (-0.1, 0.0)	74.9 ± 16.5 (1.6, 1.2)	76.1 ± 11.5 (1.8, 0.9)
HR	30'	78.5 ± 14.2 (1.1, 1.0)	72.2 ± 14.8 (-0.9, -1.4)	75.8 ± 14.1 (2.4, 0.5)
	50'	77.8 ± 13.5 (0.4, 0.3)	72.0 ± 14.8 (-1.3, -1.6)	74.5 ± 15.2 (-0.7, -0.6)
	60'	77.8 ± 14.3 (0.3, 0.3)	69.9 ± 13.9 (-4.1, -3.7)	72.1 ± 10.9 (-3.7, 3.0)
	24h	77.0 ± 14.3 (-0.7, -0.5)	72.9 ± 12.9 (0.0, -0.7)	72.6 ± 10.8 (-2.5, -2.6)

CS= Contral session; DBP= Diastolic blood pressure; HR= Heart rate; HSRE= High-speed resistance exercise; IA- Imediatelly after; LSRE= Low-speed resistance exercise; MAP= Mean arterial pressure; SBP= Systolic blood pressure. aP<0.05 vs Baseline; bP<0.05 vs CS.

DISCUSSION

The main findings of the preset study indicate that SBP is acutely reduced after LSRE and HSRE in frail older adults. However, LSRE caused longer PEH in comparison to HSRE, given that SBP was significantly reduced over the whole period after LSRE and only for approximately 20 min after HSRE. In addition, exclusive MAP reductions were observed after HSRE.

Our findings are in line with prior investigations, which observed PEH after LSRE [19–22] and HSRE [28,30] in older adults with different conditions. However, for the best of our knowledge, this is the first study investigating the acute effects of two different types of resistance exercise on hemodynamic parameters of frail institutionalized older adults.

In the last years, an increasing coupling body of evidence has investigated the acute effects of HSRE on blood pressure in older adults. Our group [28] found significant PEH after an acute session of HSRE in community-dwelling older adults, while no significant changes were observed after LSRE. On the other hand, Orsano et al. [29] did not observe significant effects of HSRE on blood pressure of community-dwelling older women. Subsequently, Machado et al. [30]. reported lower SBP and DBP values after HSRE in older adults with type II diabetes mellitus. These controversial findings among trials may be at least partially attributed to differences in the exercise design (e.g., number of exercises), blood pressure measurement (e.g., only IA or for 1 h after the exercise session), and sample characteristics (e.g., hypertensive, frail, and older adults with type II diabetes mellitus).

Contrarious to our initial hypothesis, LSRE elicited longer and greater PEH in comparison to HSRE. The time under tension could be a plausible explanation for our findings, given that the duration of muscle contractions in each set was about ~40 s during LSRE and ~ 12.5 s during HSRE. These premises are contrarious to the observation that interval and continuous trainings elicited similar blood pressure

responses [36] and may indicate that the time under tension is an important variable in the light of resistance exercise inducing PEH. In addition, we [28] previously observed a longer and greater PEH after HSRE performed at moderate intensity (3 on Borg scale adapted by Foster et al. [37]), which represents approximately 50% of 1RM. Thus, it is possible that HSRE protocols performed at low-to-moderate loads may elicit better acute cardiovascular benefits in comparison to HSRE at moderate-to-high loads. This hypothesis is supported by Figueredo et al. [20], who observed a longer PEH after resistance exercise performed at 70%1RM when compared to 80%1RM. Nevertheless, more studies are needed to confirm our inferences.

The possible mechanisms underlying the effects of RT on blood pressure were not investigated in the present study which limits possible inferences. However, prior investigations observed transiently improvements in nitric oxide (NO) [28], bradykinin [19], and autonomic modulation [38] in response to an acute session of resistance exercise.

There are some limitations to mention in addition to the lack of mechanisms. First, our findings are limited to frail older adults and should be carefully extrapolated to non-institutionalized robust older adults. Second, our sample size was prevalently composed by women. Third, the lack of ambulatory blood pressure monitoring may cover possible effects of LSRE and HSRE, given that researchers [39] found reduced night-time, but not daytime ambulatory blood pressure after an acute session of resistance exercise.

Conclusion

Our findings suggest that resistance exercise caused PEH, regardless of the velocity of concentric muscle contraction. However, a longer reduction in SBP and an exclusive decrease in MAP were observed after LSRE.

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ARTICLE 16

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Age- and Gender-Related Changes in Physical Function in Community-Dwelling Brazilian Adults Aged 50 to 102 Years

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ABSTRACT

Background and Purpose: Cutoff points for physical function tests are commonly used in clinical practice for the evaluation, monitoring, and treatment of older adults. Previous studies have shown that, while age-related patterns of muscle strength change are similar between ethnic groups, strength values differ signifi cantly independent of age. Whether the same applies to other physical function tests is presently unclear. This study investigated age- and gender-related changes of performance on a battery of physical function tests in Brazilian community dwellers. **Methods:** The study followed a cross-sectional design. Participants were community-dwelling adults. Candidates were considered eligible if they were 18 years or older, lived independently, and possessed suffi cient physical and cognitive abilities to perform all of the measurements required by the protocol. Physical function tests included isometric handgrip (IHG), 5 times sit-to-stand (5 × STS) test, Timed Up and Go, 1-leg stance, and walking speed (WS) at usual and fast pace. **Results:** Two-thousand eight-hundred and four people were enrolled. Mean age was 68.0 (7.0) years (range 50-102 years), and 2262 (80.7%) were women. Men displayed better IHG and balance, while women showed higher performance on the 5 × STS and WS tests. A gender-specifi c pattern of decline in physical performance was observed. Specifi cally, women showed a linear age-dependent decline in all tests. In men, only in the IHG, 1-leg stance, and WS test at a fast pace was there a linear decline with age. In both genders, the lowest mean values of physical function tests were higher than the proposed cutoffs for sarcopenia. **Discussion and Conclusions:** Our fi ndings indicate that the performance on different physical function tests decreases with advancing age in Brazilian adults, following a genderspecifi c pattern. In none of the tests did the lowest mean values reach the cutoffs for sarcopenia. This suggests that region-specifi c cutoffs might be necessary to identify older people at risk of adverse events.

Key Words: balance , assessment, mobility , muscle strength, physical performance

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INTRODUCTION

The World Health Organization projections indicate that the absolute and relative number of older adults will increase exponentially in the next decades. [1] This phenomenon demands special attention, since aging is associated with risk of loss of independence and greater use of health care resources. [2] Among the numerous changes that accompany aging, the deterioration of physical function is especially concerning. Indeed, the preservation of physical performance is a core element for maintaining independence and remaining engaged in social activities. [3, 4] Conversely, reduced physical function levels have been associated with a wide range of poor outcomes, such as cognitive impairment, falls, disability, institutionalization, and mortality. [5-10] Several investigations have observed a common agerelated pattern of changes in upper and lower limb muscle strength, [11-13] lower limb muscle power, [11, 12] and mobility [11] among people from Europe and Asia. However, muscle strength values were found to differ signifi cantly across ethnic groups, independent of age. [13] This suggests that region-specifi c muscle strength cutoffs may be needed to estimate the risk of adverse events in different populations. In addition, most studies have focused on the analysis of muscle strength, while other important parameters, such as mobility, have been less explored. As a consequence, it is currently unknown whether the pattern of age-related changes in other physical function tests, such as the 5 times sit-to-stand (5 × STS), the 1-leg stance, and the Timed Up and Go (TUG) tests, differ across ethnic groups.

This information is highly relevant to health care professionals, including physical therapists, given that cutoff values for physical function tests are commonly used for the evaluation, monitoring, and treatment of older adults. [14-16] The lack of a deeper understanding of age- and gender-dependent trajectories of physical function in specifi c populations might impact the interpretation of functional tests and the effects of interventions. Furthermore, popular physical function tests (eg, walking speed [WS] at usual pace over short tracks) may have a ceiling effect in the assessment of healthy older adults. [17, 18] This limitation may be overcome by testing multiple physical domains and through the use of more demanding tests (eg, WS at fast pace, maximal isokinetic handgrip [IHG] strength).

Based on these premises, the present study was undertaken to investigate the patterns of gender- and age-related changes in a comprehensive set of physical function tests in a convenience sample of Brazilian community-dwelling men and women across a wide age range.

METHODS

Design and Participants

This study had a cross-sectional design and was approved by the Research Ethics Committee of the University of Mogi das Cruzes (UMC, São Paulo, Brazil). All study procedures were conducted in compliance with the Declaration of Helsinki and the Resolution 196/96 of the National Health Council. The article was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology criteria. [19]

Participant recruitment took place between January 2015 and January 2018. Participants were recruited in a community senior center located in the metropolitan area of São Paulo, Poá, Brazil. The study was advertised through posters placed in public sites (eg, parks, city hall, public offi ces, bus stops, and train stations) as well as via local radio and newspapers. People were also invited to participate by direct contact. Candidates were considered eligible if they were 18 years or older, lived independently, and possessed suffi cient physical and cognitive abilities to perform all of the measurements required by the protocol.

No other selection criteria were set. Written informed consent was obtained prior to inclusion from each participant for this study.

Functional Assessments

All physical function tests were administered by 2 experienced exercise physiologists. One examiner was responsible for detailing the operational procedures, demonstrating the test before the assessment, quantifying performance, and evaluating motor patterns. The other examiner ensured participant safety by providing occasional verbal and/or tactile cueing, if needed, without interfering with the physical function tests. After the explanation and before each test, participants performed a familiarization trial to ensure they had fully understood each test. Except for the 1-leg stance test, participants performed all tests twice with the best result used for analysis. The tests were administered in a dedicated room within the senior center and were performed in a sequential order with a 1-minute rest between trials, as follows: (1) IHG, [20] (2) 5 × STS, [21] (3) TUG, [22] (4) 1-leg stance, [23] and (5) WS at usual and fast pace. [24]

Isometric Handgrip Strength

IHG strength of the dominant hand was measured using a Jamar handheld hydraulic dynamometer (Sammons Preston, Bolingbrook, Illinois). [20] To determine the dominant hand, participants were asked which of their hands was the strongest. The measure

was obtained while the participant was seated on a chair with the shoulder abducted, the elbow near the trunk and fl exed at 90 ° , and the wrist in a neutral position (thumbs up). The contralateral arm remained relaxed under the thigh. To measure handgrip strength, participants performed a maximal contraction during 4 seconds. The test reliability in the present study was 0.8 or more (κ = 0.97). Results were recorded in kilogram.

Five Times Sit-to-Stand Test

Participants rose from a chair 5 times as quick as possible with their arms folded across their chest. Timing began when participants raised their buttocks off the chair and was stopped when they were seated at the end of the fi fth stand. [21] The test reliability in the present study was 0.8 or more (κ = 0.97).

Timed Up and Go Test

The TUG test involved getting up from a chair (total height: 87 cm; seat height: 45 cm; width: 33 cm), walking 3 m around a cone placed on the fl oor, coming back to the same position, and sitting back on the chair. [22] Participants wore regular footwear, placed their back against the chair, rested their arms on the chair's arms, and put their feet on the ground. A researcher instructed the participant to, on the word "go," get up, walk 3 m as fast as possible without compromising safety, turn, walk 3 m back to the chair, and sit down. Timing began when the participant got up from the chair and was stopped when the participant's back touched the backrest of the chair. The test reliability in the present study was 0.8 or more (κ = 0.93).

One-Leg Stance Test

The 1-leg stance test was performed with the participant standing in a unipodal stance on the dominant lower limb, with the contralateral knee fl exed at 90 ° , arms folded across the chest, and head held straight. [23] Timing began when the participant raised the nondominant foot off the fl oor and was stopped when the foot touched the fl oor again. The maximum performance time was set at 30 seconds. [25]

Walking Speed Tests

WS was measured over 3 m. [24] This distance was chosen because of space limitations. However, high concordance has been observed between the results recorded on 3- and 6-m courses. [26] For the test, participants were required to walk 5 m (including 1-m acceleration and 1-m deceleration) at their usual and fastest possible pace (without running).

Before the evaluation, both feet of each participant were to remain on the starting line. Timing began when a foot reached the 1-m line and was stopped when a foot reached the 4-m line. The 1-m intervals at the beginning and at the end of the course were used to avoid early acceleration and/or deceleration. The test reliability in the present study was 0.8 re more ($\kappa = 0.98$).

Anthropometric Measurements

An analog weight scale with a Filizola (Brazil) stadiometer was used to measure body mass and height. The body mass index (BMI) was calculated as the ratio between body mass (kg) and the square of height (m^2).

Disease Conditions

Information pertaining to disease conditions was collected by 2 researchers (H.J.C.-J. and I.O.G.) through self-report and careful review of medical charts of the community senior center. Medical charts, which are updated every 6 months by a local physician, were reviewed to determine the prevalence of disease conditions that may impact physical performance (eg, osteoarthritis).

Statistical Analysis

Normality of data was ascertained using the KolmogorovSmirnov test. [27] Data are presented as mean (standard deviation) or absolute numbers (percentages) for continuous and categorical variables, respectively. Differences in continuous variables among groups were assessed via 1-way analysis of variance. When appropriate, Bonferroni post hoc analyses were performed to determine whether there were signifi cant differences between groups. Posttests were performed to investigate whether or not there was a linear trend of decline in physical function in relation to age. Comparisons of categorical variables were performed by χ^2 statistics. Pearson correlations were used to explore the relationships between physical function tests and age. For all tests, the level of signifi cance was set at 5% ($P < .05$). All analyses were conducted using the IBM SPSS Statistics, version 20.0, software (IBM Corp, Armonk, New York).

Physical Function Across Ages

Overall, performance on the various physical function tests declined linearly with advancing age in women (F igure1). On the other hand, only the performance on IHG, 1-leg stance, and WS at fast pace showed a linear age-associated decline in men (F igure 2).

Isometric handgrip strength

IHG performance was signifi cantly affected by age in women (F_{1638} = 60.51; P < .001). IHG strength in 80 + (20.0 [6.9] kg; P < .001) and 71 to 80 years' groups (23.4 [6.9] kg; P < .001) was signifi cantly lower than in the 50 to 60 years' group (27.6 [6.0] kg) (Figure 1A). Furthermore, the IHG strength recorded in the 80 + years' group (P < .001), but not in the 71 to 80 years' group, was signifi cantly lower than that observed in the 61 to 70 years' group. In men, although IHG strength declined linearly with advancing age (P for linear trend < .05; Figure 2A), no signifi cant differences were detected between age groups (F_{382}= 2.202; P = .08).

Five times sit-to-stand test

5× STS performance was signifi cantly affected by age in women (F_{1696} = 41.74; P < .001; F igure 1B). The performance on the 5 × STS in 80 + (13.3 [4.0] seconds) and 71 to 80 years' groups (13.1 [3.5] seconds) was slower than that recorded in both 61 to 70 (11.9 [3.7] seconds; P < .001 for both) and 50 to 60 years' groups (10.8 [3.1] seconds; P < .001 for both). In turn, participants in the 61 to 70 years' group performed slower than the younger group (P < .001). No effects of age were observed in men (F_{383} = 1.400; P = .25; Figure 2B) .

Timed Up and Go test

TUG performance was signifi cantly affected by age in women (F_{1698} = 51.74; P < .001; Figure 1C) and men (F_{382}= 5.98; P < .001; F igure 2C). In women, the performance on the TUG test of 80 + (9.3 [5.6] seconds) and 71 to 80 years' groups (7.6 [1.8] seconds) was worse than both 50 to 60 (6.5 [1.2] seconds; P < .001 for both) and 61 to 70 years' groups (6.9 [2.2] seconds; P < .001 for both). No differences were detected between participants in 50 to 60 and 61 to 70 years' groups. In men, participants in the 80 + years' group showed worse performance than both 50 to 60 (6.2 [0.7] seconds; P = .01) and 61 to 70 years' groups (6.5 [1.6] seconds; P < .001). No differences were found in TUG performance between 80 + and 71 to 80 years' groups.

Table. Participant Characteristics According to Gender and Age Groups.

Age Group	Sample Size, n	Age, y Mean (SD)	BMI, kg/m² Mean (SD)	HTN n (%)	T1DM n (%)	T2DM n (%)	Osteoarthritis n (%)	CVD n (%)
Overall								

Range: 50-102	2804	68.0 (7.0)	27.9 (8.9)	1140 (40.7)	120 (4.3)	681 (24.3)	1532 (54.6)	216 (7.7)
Women								
All age groups	2262	67.1 (7.6)	26.9 (8.5)	1037 (46.5)	108 (4.8)	589 (26.4)	1300 (58.4)	189 (8.5)
50-60	448	56.7 (2.7)	25.5 (9.2)	223 (49.8)	41 (9.2)	155 (34.6)	183 (40.8)	27 (6.0)
61-70	1128	65.7 (2.7)	27.2 (9.0)	544 (48.2)	42 (3.7)	297 (25.9)	649 (57.5)	92 (8.2)
71-80	576	74.6 (2.8)	28.4 (6.5)	243 (42.2)	24 (4.2)	126 (21.9)	393 (68.2)	60 (10.4)
> 80	110	83.8 (2.4)	28.0 (6.9)	27 (24.5)	1 (0.9)	11 (10)	73 (66.4)	6 (5.5)
Men								
All age groups	542	71.5 (6.2)[a]	32.1 (9.2)[a]	103 (19)[a]	12 (2.2) [a]	92 (17.0) [a]	232 (42.8)[a]	27 (5.0) [a]
50-60	17	57.2 (2.7)	30.3 (4.7)[a]	9 (52.9)	2 (11.8)	3 (17.6) [a]	4 (23.5) [a]	2 (11.8)
61-70	187	65.9 (2.8)	31.1 (10.1)[a]	57 (30.5) [a]	4 (2.1)	16 (8.6) [a]	86 (46.0)	17 (9.1)
71-80	302	74.4 (2.7)	31.6 (9.0)[a]	20 (6.6) [a]	6 (2.0)	35 (11.6)	36 (11.9) [a]	6 (2.0) [a]
> 80	36	82.9 (1.6)	33.2 (10.5)[a]	3 (8.3) [a]	0 (0)	30 (8.3)	22 (61.1)	0 (0) [a]

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; HTN, hypertension; SD, standard deviation; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellit [a] P < .05 vs. women.

One-leg stance test

One-leg stance performance was signifi cantly affected by age in women (F_{1558} = 51.59; P < .001; F igure 1D). The performance on the 1-leg stance test in 80 + (12.6 [10.0] seconds) and 71 to 80 years' groups (16.1 [11.0] seconds) was poorer than in both 50 to 60 (23.8 [10.3] seconds; P < .001 for both) and 61 to 70 years' groups (18.4 [12.2] seconds; P < .001 for both). In addition, participants in the 61 to 70 years' group showed poorer performance than the youngest group (P < .001). In men, although balance performance declined linearly with advancing age (P for linear trend < .05), no signifi cant differences were detected between individual age groups (F_{347}= 13.13; P = .08; Figure 2D). An additional analysis was performed to compare the distribution of participants able to achieve maximum performance on the 1-leg stance test (30 seconds) in the 2 genders across age groups. Results demonstrated a decreasing number of participants achieving maximum performance in both genders with advancing age (see Supplemental Digital Content, Figure S1, available at: h ttp://links.lww.com/JGPT/A38).

Walking speed at usual pace

Walking speed at usual pace was signifi cantly affected by age in women (F_{3364}= 51.01; P < .001; Figure 1E) and men (F_{186} = 5.28; P = .01; F igure 2E). In women, WS at usual pace in 80 + (1.06 [0.28] m/s) and 71 to 80 years' groups (1.27 [0.28] m/s) was lower than in both 61 to 70 (1.35 [0.26] m/s; P < .001 for both) and 50 to 60 years' groups (1.42 [0.31] m/s; P < .001 for both). In addition, the 61 to 70 years' group showed a slower WS at usual pace than the 50 to 60 years' group (P < .001). In men, the slowest WS at usual pace was observed in the 71 to 80 years' group (1.35 [0.24] m/s). Participants in this age group had a signifi cantly lower performance in comparison to the 61 to 70 years' group (1.54 [0.33] m/s; P = .01). No other signifi cant between-group differences were observed.

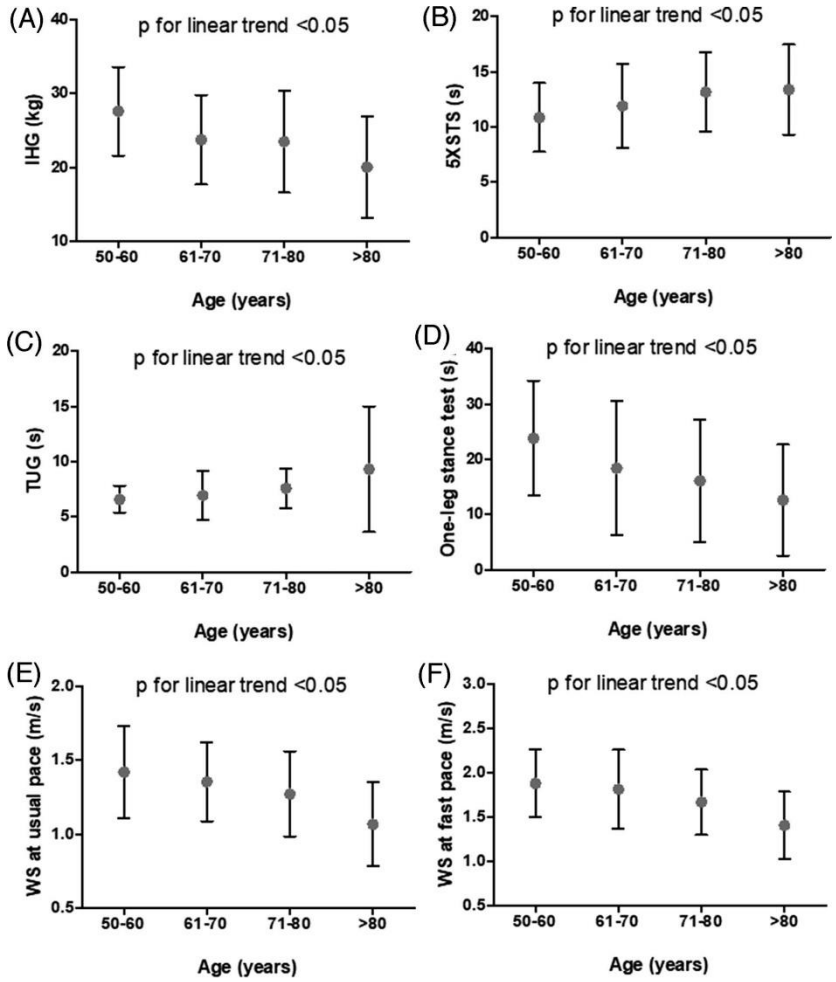

Figure 1. Upper limb muscle strength (A), lower limb muscle power (B), mobility (C, E, and F), and balance (D) across age groups in women. 5 × STS indicates 5 times sit-to-stand test; IHG, isometric handgrip strength; TUG, Timed Up and Go; WS, walking speed.

Walking speed at fast pace

Walking speed at fast pace was signifi cantly affected by age in women (F_{1267} = 33.02; P < .001; Figure 1F) . WS at fast pace in 80 + (1.41 [0.37] m/s) and 71 to 80 years' groups (1.67 [0.36] m/s) was lower than in both 50 to 60 (1.88 [0.91] m/s; P < .001 for both) and 61 to 70 years' groups (1.81 [0.44] m/s; P < .001 for both). In men, WS at fast pace showed a linear decline across ages (P for linear trend < .05), with no signifi cant differences between groups (F_{183}= 2.94; P = .03; Figure 2F) .

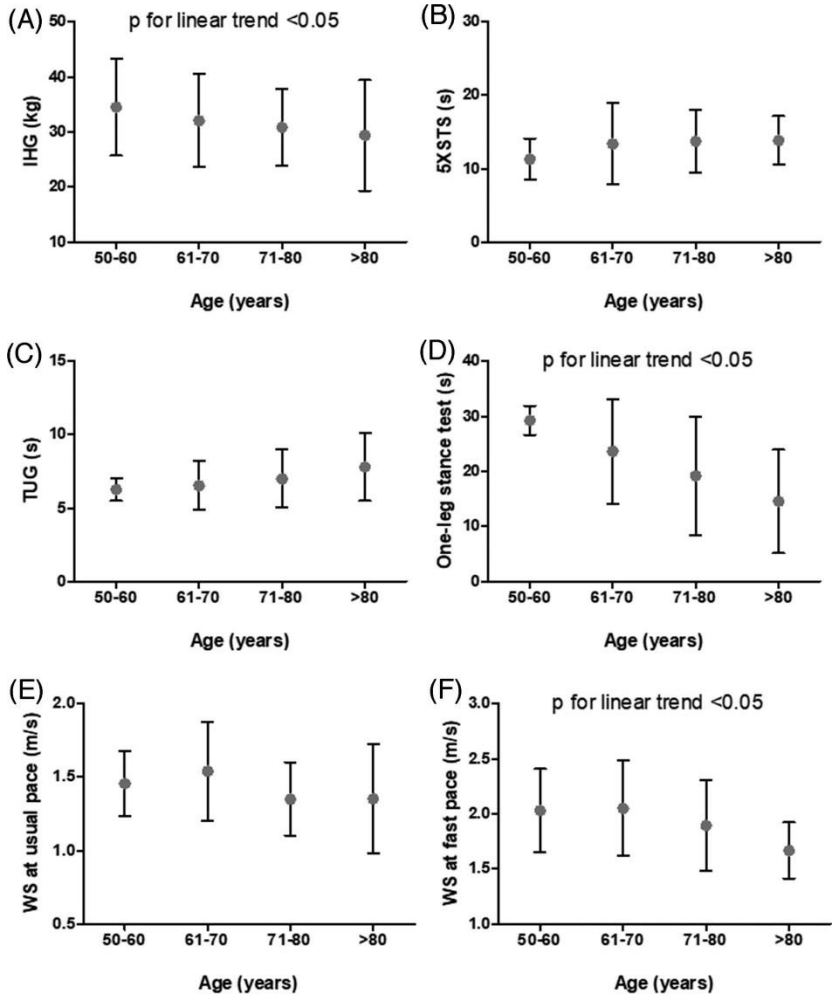

Figure 2. Upper limb muscle strength (A), lower limb muscle power (B), mobility (C, E, and F), and balance (D) across age groups in men. 5 × STS indicates 5 times sit-to-stand test; IHG, isometric handgrip strength; TUG, Timed Up and Go; WS, walking speed.

Physical Function Across Genders

Figure 3 compares the results of physical function tests in men and women across ages. A gender-specifi c pattern was observed in individual tests. Men showed greater IHG strength than women in all age groups (P < .001; Figure 3A).

Conversely, women performed better than men on the 5× STS test at ages 61 to 70 and 71 to 80 years (P < .001 for both; Figure 3B). No significant differences in TUG performance were observed between genders in any age group (Figure 3C). Men performed the 1-leg stance longer than women in 61 to 70 and 71 to 80 years' groups (P < .001 for both; F igure 3D). Finally, men had a slower WS at usual pace than women in 61 to 70 and 80 + years' groups, as well as a reduced WS at fast pace in the 61 to 70 years' group (P < .001 for both; Figures 3E and 3 F).

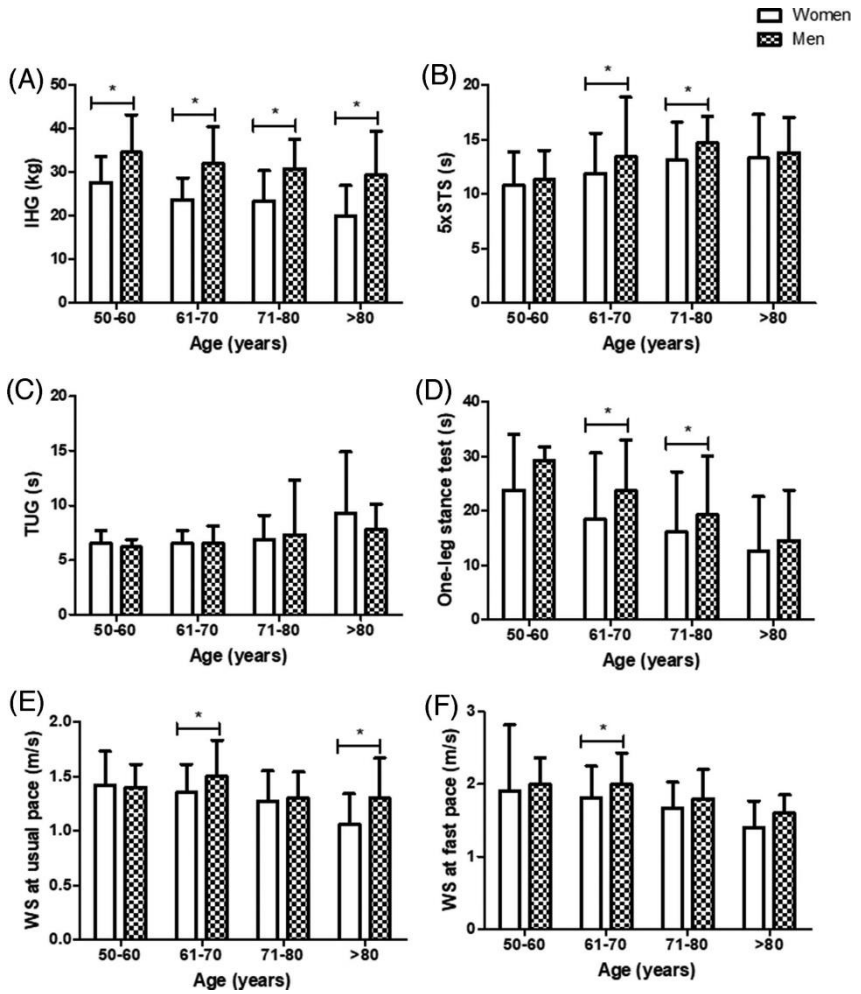

Figure 3. Upper limb muscle strength (A), lower limb muscle power (B), mobility (C, E, F), and balance (D) in men and women across age groups. 5 × STS indicates 5 times sit-to-stand test; IHG, isometric handgrip strength; TUG, Timed Up and Go; WS, walking speed. * P < .05.

Pearson's Correlations

Pearson's correlations were run to explore the relationship between physical function tests and age in the whole sample (Figure 4) and according to gender (see Supplemental Digital Content, Figures S2 and S3, available at: http:// links.lww.com/JGPT/A39 and http://links.lww.com/JGPT/ A40). In women, men, and in the whole sample, age was signifi cantly correlated with IHG (women $r = -0.31$, P < .001; men

$r = -0.14$, $P = .004$; whole sample $r = -0.24$, $P < .001$), 5 × STS (women $r = 0.33$, $P < .001$; men $r = 0.15$, $P = .04$; whole sample $r = 0.31$, $P < .001$), TUG (women $r = 0.33$, men $r = 0.24$, whole sample $r = 0.30$; $P < .001$ for all), WS at usual pace (women $r = -0.28$, men $r = -0.24$, whole sample $r = -0.26$; $P < .001$ for all), and WS at fast pace (women $r = -0.28$, men $r = -0.28$, whole sample $r = -0.26$; $P < .001$ for all). These results further indicate that physical performance declines with advancing age in both genders.

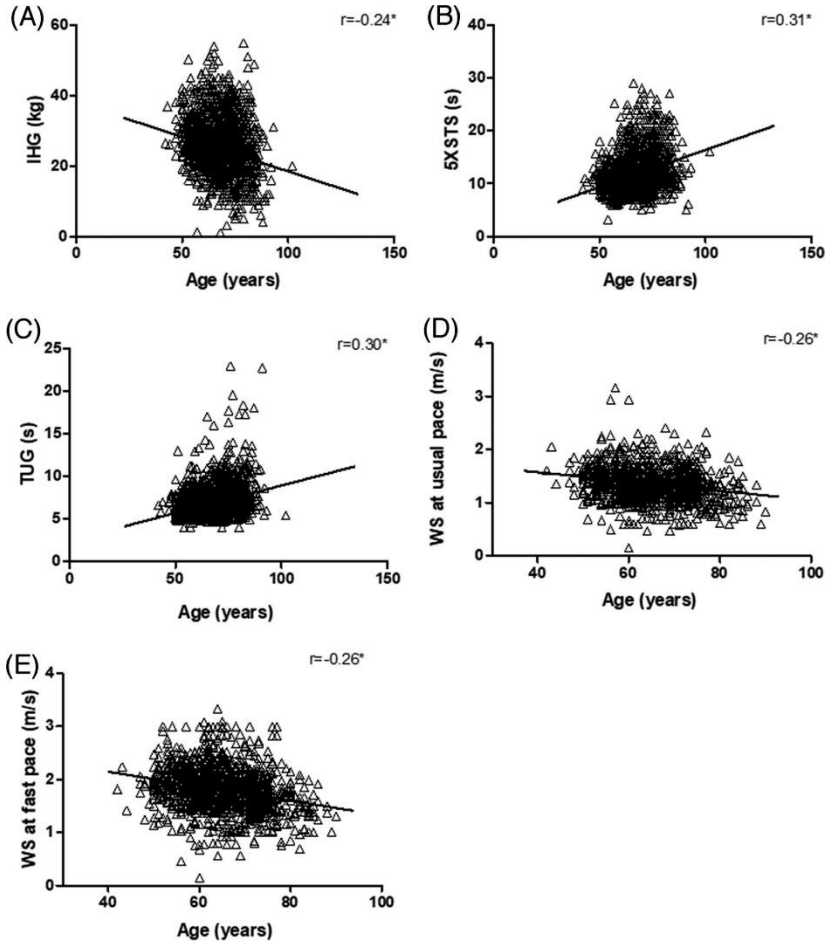

Figure 4. Relationship between age and physical function in the whole study population. 5 × STS indicates 5 times sit-tostand test; IHG, isometric handgrip strength; TUG, Timed Up and Go; WS, walking speed. * $P < .05$.

DISCUSSION

The maintenance of physical function is a central component of successful aging. [28] Conversely, declining physical performance is associated with a vast array of nega-tive health-related outcomes, including disability, [29] falls, [10] dementia, [30] institutionalization, [7] and mortality. [8] Poor performance on the IHG (< 27 kg in men and < 16 kg in women), TUG (≥ 20 seconds), 5 × STS (> 15 seconds), and WS at usual pace (≤ 0.8 m/s) is listed among the

items of the diagnostic algorithm of sarcopenia. [31] Yet, limited evidence exists on the impact of ethnicity on age-related declines in physical performance. [13]

In the present study, a comprehensive set of physical function tests were administered to a large sample of community-dwelling Brazilian adults across a wide age spectrum to investigate how physical performance varied with age and gender. Our fi ndings indicate that performance on all physical function tests declines linearly with age in women (Figure 1 and Figure S2, available at: http://links.lww.com/JGPT/ A39). In men, although all physical function tests were negatively correlated with age, only IHG, 1-leg stance, and WS at fast pace displayed linear age-related declines. Comparisons between genders showed that women walked faster and had greater lower limb muscle power, while men displayed greater upper limb muscle strength and better balance.

Our fi ndings are in line with prior investigations in European [11-13] and Asian people, [13] and add to existing knowledge by demonstrating that this phenomenon is also observed in community-dwelling Brazilians across different functional domains. In women, participants in their seventh and eighth decade of life showed lower physical function than those younger than 60 years, with the greater difference observed in the TUG test and 1-leg stance (43.0% and 48.3%, respectively). In men, 70- to 80-year-old participants showed a balance performance approximately 50% lower than those younger than 60 years, while WS at fast pace was reduced by around 69%.

Irrespective of the signifi cant age-related declines in physical function, mean IHG, TUG, 5 × STS, and WS values in men and women were higher than the proposed cutoffs for sarcopenia. [31] Regarding IHG, for example, the lowest mean values observed were 29.4 and 20.0 kg, for men and women, respectively, while the recent revised European consensus on sarcopenia has set cutoff points at 27 kg for men and 16 kg for women. [31] These results could be expected since a recent systematic review and metaanalysis demonstrated a low prevalence of sarcopenia (17%) among Brazilian older adults. [32] However, the investigations included in the meta-analysis were based on different cutoffs (eg, Baumgartner's criteria, populationbased) and the prevalence of sarcopenia ranged from 4% to 72.7%, [32] limiting comparison across studies.

Although all participants of the present study were recruited from the same community senior center, a high rate of variability was observed in physical performance, which may explain its low correlation with age. This variability might be attributed to environmental and behavioral factors, including mid-life lifestyle, [33] neighborhood environment (eg, number of recreational facilities, community center, and criminality), [34, 35]

protein intake, [36, 37] and street walkability. [38] However, these assumptions are only speculative and should be investigated further in future studies.

In contrast to upper limb muscle strength, lower extremity muscle power and WS were greater in women than in men. This result differs from a previous investigation showing that men performed better than women on the 5 ×STS from middle age through senescence. [12] A possible explanation for these fi ndings may be found in the different patterns of physical activity between participants enrolled in the 2 studies. In addition to a similar time spent in paid work, women typically spend more time in domestic work than men. [39-41] In some cases, the time spent doing domestic work by women may reach as many as 20 hours per week. [40] Domestic work is commonly based on moving from one room to another, combined with numerous squats to collect objects from the ground, and standing periods to cook, clean, and organize. The physical function profi le observed in women may therefore refl ect an adaptation to a set of movements repetitively performed every day throughout life. In contrast, men's domestic work is often restricted to strength-requiring tasks. Studies taking into consideration economic and social status, physical activity levels, and time spent in domestic work are necessary to validate our results. The existence of gender-specifi c patterns of physical function also calls for a comprehensive assessment of physical performance to capture its various domains (eg, mobility, upper limb muscle strength, lower limb muscle power, and balance).

As a practical application of our fi ndings, physical therapists should be cautious when using cutoffs for physical function tests to evaluate patients or to set rehabilitation goals and exercise programs for older adults. Indeed, the extrapolation of cutoffs to populations different from those in which they were established might lead to erroneous interpretations of a person's condition and the effectiveness of physical interventions. Therefore, in the absence of region-specifi c cutoffs for physical function, the inclusion of other tools (eg, self-reported scales) may be advisable for the evaluation and treatment of community-dwelling older adults.

Our study presents some limitations that need to be discussed. First, the results shown in this work are derived from cross-sectional observations. The possibility cannot be ruled out that the differences in birth cohorts may have infl uenced some of the assessed parameters. A deeper understanding of age-dependent trajectories of physical function requires an analysis of prospective data that are not available at this stage for our study. Furthermore, neither objectively measured nor self-reported physical activity throughout life was collected. Hence, the impact of physical activity on functional tests across ages and genders could not be established. In addition, no measures of muscle mass were obtained, which prevented exploration of the relationship between muscle quantity and physical function. The relatively

small number of men enrolled may be viewed as a further limitation of this study, given that a small sample size increases the risk of type 2 statistical errors. However, according to the most recent report of the Brazilian Institute of Geography and Statistics, [42] the gender distribution of our study sample is comparable to that of the geographic area where participants were recruited.

CONCLUSIONS

Findings of the present study indicate that performance decreases on different physical function tests with advancing age in Brazilian adults, following a gender-specifi c pattern. Remarkably, the lowest mean values of physical function tests recorded in our study population did not reach the cutoffs for sarcopenia recently proposed by the European Working Group on Sarcopenia in Older People 2. [31] This may suggest that region-specifi c cutoffs of physical function may be necessary to estimate the risk of adverse events in different populations. Therefore, health professionals, including physical therapists, should use caution when applying cutoffs for physical function tests in clinical practice. Unless region-specifi c reference values for physical function are available, other tools (eg, self-reported scales) should be adopted for the careful evaluation and treatment of community-dwelling older people.

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CONCLUSION

A) Prevalence of frailty in South America. Our findings suggest that prefrailty and frailty are highly prevalent in South American older adults, with rates higher than those observed in Europe and Asia. In the community, almost one-in-two are prefrail and one-in-five are frail, while institutionalized individuals are more frequently affected. These findings indicate the need for immediate attention to avoid frailty progression toward negative health outcomes. Our findings also highlight the need for specific guidelines for frailty in South America.

B) The relationship between frailty status and protein intake, physical performance, and hypertension-related parameters using 4 different frailty instruments. Protein intake, regardless of the source, is significantly associated with physical function in older adults. The systematic review and metanalysis suggest that high protein consumption is negatively associated with frailty prevalence. When was compared the relationship between frailty status using 4 different instruments and many protein-related parameters, findings suggested that the results are tool-dependent. In addition, a lower consumption of protein and BCAA is observed in frail older adults. Similarly, frailty status is only related with physical function when frailty tools use performance-based measures to assess physical performance. Finally, no significant association between hypertension-related parameters and frailty status was observed.

C) The effects of HSRT and LSRT on frailty status, physical performance, cognitive function, and blood pressure. Both LSRT and HSRT reversed frailty status and improved physical performance in prefrail and frail older adults. However, different patterns of improvement were observed among RT protocols. Regarding frailty status, LSRT seemed to be more effective in reverse prefrailty and frailty when compared to HSRT. Greater improvements in muscle strength and power were also observed after LSRT, while HSRT caused greater improvements in mobility and dual-task performance. Finally, RT programs similarly improved verbal memory in prefrail.

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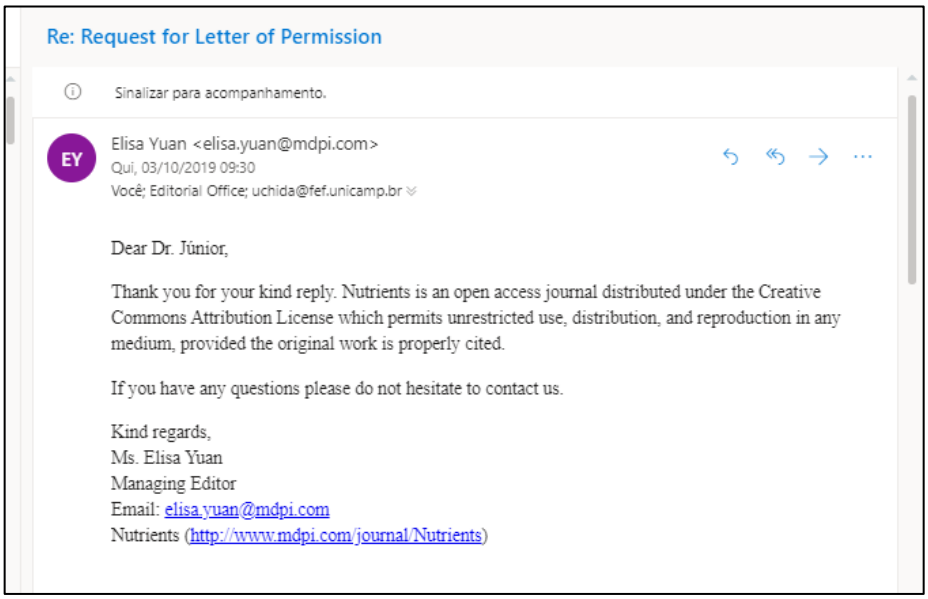
APPENDIX

APPENDIX 1- JOURNALS' AUTHORIZATIONS



Re: Request for Letter of Permission

Sinalizar para acompanhamento.

EY

Elisa Yuan <elisa.yuan@mdpi.com>
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Dear Dr. Júnior,

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If you have any questions please do not hesitate to contact us.

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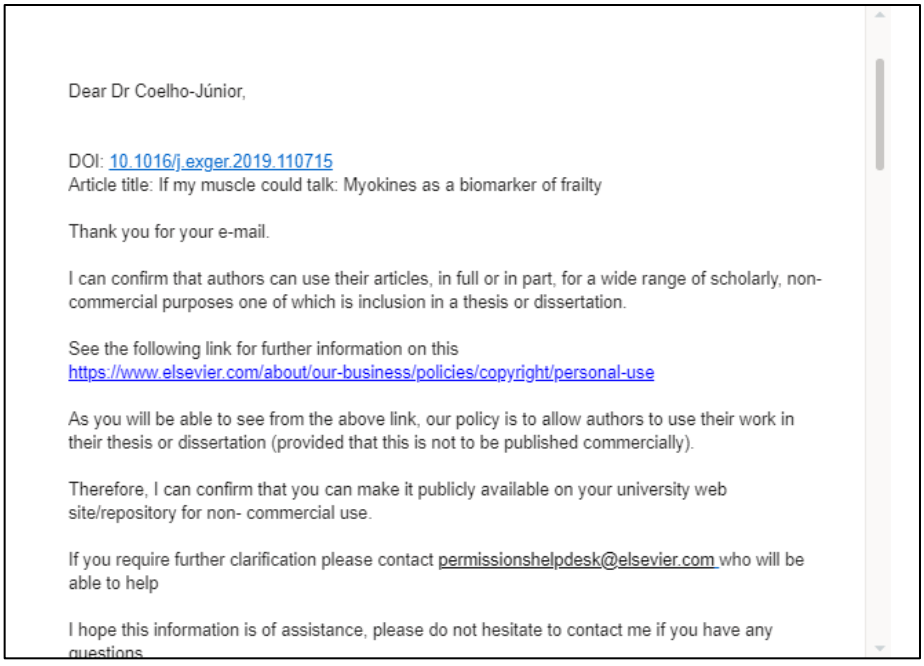

Dear Dr Coelho-Júnior,

DOI: 10.1016/j.exger.2019.110715
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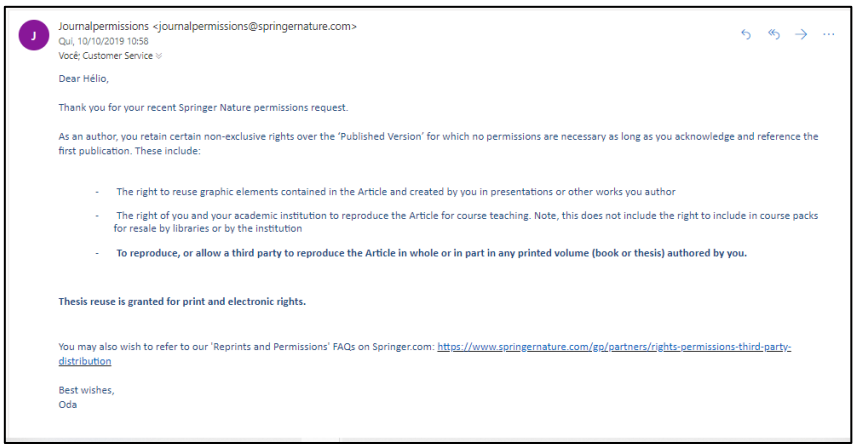

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APPENDIX 2- HUMAN RESEARCH ETHICS COMMITTEE

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: EFEITOS DOS TREINAMENTOS DE FORÇA E POTÊNCIA MUSCULAR NOS ASPECTOS MORFOFUNCIONAIS, COGNITIVOS, E HEMODINÂMICOS DE IDOSOS PRÉ-FRÁGEIS E FRÁGEIS **Pesquisador:** Helio José Coelho Junior **Área Temática:**
Versão: 3

CAAE: 20021919.7.0000.5404

Instituição Proponente: Faculdade de Educação Física

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.652.741

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

CAMPINAS, 21 de Outubro de 2019

Assinado por:
Renata Maria dos Santos Celeghini
(Coordenador(a))

APPENDIX 3- FRAILTY STATUS

NOME_____ ID_____ DATA_____ AVALIADOR_____

 PERDA DE PESO NÃO INTENCIONAL- (mais que 4.5 kg no último ano);

 FRAQUEZA - (resultado abaixo de 20kgf para mulheres e abaixo de 30kgf para homem no teste de preensão manual);

 FADIGA - O senhor(a) se sente cansado ao realizar as atividades da vida diária? 1) Nunca; 2) Às vezes; 3) Frequentemente; 4) Sempre. Se 3 ou 4, assinale como SIM.

 MOBILIDADE- Velocidade da marcha no teste de 10 metros (≤1.0 m/s);

 Nível de atividade física – IPAQ para idosos.

• Robusto: 0

• Pré-frágil: 1-2

• Frágil:≥3

APPENDIX 4- MINI-MENTAL STATE EXAMINATION (MMSE)

Voluntário: _____

Data de avaliação: _____ Avaliador: _____

Orientação

1) Dia da Semana (1 ponto) ( )
2) Dia do Mês (1 ponto) ( )
3) Mês (1 ponto) ( )
4) Ano (1 ponto) ( )
5) Hora aproximada (1 ponto) ( )
6) Local específico (andar ou setor) (1 ponto) ( )
7) Instituição (residência, hospital, clínica) (1 ponto) ( )
8) Bairro ou rua próxima (1 ponto) ( )
9) Cidade (1 ponto) ( )
10) Estado (1 ponto) ( )

Memória Imediata

Fale três palavras não relacionadas.
Posteriormente pergunte ao paciente pelas 3 palavras.
Dê 1 ponto para cada resposta correta. ( )
Depois repita as palavras e certifique-se de que o paciente as aprendeu, pois mais adiante você irá perguntá-las novamente.

Atenção e Cálculo

(100-7) sucessivos, 5 vezes sucessivamente (93,86,79,72,65) (1 ponto para cada cálculo correto) ( )

Evocação

Pergunte pelas três palavras ditas anteriormente (1 ponto por palavra) ( )

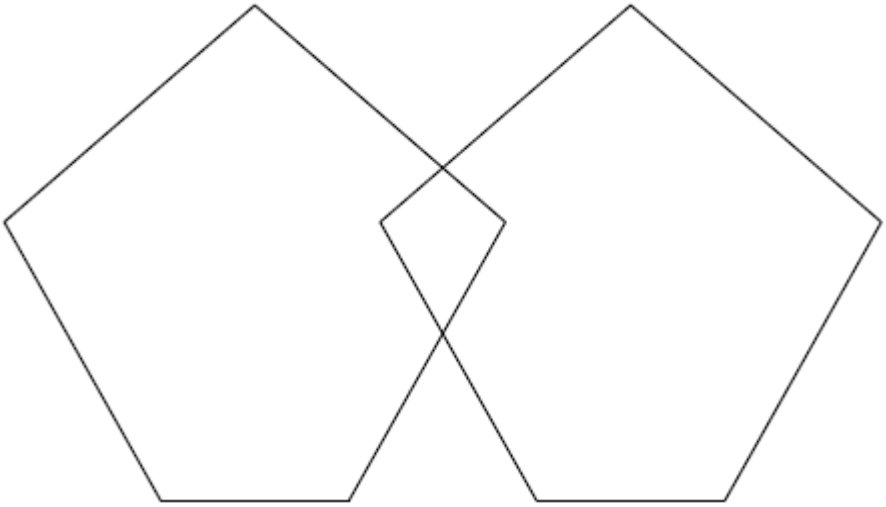
Linguagem

1) Nomear um relógio e uma caneta (2 pontos) ( )
2) Repetir “nem aqui, nem ali, nem lá” (1 ponto) ( )
3) Comando:”pegue este papel com a mão direita, dobre ao meio e coloque no chão (3 pontos) ( )
4) Ler e obedecer:”feche os olhos” (1 ponto) ( )
5) Escrever uma frase (1 ponto) ( )

6) Copiar um desenho (1 ponto) ( )

Resultado: (/ 30)

COPIE O DESENHO



APPENDIX 5- Rey's Auditory Verbal Learning Test (RAVLT)

TESTE DE APRENDIZAGEM AUDITIVO-VERBAL (DE REY)- RAVLT

Voluntário: _____

Data de avaliação: _____ Avaliador: _____

	LISTA A	*A1*	*A2*	*A3*	*A4*	*A5*	**LISTA B**	*B1*	*A6*	*A7*	**LISTA A**
1	Tambor						Carteira				Tambor
2	Cortina						Guarda				Cortina
3	Sino						Ave				Sino
4	Café						Sapato				Café
5	Escola						Forno				Escola
6	Pai						Montanha				Pai
7	Lua						Óculos				Lua
8	Jardim						Toalha				Jardim
9	Chapéu						Nuvem				Chapéu
10	Cantor						Barco				Cantor
11	Nariz						Carneiro				Nariz
12	Peru						Canhão				Peru
13	Cor						Lápis				Cor
14	Casa						Igreja				Casa
15	Rio						Peixe				Rio
	TOTAL						**TOTAL**				

SINO (A)		LAR (SA)		TOALHA (B)		BARCO (B)		ÓCULOS (B)	
JANELA (SA)		PEIXE (B)		CORTINA (A)		ESTOLA (FA)		BOTA (SB)	
CHAPÉU (A)		LUA (A)		FLOR (SA)		PAI (A)		SAPATO (B)	
MÚSICA (SA)		PINO (FA)		COR (A)		ÁGUA (SA)		PROFESSOR (SA)	
GUARDA (B)		RUA (FA)		CARTEIRA (B)		CANTOR (A)		FORNO (B)	
NARIZ (A)		AVE (B)		CANHÃO (B)		BULE (SA)		NINHO (SB)	
CHUVA (SB)		MONTANHA (B)		GIZ (SA)		NUVEM (B)		FILHO (SA)	

ESCOLA (A)		CAFÉ (A)		IGREJA (B)		CASA (A)		TAMBOR (A)	
PAPEL (FA)		ASA (FA)		PERU (A)		FEIXE (FB)		RAPÉ (SA)	
LÁPIS (B)		RIO (A)		TORNO (FB)		JARDIM (A)		CARNEIRO (B)	