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Guilherme Eustáquio Furtado

Exploring the contribution of Biopsychological makers to explain physical frailty and the exercise mediation on hormonal, immnue and psychological well-being in institutionalized frail older woman

Thesis in the field of Doctoral degree in Sports Sciences, the branch of Physical Activity and Health, supervised by Doctors Ana Maria Teixeira and José Pedro Ferreira and presented to the Faculty of Sports Sciences and Physical Education of the University of Coimbra.

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EXPLORANDO A CONTRIBUIÇÃO DE INDICADORES BIOPSICOLÓGICOS PARA EXPLICAR A FRAGILIDADE FÍSICA E A MEDIAÇÃO DO EXERCÍCIO NOS INDICADORES DO BEM-ESTAR PSICOLÓGICO, PARÂMETROS HORMONAS E IMUNITÁRIOS EM MULHERES IDOSAS FISICAMENTE FRÁGEIS

Guilherme Eustáquio Furtado

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ABSTRACT

Frailty syndrome is a complex aging expression determined by ontogenetic and phylogenetic factors. Chronic stress has been shown to have immunosuppressive effects, to accelerate immunosenescence and to cause cumulative disorders in many physiological systems, resulting in frail state. In a recent approach, Linda Fried and colleagues have developed a construct whose bases are muscle loss, negative energy balance and physical inactivity, called ‘Frailty Cycle’. They identified five dimensions in the construct: weakness, low resistance to an effort, slowness, low physical activity, and weight loss, which were operationalized on five criteria to identify the Physical Frailty (PF), and divide the population in frail, pre-frail and non-frail. Recently, epidemiological studies reported that cognitive impairments, low immune expression, and others global health dimensions have a powerful association with physical frailty. However, there is a need for the search for new correlated markers for the frail condition, for a better understanding of the phenomenon. On the other hand, exercise has been shown as a co-adjuvant treatment to have positive effects on several factors linked to physical frailty (e.g. improve immunity and prevent chronic diseases), because of it’s potential effect on hormonal mediation. Looking at Fried PF Phenotype construct, their dimensions share biological ‘commonalities’ that can be explained by studying the biopsychological mechanisms with exercise being a key factor in the study of these relationships.

The current research was designed to investigate and characterize the prevalence of the PF in a cross-sectional Portuguese samples (institutionalized participants), to examine the relationship between PF and each one of the general health status domain such as physical fitness and functioning status; neuroendocrine and immune parameters; psychological and cognitive ability of these populations; and to verified the impact of different types of exercise in each domain of general health status. However, this doctoral thesis is presented in the form of articles, divided into five sections and their respective chapters. In total, 3 preliminary studies (2 systematic reviews of studies 1 and 2 and one exercise-intervention pilot study 3), 5 cross-sectional studies (4,5,6,7, and 8) and 3 intervention studies (9,10 and 11) were completed. The cross-sectional design consisted of the assessment of 140 older women (≥75 years old), living in different centres of heath care and social support, located in the city of Coimbra, Portugal. The participants were selected using a non-probabilistic convenience sampling based on the geographical area of the center region of Coimbra city.

The experimental design characterizes as a naturalist controlled trial exercise-based intervention study with two different chair-based exercise programs. In the preliminary study 3, the group of 20 participants was submitted to 14 weeks of chair-based yoga type flexibility exercises. The control group consisted of 15 participants. The subsequent phase was designed to assess the effect of muscle-strength with elastic band exercises (n = 24) and multimodal exercise (n = 18) interventions on biopsychological outcomes in frail and pre-frail individuals. Participants in these groups attended a 45 minutes' exercise session, two-three times per week over 24 weeks. All participants were evaluated in the pre- and post intervention moments. In this phase, the participants were extracted by PF protocol from the cross-sectional study design.

Several interesting findings from different studies were found. Firstly, preliminary metanalysis review of study 01, exposed a strong association between the decline in the cognitive profile and PF, which presents a similar pattern in countries of several regions in the world (global effect size = 95%CI: 0.50-0.62, p<0.001). The systematic review of reviews (study 2) has confirmed that there was concrete evidence of a promising effect of the multimodal exercise with a long-term duration (more than five months) and a weekly frequency that varies between 3-5 times per week seems to have a superior effect to other types of exercise in improving different global health variables, attenuating and reversing the PF. In yoga intervention of study 3, it was possible to verify that chair-based exercise, being a method integrated with the conventional exercise programs of group classes, also promotes promising results in the modulation of functional fitness and salivary stress hormones indicators. However, it was clear that exercises of light intensity have little impact on these variables.

The cross-sectional studies presented important evidence regarding the identification of new correlates of PF, as well as the power of some of these variables to explain the variance associated with frailty status in the institutionalized older women. Study 4 demonstrated that only aerobic resistance (AUC = sensitivity [93-96%]; specificity [74-77%], p=0.001) and cognition (AUC = sensitivity [77-88%]; specificity [65-71%], p<0.001) were the variables that had the greatest strong power of explanation of the PF status when compared to several other global health markers. Study 5 demonstrated that the agility-dynamic balance test can be used as a simple and fast tool for the detection of physical frailty (AUC=.82, 95% CI [0.74, 0.90]). Study 6 revealed clearly that low activity levels and slow gait speed were independent dimensions of PF that contribute to functional disability (p < 0.05). Central results from study 7 revealed that attitudes towards aging and the subjective perception of happiness, explaining 34% and 40% of variance respectively, were highlighted as new psychological dimensions that may explain the variance associated with PF.

In study 8 the results pointed to salivary α-amylase (AUC = 0.613, AUC 95%CI = [0.518; 0.707]) as a promising marker for prognosis of PF condition. Intervention studies with different types of multimodal (CME) and muscle strength elastic bands exercise (CSE) presented some important results. In study 9 it was possible to verify the positive effect of exercise modulation on the independent components of PF in several domains of physical function, namely in the reduction of the subjective perception of the risk of falls and in the proficiency to perform daily life activities ($p < 0.05$), showing a small increase in sex hormones such as DHEA and testosterone. Study 10 demonstrated the effect of exercise on the positive mediation of immune markers, specifically in the balance of the IL-10 / TNF-α ratio ($p < 0.05$). Study 11 showed the effect of exercise on the maintenance and improvement of psychological well-being and cognitive abilities of exercise practitioners, as well as the effect of exercise on the modulation of biological stress markers (COR and α-amylase) and immune function of IgA ($p < 0.05$).

Overall, we believe that this multidimensional approach offers a more comprehensive understanding of the causes and consequences of PF status. The results help us to make some essential assumptions. In this sample, we verified the presence of new phenotypes associated with to physical frailty status: Disability of Frailty, Cognitive Frailty, Psychological Frailty, Poor functional fitness of Frailty and Neuroendocrine-immune of Frailty. Looking at the interconnection between studies, we can see that it makes sense that frail individuals have lower physical fitness, accompanied by a physical inability to perform daily tasks and a high fear of falling. An interconnection between the low profile of psychological and cognitive state and a lower functional fitness, since the literature points out a relationship between a good functioning of the executive function and a greater capacity to solve physical tasks and daily problems, also including the management of the stress, was also found.

Finally, the relationship between the unsatisfactory hormonal balance and the poor functioning of the skeletal muscle system was also seen. On the other hand, exercise intervention proved that chair-based exercise, was an appropriate method to integrate with the conventional methods of exercise prescription to be used in the older-frail individuals. The impact of different exercise programs (multimodal and muscle strength exercise) showed similar findings in the several indocators. Despite the different results presented in the intervention studies, we can speculate that exercise change positively the levels of physical activity and physical fitness, which may be related to an improvement in subjective perception of fear of falling and proficiency in daily activities. The improvement of the physical performance seems to have influenced attitudes toward aging, global self-esteem and general self-efficacy, corroborating the previous findings that already had exposed correlations between physiological well-being and some physical-functional fitness components.

Although not directly assessed the social interaction component promoted by both exercise programs, this 'parallel-effect' may have exercised a positive influence on the improvement of emotional well-being and mood status of participants, since controls did not show similar results. For the future interventions and based on our cross-sectional studies as a pilot trial, we can recommend to extend this type of study to older populations of different settings (e.g. hospitalization, community, social vulnerability). In addition, a longitudinal design that focuses in the study of the life-time course, starting at age 40 and above (middle-age) may produce clues about how the physical Frailty phenotype develops across the time. This was the main recommendation from the World Health Organization Scientific Committee on the International Conference on Frailty and Sarcopenia 2017, Barcelona. Exercise as an adjuvant treatment may be combined with other therapies (i.e., dietary supplementation, medication) to potentiate its beneficial effects, and this type of strategy is the future of public health interventions.

Key-words: Physical Frailty, Older Adults, Exercise, Psychological well-being, immune system, stress hormones, disability, cognition, physical fitness.

RESUMO

A síndrome da fragilidade é um complexo desfecho associado ao envelhecimento, determinada por fatores ontogenéticos e filogenéticos. O estresse crônico demonstrou ter efeitos imunossupressores, causando distúrbios cumulativos em muitos sistemas fisiológicos, resultando num idoso frágil. Numa abordagem recente, Linda Fried e seus colegas fizeram emergir um construto cujas bases são a perda de massa muscular, o balanço energético negativo e a inatividade física, chamados de "Ciclo da Fragilidade". Eles identificaram cinco dimensões deste construto: fraqueza muscular, baixa resistência, lentidão da marcha, baixos níveis de atividade física e perda de peso não intencional e que serviram de base para operacionalizar os cinco critérios do 'Fenótipo da Fragilidade Física (FF), capaz de dividir a população em idosos fragilizados, pré-fragilizados e não-fragilizados.

Recentemente, estudos epidemiológicos relataram que o declínio cognitivo, baixo perfil imunológico e outras dimensões da saúde global têm uma poderosa associação com a fragilidade física. Existe a necessidade de busca de novos marcadores correlacionados com a FF para uma melhor compreensão do fenómeno. Por outro lado, o exercício tem sido demonstrado como um tratamento coadjuvante na modulação positiva de vários fatores associados à condição frágil (i.e., melhorar a imunidade e prevenir doenças crónicas), devido ao seu efeito potencial sobre a mediação hormonal. Olhando para o construto de Fried, suas dimensões compartilham correspondências no desfecho de algumas variáveis, que podem ser explicadas pelo estudo dos mecanismos biopsicológicos com o exercício sendo um "fator-chave" no estudo dessas relações. A presente tese doutoral foi concebida para investigar a caracterização da prevalência da FF numa amostra transversal, de participantes idosos que vivem em regime de institucionalização, examinando a relação entre a FF e cada domínio do estado de saúde global, tais como aptidão física e estado funcional; parâmetros neuroendócrinos e imunitários; bem estar psicológico e perfil cognitivo; e ainda, e verificar o impacto de diferentes tipos de exercício em cada domínio do estado de saúde global destes indivíduos. No entanto, esta tese foi elaborada na forma de artigos, divididos em cinco seções e seus respectivos capítulos. No total, foram realizados 3 estudos preliminares (2 revisões sistemáticas (estudos 1 e 2) e um estudo piloto de intervenção com exercício (estudo 3), 5 estudos transversais (4,5,6,7 e 8) e 3 estudos de intervenção (9,10 e 11).

O desenho transversal consistiu na avaliação de 140 mulheres idosas (≥75 anos), residentes em diferentes centros de saúde e apoio social, localizadas na cidade de Coimbra, Portugal. Os participantes foram selecionados por amostragem de conveniência não probabilística, com base na área geográfica da região central da cidade de Coimbra. O desenho experimental caracteriza-se como um estudo-naturalista controlado, baseado em diferentes programas de intervenção com exercício suportados por cadeiras. No estudo preliminar 3, o grupo de 20 participantes foi submetido a 14 semanas de exercícios de flexibilidade do tipo ioga baseados em cadeira. O grupo controle consistiu de 15 participantes.

A fase subsequente, foi planeada para testar o efeito de um programa de exercícios de força muscular com bandas elásticas (CSE, n = 24) e outro, caracterizado como multimodal, que engloba resistência muscular, equilíbrio, coordenação (CME, n = 18) sobre os indicadores biopsicológicos em indivíduos frágeis e pré-frágeis. Os participantes desses grupos realizam de uma sessão de exercícios de 45 minutos, com frequência de duas a três vezes por semana, durante 28 semanas. Juntos, o grupo controle, que não exercitou (CG_{ne} = 15) qualquer tipo de atividade, foram avaliados nos momentos pré e pós-intervenção. Para esta fase, os participantes foram estratificados do desenho de estudo transversal em função do protocolo de fragilidade física.

Alguns resultados interessantes nos diferentes estudos apresentados foram encontrados. Primeiramente, a revisão sistemática com metanálise (estudo 01), encontrou uma forte associação entre o declínio do perfil cognitivo e a FF, cujo os resultados revelam um padrão semelhante de associação em países de diversas regiões do mundo (tamanho do efeito global = CI:95%: 0,50-0,62, p <0,001). A revisão sistemática de estudos de revisões (estudo 2) confirmou a existência de evidências concretas sobre o efeito promissor do exercício multimodal, realizado com uma duração de cinco meses (ou mais) sendo que, uma frequência semanal que varia entre 3-5 vezes por semana, parece ter um efeito superior a outros tipos de exercício na melhoraria diferentes variáveis de saúde global em idosos frágeis, atenuando e até mesmo revertendo o FF. No estudo (piloto) 3 de intervenção com yoga, foi possível verificar que o exercício com base na cadeira, sendo um método integrado nos programas convencionais de exercícios em grupo, também promove resultados promissores na modulação dos indicadores de aptidão funcional e hormônios salivares do estresse salivar. No entanto, ficou claro que os exercícios de baixa intensidade têm pouco impacto sobre essas variáveis.

Os estudos transversais apresentaram evidências importantes em relação à identificação de novos correlatos à FF. O estudo 4 demonstrou que a resistência aeróbia (AUC = sensibilidade [93-96%], especificidade [74-77%], p = 0,001) e cognição (AUC = sensibilidade [77-88%]; especificidade [65-71%], p <0,001) foram as variáveis que melhor explicaram a condição frágil, quando comparados a vários outros marcadores. O Estudo 5 demonstrou que o teste de equilíbrio dinâmico-agilidade pode ser usado como uma ferramenta simples e rápida para a detecção da FF em idosos institucionalizados (AUC = 0,82, IC 95% [0,74, 0,90]). O estudo 6 mostrou claramente que os 'baixos níveis de atividade' e 'lentidão da marcha' eram dimensões independentes da FF que contribuem para a incapacidade funcional (p <0,05). No estudo 7, os resultados centrais revelaram que as 'atitudes face ao envelhecimento' e a 'percepção subjetiva da felicidade', explicam 34% e 40% da variância, sendo apontadas como novas dimensões psicológicas que podem explicar a variância associada à FF. No estudo 8, os resultados apontaram a α-amilase salivar (AUC = 0,613, AUC 95% CI = [0,518; 0,707]) como sendo um marcador promissor para o prognóstico da condição de FF.

Os estudos de intervenção com diferentes tipos de exercício (CME and CSE) apresentaram alguns resultados importantes. No estudo 9, por exemplo, foi possível verificar o efeito positivo da modulação do exercício sobre os componentes independentes da FF e nos vários domínios da aptidão física-funcional, na redução da percepção subjetiva do risco de quedas e na proficiência em realizar atividades de vida diária ($p < 0,05$), mostrando ainda, um ligeiro incremento nas hormonas sexuais esteroides tais como o DHEA e a testosterona. Já o estudo 10 demonstrou o efeito dos diferentes programas de exercício na modulação positiva de marcadores imunológicos, especificamente no equilíbrio do rácio IL-10/TNF-α ($p < 0,05$). O estudo 11 mostrou o efeito do exercício sobre a manutenção e melhora do bem-estar psicológico e habilidades cognitivas de praticantes de exercício, bem como o efeito do exercício sobre a modulação de marcadores de estresse biológico (COR e α-amilase) e função imune de IgA ($p < 0,05$).

Em geral, acreditamos que essa abordagem multidimensional oferece uma compreensão mais abrangente das causas e consequências do estado da FF. Os resultados nos ajudam a fazer algumas reflexões importantes. Verificou-se a presença de novos fenótipos associados ao estado de fragilidade física: fragilidade associada às incapacidades, fragilidade cognitiva, fragilidade psicológica, baixa aptidão físico-motora associada à fragilidade e fragilidade do sistema endócrino-imune. Observando a interligação entre os estudos, percebeu-se que faz sentido uma reduzida aptidão física em indivíduos frágeis, acompanhados de uma incapacidade física para realizar tarefas cotidianas e o elevado medo de cair. Uma interligação entre o baixo perfil do estado psicológico e cognitivo e uma menor aptidão funcional também faz sentido, uma vez que a literatura aponta para uma relação entre um bom funcionamento da função executiva e uma maior capacidade de resolver tarefas físicas e problemas cotidianos, incluindo também a gestão do stress psicológico. Finalmente, a relação entre um baixo perfil imunitário/hormonal e o funcionamento do sistema muscular esquelético deficitário, cujas evidências apontam para uma correlação bastante sólida.

Por outro lado, ambas as intervenções comprovaram que o exercício com base na cadeira, pode ser um método adequado para integrar aos métodos convencionais de prescrição de exercício na aplicação com amostras de idosos mais frágeis. O impacto de diferentes programas de exercícios (CME e CSE) mostrou resultados semelhantes nos vários indicadores. Podemos especular ainda, que o exercício influenciou positivamente nos níveis de atividade física e aptidão física-funcional o que pode estar relacionado com uma melhoria na percepção subjetiva do medo de cair e proficiência nas atividades cotidianas. A melhoria do desempenho físico parece igualmente ter influenciado nas atitudes em relação ao envelhecimento, na autoestima global e auto-eficácia geral.

Embora não tenha avaliado diretamente o componente de interação social promovido por ambos os programas de exercícios, esse efeito paralelo pode ter exercido influência positiva na melhoria do bem-estar emocional e no estado de humor dos participantes, enquanto que o grupo controlo demostrou resultados negativos. Com base nos resultados dos nossos estudos transversais e tendo em conta que este estudo pode ser considerado um piloto, para as futuras intervenções podemos recomendar a extensão desse tipo de estudo para populações mais velhas de diferentes contextos (por exemplo, hospitalização, comunidade, vulnerabilidade social) e com amostras representativas. Além disso, um desenho longitudinal que analisa o comportamento para adesão ao exercício ao logo da vida, começando com amostras acima de 40 anos (adulto de meia-idade), pode produzir pistas sobre como o fenótipo da fragilidade física se desenvolve ao longo do tempo. Esta foi a recomendação máxima do Comitê Científico da Organização Mundial de Saúde sobre a Conferência Internacional sobre Fragilidade e Sarcopénia 2017 (Barcelona). No que concerne aos resultados dos estudos de intervenção podemos afirmar que o exercício, utilizado como uma terapia coadjuvante poderá ser combinado com outras terapias (i. e. suplementação alimentar, medicação) para potencializar seus efeitos benéficos sendo esse tipo de estratégia o futuro das intervenções em saúde pública.

Palavras-chave: Fragilidade física, idosos, exercício, bem-estar psicológico, sistema imunitário, hormonas do estresse, incapacidades, cognição, aptidão física-funcional.

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2mST	2-minute step test
30s-AC	30 seconds arm-curl test
30s-CS	30 second chair-and-stand test
8-UGT	8-foot up-and-go test
AAQ	Attitudes toward aging questionnaire
ACSM	American College of Sport Medicine Science
ADBT	Agility-dynamic balance test
ADL	Katz index of independence in activities of daily living
AMSTAR	A Measurement Tool to Assess Systematic Reviews
AUC	Area under the curve
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
BPM	Beat per minute
BST	Back stretch test
C-α	Cronbach's alpha
CCI	Charlson comorbidity index
CES-D	Center of Epidemiologic Studies on Depression
CHS	Nursing homes of social and health care support
CI	Confidence interval
COR	Cortisol
CRP	C-reactive protein
CSR	Chair sit-and-reach test
CME	Chair multimodal exercise
CSE	Chair muscle strength exercises
CY	Chair yoga type flexibility exercises
DHEA	Dehydroepiandrosterone
ES	Effect size
FCDEF-UC	Faculty of Sport science and physical education
FES	Falls efficacy scale
FS	Frailty syndrome

GC_{ne}	Control group non-exercising
GSES	General self efficacy scale
HFS	Happiness face scale
HGT	Hand grip test
HPA axis	Hypothalamic–pituitary–adrenal axis
HR	Heart rate
HRmax	Maximal heart rate
IADL	Lawton of independence in activities of daily living
ICR	Internal consistency reliability scores
IFN-γ	Interferon gamma
IgA	Immunoglobulin-A
IL-10	Interleukin 10
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
k	Cohen's kappa coefficient
K-S	Kolmogorov–Smirnov test with Lilliefors
Lys	Lysozyme
M±SD	Mean ± standard deviation
M1; 3	The first and third quartile in the bracket
MCI	Mild cognitive impairment
Mesh	Medical Subject Headings
MME	Chair-multimodal exercises
MMSE	Mini mental state examination
MNA	Mini-nutritional assessment
MN	Not menditoned
MU	Medication use
NFvsF	Non-frail *versus* frail
NFvsPF	Non-frail versus pre-frail
nRCT	Non-randomized controlled trials
PA	Physical activity
PF	Physical frailty
PhFi	Physical Fitness
PICOS	Patient, intervention, comparison, outcomes

PPR	Pattern Recognition Receptors
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO-HMECSI	Hormonal mediation of exercise on cognition, stress, and immunity project
PSE	Perceived effort scale
PSS	Perceived stress scale
PsyF	Psychological frailty
PwB	Psychological well-being
QA	Quality assessment
RCT	randomized controlled trials
ROC	Receiver operating characteristics analysis
RSES	Rosenberg self-esteem scale
SAM	sympathetic adrenomedullary system
SR	Systematic review
SRM	Systematic review with metanalysis
SRofR	Aystematic reviews of reviews
STROBE	Strengthening Reporting of Observational studies in Epidemiology
SWLS	Satisfaction with life scale
TNF-α	Tumour necrosis factor alpha
TSB	Tandem Balance Test
TT	Testosterone
Vs	Versus
α-amylase	Alpha amylase

CONTENTS

SECTION I

Initial considerations: Rationale, methodologies and state of art.

CHAPTER 1:

GENERAL INTRODUCTION

Authors:

Guilherme Eustáquio Furtado

José Pedro Ferreira

Ana Maria Teixeira

1.1 Background

The Frailty syndrome is a complex ageing expression determined by ontogenetic and phylogenetic factors (1). Biological and psychosocial chronic stress has been shown to have immuno-suppressive effects, to accelerate immunosenescence and to cause cumulative disorders in many physiological systems, resulting in a frail state. Sedentary life style also proves to be a powerful condition linked to frailty (2). The phenotype of frailty is characterized as a state related to an elderly person, in which reserve function across multiple physiologic domains declines, compromising the individuals' capacity to withstand stress, leading to institutionalization/hospitalization and death (3). In a recent approach, Fried and colleagues have developed a construct whose bases are the sarcopenia, negative energy balance and physical inactivity, called the "Frail Cycle" (4). They identified five dimensions in the construct, operationalized on five criteria to identify Physical Frailty (PF) and divide the population in three subgroups as know as non-frail, pre-frail and frail (1). Lately, epidemiological studies around the world reported that mental health and high comorbidities, have a powerful association with PF (5,6). Older individuals with advanced frailty, with or without cognitive impairment, have an end-of-life functional course marked by slowly progressive physical deterioration, with only a slight acceleration in the trajectory of functional loss as death approaches (3).

Similar to Portugal, the population of many parts of the world is getting older posing many serious problems but a relatively small number of good research studies to provide practical answers (7). Due to the medical advances and increased life expectancy European adults are reaching old age with more comorbidities, physical impairments and cognitive decline, and these several global health conditions are intrinsically related to PF condition in old people (8). Health is one of the most significant factors, associated with assessing psychosocial wellbeing and quality of life (9). Some findings revealed that the high scores of self-reported health are predictors of a better aging trajectory (10). This is specially true/relevant in advanced age, where health-related quality of life is recognised by a set of physical (long-term illness) and mental outcomes (depression), that impact on people's functional limitations, mobility difficulties, reflecting in an early physical and cognitive frail condition (11,12). Recently, longitudinal and cross-sectional studies reported that low immune function has a powerful association with PF (5). Immunosenescence is also a part of the aging process and is associated with an increase in autoimmune disorders, tumors or infectious disease (13). The mucosal immune system, including the upper respiratory tract, is considered as a first barrier to colonization by pathogenic agents, reducing the incidence of upper respiratory tract infections (URTI) in humans (14). During aging, for example, there is a decrease in salivary Immunoglobulin-A (IgA) and interferon gamma (IFN-γ) secretion which are also linked to higher URTI incidence (15).

Engaging in regular sports, exercise or systematic physical activity (PA) is known to protect against many factors associated with poor physical and psychological health and improves life expectancy. With an aging population on the rise, it is important to assess interventions and programs that may maintain mental-health and physical function and quality of life in late life (16). It is very important for public health and political decision-makers to identify the main factors associated with physical decline in older populations, which subsidize the creation of new methods of adjuvants and co-adjuvants therapies (17,18). Looking at Fried's PF construct, their independent components share biopsychological «commonalities» that can be explained by studying the biochemical mechanisms, with exercise being a "key-factor" in the study of these relationships (19,20).

The impact of exercise-mediation on independent frailty components such as muscle hand-grip strength, gait speed, and subjective perception of vigour to conduct day-to-day tasks is well tested and understood (21,22). However, there are some factors that may be influential in this positive exercise mediator effect on the physical functioning, such as positive changes in hormonal balance and in mood states (23,24). Regular exercise (RE) has been shown to have positive effects on several factors related to PFS (e.g. improve immunity, prevent/attenuate chronic diseases and ameliorate cognitive functions), because of its potential effects on biological mediation and their positive impact on psychosocial health outcomes (23,25). RE may have the largest positive effect on older women who have low levels of sex steroids after menopause and that at the same time increase the risk for cardiovascular disease and dementia (26). The type of exercise seems to be crucial on increasing the aerobic capacity, but the evidence to support the involvement of multimodal, aerobic and muscle-strength resistance exercise programs in improving cognition and psychological well-being related to mental health are not yet clear (27), and their effectiveness should to be investigated.

The realization of dysregulated immune function and increased disease prevalence in the humans has been the motivation for interventions designed to improve immune functions in the older populations (28). Regarding the influence of exercise intensity on the immune function, data suggests that moderate RE may reduce URTI incidence and symptomatology (29). Also, the immune function is less impaired in highly conditioned versus sedentary old subjects. However, very few studies have looked at the effect of moderate RE on salivary IgA, and there are no sufficient evidence to support the effect of exercise on IFN-y and C-reactive protein (CRP) levels in old frail people (13). Some recent systematic review studies have identified a lack of studies that aimed to investigate the impact of regular exercise on the immune system of frail older individuals, opening some precedents for further investigations (24,30).

These same studies indicate that the biomarkers of pro and anti-inflammatory system of interleukin-6, TNF and CRP appear to be the most investigated markers (20,23). Exercise has also been shown to diminish the level of stress and anxiety and the risk of psychological diseases and emotional decline in old people (31). The responses of saliva flow rate and their composition during exercise are influenced by the sympathetic nervous system activity and the Hypothalamic–pituitary–adrenal axis (HPA axis), the salivary glands being enervated by both parasympathetic and sympathetic nerves (32). Recent studies have identified salivary α-amylase (α-Amy) as a potential marker of sympathetic activity while salivary cortisol (COR) seems to be a valid measure for the HPA axis activity (33). The adaptation to physical or psychological stress usually involves the activation of the hypothalamic-pituitary-adrenal axis (33). Normally it is hyper-activated and changes in diurnal or stress-induced secretion of the cortisol hormone could predispose older adults to negative health outcomes associated with the development of cognitive impairment (34). Cortisol levels are also affected by exercise, depending on its intensity and duration, however the role of alpha-amylase needs to be explored in relation of exercise modulation (35).

Cross-sectional studies have well established that low participation in RE is negatively associated with symptoms of anxiety and depression (36). A meta-analysis suggested that exercise can improve mental well-being of frail old people and that mental well-being in later life is changeable through exercise (37). Positive effects of exercise participation have been reported suggesting increases on older adult's self-efficacy, that might improve more positive perceptions of well-being and effectively enhance quality of life (38–41). Other studies revealed that physical activity has an effective contribution for improving mood states (42), Self-esteem (43,44) and satisfaction with life in older adults (45), all important indicators of mental health and well-being. Further evidence for these positive effects of exercise on mental health and well-being in old people have recently been provided as a guideline for exercise, offering a strong evidence base for their both preventive and therapeutic benefits (43,46).

In contrast to other studies, the current research was designed to investigate the hormonal mediation of RE in immune and neuroendocrine biomarkers; analyse the impact of RE in the decrease of several factors associated with PF namely, psychological well-being and cognitive impairments; analyse what type of exercise is more effective in improving immunity and psychological/mental health as well as increasing cognitive abilities. However, before testing the effect of the RE, it was necessary to test the interactions between independent components of PF and several geriatric global health factors, aimed to understand how exercise could have a more positive impact on these outcomes.

Specifically, the production of new knowledge of these relationships is necessary to understand the role of different type of exercises in mediating the biomarkers reported above; the effectiveness to improve immunity, prevent/attenuate chronic diseases and the PF condition. Aerobic exercise, for example, is thought to be most effective in improving cognitive and physical health, however, different types of exercise, frequency and intensity can trigger different adaptations or impacts. The role of resistance exercise using elastic band systems as a muscle-strength type training or the multimodal exercise method aimed to improve multifunctional skills in population aged 75 and over, for example, are less clear and its effectiveness should be investigated.

In this sense, the main goals of this study was to explore the association between the different dimensions of overall geriatric health and the frailty status in a cross-sectional sample of institutionalized old people, and subsequently, understand how the participation in different types of exercise programs was able to promote potential stimuli to provoking positive changes in biopsychological outcomes. In addition, the hypothesis that not type, but the specific exercise intensity is capable of attenuating and even reversing PF in frail and pre-frail cases of octogenarians was tested. Notwithstanding the central objectives, the primarily procedure of this research was to build a review of literature related to the aging process, frailty and exercise, aiming to organize important information in a robust state of the art and systematic review approach.

1.2 Research question

The present investigation focused on two distinct problems, that are interconnected or complementary. It is worth mentioning that as preliminary studies, a group of 3 systematic reviews studies are highlighted, aimed to present systematized and relevant information for the present thesis and answer some initial questions. In the first part of the study, the objective was to evaluate and characterize the population of older people living in an institutionalized regime, based on the prevalence of the PF, taking into account the following biopsychological dimensions: sociodemographic, global health, physical fitness and functional autonomy as well psychological/mental health and immune and hormonal biochemical blood and salivary markers. In this sense, the associations between these dimensions and PF indicators were explored, presented through a set of 4 independent studies. In this sense, the study question focused on the following question: 'Are there associations between PF and the different biopsychological geriatric health outcmes in institutionalized Portuguese older adults?

The second part of the study aimed to look at the modulatory responses caused by two different types of exercise programs on biopsychological outcomes of older frail adults on PF and how they differed. According to scientific evidence, the provision of systematic exercise programs and the actual knowledge of its benefits for this population can be further explored (47). In this sense, two different types of physical exercise programs were implemented, and their central objective was to submit the different groups of pre-frail and frail older individuals to either a program of muscular-strength or another characterized as a multicompetent exercise program, both with a total duration of 24 weeks and look at the psychological outcomes of the intervention.

1.3 General and specific objectives

The thesis is organized in 10 independent studies, summarized in three research questions and papers to be submitted to international peer review journals, each having its own general and specific goals listed bellow:

i) The first research question was to review the bibliography related to the frailty, their correlates and aging related-exercise programs. In this sense, the aim of this preliminary step is to organize the information in a systematic review with and without metanalysis;

ii) Study 1 was designed to examine the physical frailty sub-groups effect on cognitive status. Thus, two studies of systematic review with metanalysis were performed;

iii) Study 2 aims to investigate the effectiveness of regular exercise on frail adults, using a recent approach described as a systematic review of systematic reviews.

iv) Study 3 was carried out as a preliminary exercise-based research, aimed to explore the effects of yoga type-flexibility exercises on stress hormones and disabilities domains in older women;

v) The second research question aimed to examine the PF incidence, PF-associated variation of physical fitness, physical functioning and biochemical makers' parameters as well as psychological well-being and cognitive status in older people with PF. For this purpose, a cross-sectional design was completed;

vi) Study 4 was targeted at analysing the relationship between PF and adverse general health outcomes and assessed how the latter might explain the former;

vii) Study 5 was targeted to analyse the relationship between PF and physical fitness indicators and assessed how the latter might explain the former;

viii) Cross-sectional study 6 aimed to explore the relationships between the Fried's frailty model and functional disability outcomes in institutionalized-dwelling older women;

ix) Study 7 analysed the relationship between independent components of physical frailty and psychological well-being, and explored the contribution that these outcomes can exerted in the frail older women;

x) Cross-sectional study 8 aimed to explore the potential of adverse immune blood and salivary biochemical markers to explain frailty status and test the relationship with frailty independent components in institutionalized older women.

xii) The third research question aimed to describe the hypothetical effect of muscle-strength and multimodal exercise programs on biochemical makers, physical functioning and mental health domains in institutionalized frail and pre-frail women. A longitudinal experimental design was used to test the hypothetical positive impact of two different types of exercise programs;

xii) Based-intervention study 09 aimed to verify the effect of the multimodal and muscle-strength exercise programs on frailty independent components, functional disability and balance of sex steroid hormones in frail older women;

xiii) Study 10 aimed to investigate the impact of multimodal and muscle-strength exercise programs on pro and anti- inflammatory immunity markers and physical fitness in institutionalized older women;

xiv) Study 11 aimed to verify the modulator-effect of different types of exercise programs on health-psychological status and salivary stress hormones associated with mood, subjective well-being and self-perception status in frail-older women.

1.4 Study relevance

The reasons for the present study were based on the premise that up to the moment, there is a lack of research explaining the associations between physical frailty and some correlated health indicators, and also the potential effect of exercise as a complementary therapy for the treatment of physical frailty in institutionalized older Portuguese populations.

However, a small number of studies have investigated the profile of neuroendocrine and immunological makers, and possible associations with the PF variables that have been identified in the literature (73). This study will also contribute to determine the incidence of PF in older people living in social and health care support centers, an issue that may be of interest to local public health. In addition, the lack of information on exercise modulation responses in physiological systems is highlighted, since the integrated action of the aforementioned biomarkers modulated by different exercise programs may be revealing of events not observed in samples of pre-frail and frail elderly. This study is also justified by the need to analyze the chronic responses to the multi-component exercise (muscular endurance, flexibility and balance), compared to those of muscle strength (with elastic bands), since the circumscribed evidence in the literature focus mainly on the benefits of aerobic exercise (49–52).

1.5 Assumptions and limitations

The conception, experimental application and data processing of this research study was developed considering the existence of certain assumptions and also some study limitations, which are important to identify. The rational premises on which the problem was presented are based on the subsequent assumptions: i) given the reproducibility of the theory of physical frailty and its application in numerous longitudinal studies, the same will occur in the Portuguese population; ii) the same pattern of associations between PF and the different overall health dimensions associated with old people can be found; iii) the hypothetical positive effect of physical exercise as complementary therapy in the attenuation of the frail condition, can also cause positive impact in the other global health outcomes investigated. Regarding the study limitations, they are closely related to the assumptions. Based on this consideration, the following issues are addressed: i) low adherence of participants to different physical exercise programs; ii) the lack of authorization by the directors of the institutions to take the participants to the FCDEF-UC laboratory and consequent evaluation of anthropometric physical fitness assessment iii) the need to conduct exercise programs *in loco*, which narrowed the number of institutions able to participate in this study since not all had the physical space (exercise room) suitable for group exercise classes in each institution.

1.6 Organization of PhD thesis document

The three research questions outlined above, containing their respective objectives, served as a guiding thread for the development of the studies that, in a systematic and orderly manner, translated into a 'doctoral thesis' carried out through a model of chapter construction based on scientific articles or the Scandinavian model. This format has been an alternative for a methodical and consistent way of gathering and processing scientific information (53). However, despite the objectives of constructing a document of high scientific content and rigor, due care was taken that this document contemplates a high quality of information in the construction of its constituent parts, since it is the construction of a valid thesis to obtain the degree that it is proposed here. In this sense, this thesis is presented in the form of articles, divided into five sections and their respective chapters (studies).

The first section presents the chapters of General Introduction (e.g. objectives, research question, assumptions and directions for the future studies) and Materials and Methods (study design, methodologies, characteristics of participants and assessments) used in different phases of both cross-sectional and experimental studies, which comprise the “central axis” of this research purpose. Additionally, this part presented the organization of the PhD thesis document. The section II includes a sequence of three preliminary studies. In the study 01 (chapter 1), the metanalysis approach to examine the magnitude of effect size of differences on cognitive status comparing the three physical frailty subgroups was used. The study 2 presents the systematic reviews of systematic reviews regarding exercise-based interventions to reverse frailty condition, as a contemporary approach to design this type of review (chapter 2). Additionally, this section presented in the chapter 3 a short-term exercise-based intervention pilot study 3, aimed to explore the effects of yoga on disabilities, stress hormones and functional fitness.

In the studies of cross-sectional design (section III), the general aim was to investigate the relationship between frailty and each biopsychological dimension in the institutionalized older women sample. Chapter 4 aimed to investigate the relationship between the PF and adverse health outcomes indicators and to assess how the latter might explain the former. Chapter 5 aimed to investigate the relationship between the PF and physical-functional fitness indicators and to assess how the latter might predict the former (study 5). In chapter 6 of study 6, the focuses were on the contribution of the independent components of PF as indicators of functional disability. To examine the relationship between PF and psychological well-being, as well as assessing the contribution of different psychological domains to understand psychological of frailty trajectory were the purposes of this study 7 (Chapter 7). Finally, the study on Chapter 8 (study 8) aimed to explore the potential contribute of adverse blood and salivary biochemical immune markers to predict frailty status and the relationship between some markers and independents components of PF was tested.

In the three chapters of section IV, the exercise-based intervention was used to explore the modulated effect of two types of 24-weeks chair-based exercise programs (elastic-band muscle strength and multimodal exercises) on different global health indicators in institutionalized older women. In these studies, all outcomes measures were organized according to their biopsychological communalities, since the objective was to verify the impact of the exercise on different variables of each dimension simultaneously. The study of Chapter 8 comprises analyses of physical functioning dimension and included functional disability, sex steroid hormones, independent and combined components of physical frailty markers. Chapter 9 describes the analysis of exercise impact on psychological wellbeing (self-perception, mood state and subjective well-being) outcomes and stress system regulation hormones. Finally, in chapter 10, the central goal was to examine the exercise modulation effect on several blood and salivary immune markers were included in the statistical model, in addition to some markers of physical fitness associated with frailty. Finally, in chapter 11 of section V a global discussion and conclusion together with some directions for future research in the areas of exercise, frailty and their general global health correlates is presented. In the Final Considerations Section V, was presented the general discussion, conclusions, limitations and directions for the future studies. The objective was to make clear which were the main findings of the studies, establishing an interconnection between them. It is important to note that all the manuscripts presented in this thesis have a similar structure, according to the type of design (systematic reviews, cross-sectional and exercise-based interventions studies).

Taking into account the reference style of the last target journal where the different manuscripts were submitted, minor adjustments in the sections and subsections of the chapters were needed. However, in the topics of Section I and Section V, the Vancouver citation style formatting rules were adopted.

1.7 State of the art

The biopsychosocial condition in which we reach old age is different depending on the lifestyles maintained during the earlier stages of life (31). While some individuals manage to get there with full physical and mental capacities, others suffer unpleasant experiences, especially in later phases, often in consequence of many years of progressive physical and cognitive decline, ending in care facilities that condition the final course of their life's (54,55). Initiatives focused on an active lifestyle such as promoting the increase in the participation of the old population in programs aimed to reduce sedentary behaviors and increase levels of physical activity, seem to assume a key role in contemporary societies (56,57). Despite this, some doubts regarding the effectiveness of translating the guidelines of the main world organizations (which organize and justify directives for their implementation), in public policies that show positive results in a given population (58) remain.

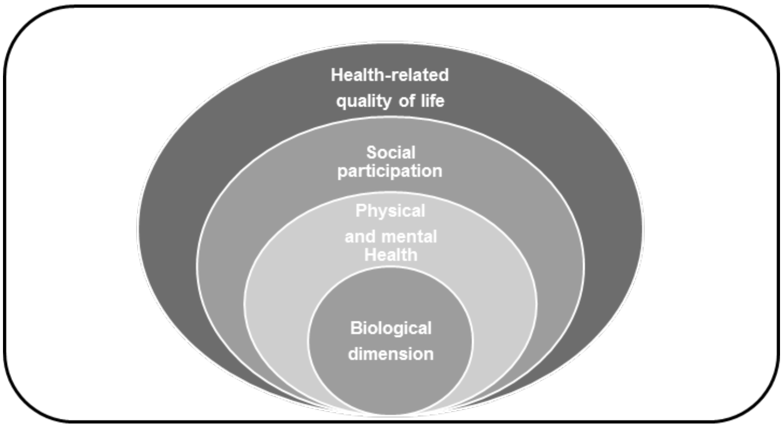

Figure 1.1 The ecologic model of health-related quality of life structural concept, adapted from the World Health Organization report, 2009.

In this context, the recognition of regular exercise and its positive modulating effect on various aspects of the overall health of the elderly (59), as well as their contribution in making older people more active and less dependent was recognized by the World Health Organization (WHO) through strong stand positions (60). According to the WHO, in 2025, the proportion between young and older adults will be similar, due to the decrease in fertility and the increase in life expectancy and this growth will happen faster than in any other age group (61).

For this reason, the exponential increase in research in the field of the aging process (62), seems to be centered on the challenge of maximizing the quality of life in the population above 60 years of age through access to health, leisure (see Figure 1.1), increased literacy, security, participation and social involvement (58,60,63). Nowadays, the improvement in the health-related quality of life model presented by WHO in the recent past years was increasingly more specific, being recently associated with the concept of dignified aging in the social participation domain (64). Currently, the WHO presents the "Active and Healthy Aging" concept, as a process to optimize opportunities to improve health-related quality of life when reaching adulthood (65).

FIGURE 1.2 show the biological model. This concept presents some bioecological aspects in a more specific way, directing the stakeholders to specific changes that will have a more decisive impact on the aging life-course and also, taking into account the specificities of each population as (66). In general, the term 'health' encompasses the promotion of physical, mental and psychosocial well-being (66). The term 'active' is understood as the increase in life expectancy associated with the promotion of active lifestyles, with access to physical/sport activities or similar body practices (56). On the other hand, the term 'participative' is added to this concept and is understood, in its broadest sense, by the offer of initiatives and opportunities for adherence to different population programs (i.e. health therapies, physical and sport activities, cultural and artistic manifestations) which can positively influence the general well-being through a diminished sedentary lifestyle, without exclusion of the over 65-year-old classified as an older-frail population (65).

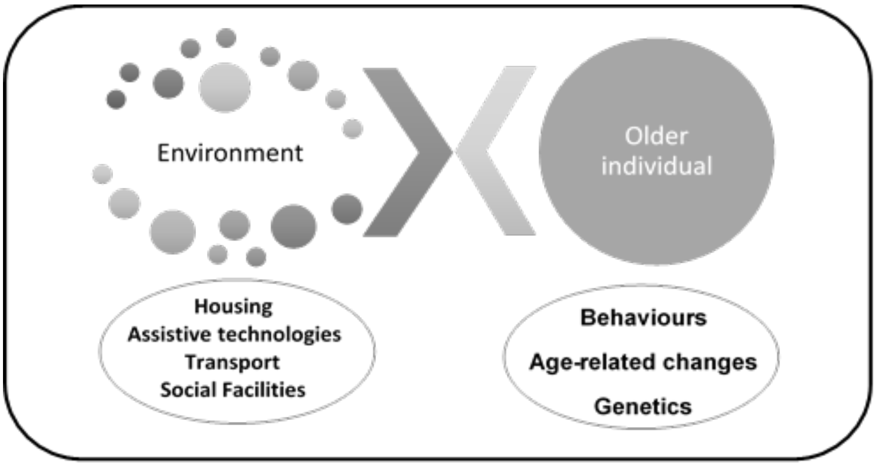

Figure 1.2 Bioecological model of the determinant factors in active and health aging policies, adapted from World Health Organization report, 2009.

1.7.1 The physical frailty syndrome

The frailty syndrome is a complex condition related to the aging process, characterized by the decline of multiple physiological systems, which in turn compromises the body's ability to resist to the deleterious effects of chronic stress (1,2). This phenotype, as thus treated by the specialists, had a strong influence on the biological theories of aging (67), that explain this process as an accumulation of harmful biochemical alterations, whose occurrence accompanies the course of ageing (14,68). The progressive losses of energy and functional reserves that occur in the body are a hallmark of this negative process (5). The vulnerability induced by these losses can lead to a weakening state, if he or she is exposed to more severe aggressions (2). From a frail state this individual tends to cycle through institutionalization (see Figure 1.3), intensive care and hospitalization, often followed by early death (69).

It was based on this theoretical influence, that Linda Fried and her collaborators (2001), through successive cross-sectional studies and the follow-up of samples of individuals over 50 years coming from a hospital context, have proposed a construct called the Physical Frailty Syndrome (PF) (70). Fried et al. (2001) argue that even though 'deregulation of hormonal systems is seen as an important age-related phylogenetic feature of PF theory, progressive loss of mass muscle, energy balance deregulation, and sedentary lifestyle are considered as central factors of frailty phenotype. The interconnection between these factors is currently corroborated in epidemiological studies in which different authors recognize these pillars as the central pathophysiological core of PF (4,7,8).

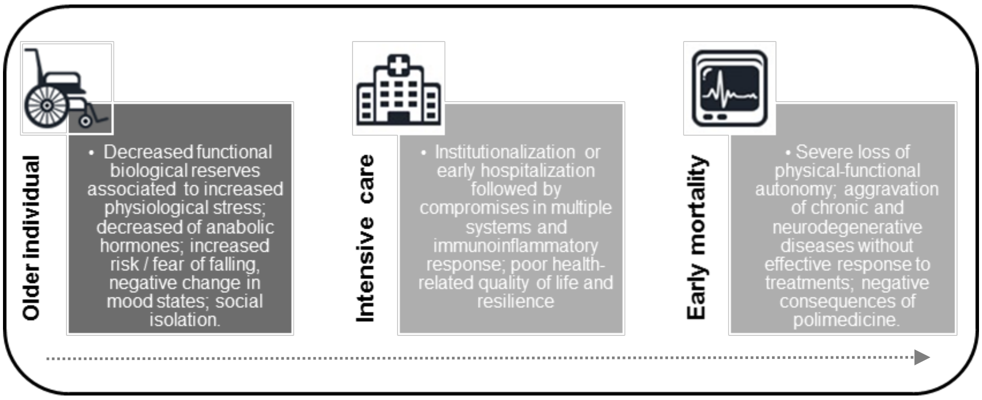

Figure 1.3 The physical frailty trajectory associated with several biopsychosocial declines, adapted from of Fried (2001).

In this sense, there is an high potential effect of PF on the acceleration of the already characteristic biological decline of elderly populations (55,71). In this way, five dimensions were identified, which translated into criteria for the operationalization of the PF phenotype (Figure 1.4), such as: muscular weakness, subjective perception of exhaustion, low levels of physical activity, unintentional weight loss and slow gait speed. The evaluation under these criteria makes it possible to classify the subjects as frail (three or more manifested criteria); pre-frail (one or two of the overt conditions) and non-frail, when none of the five criteria are meet (1). This construct has proved to be an excellent predictor of comorbidities and physical disabilities, with excellent internal validity to evaluate what it is proposed, proved in epidemiological studies carried out in several parts of the world. (7,18).

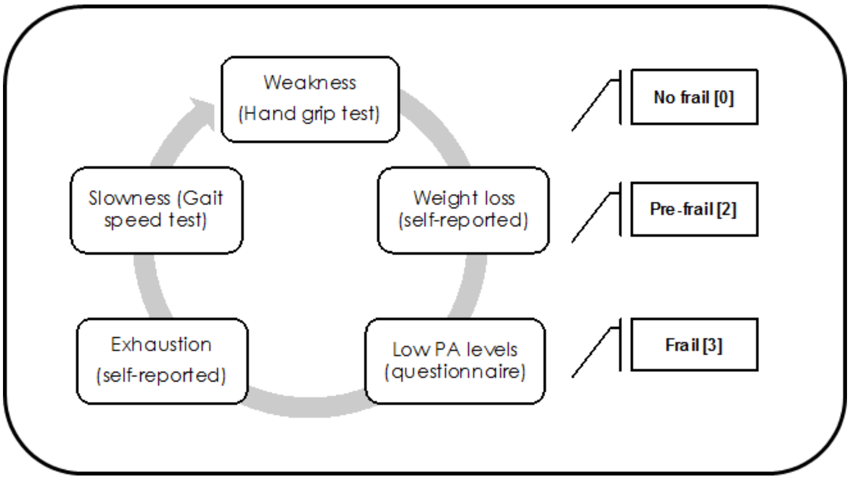

Figure 1.4 The five main components of the Fried's Physical Frailty phenotype and their negative scores to classify the frail sub-groups, adapted from (Fried, 2001).

1.7.2 Epidemiology of PF

Recent studies carried out in the European countries found similar values in the percentage of elderly with PF in hospital context, when compared to the original study of Fried (8). An incidence that ranges from 20% to 40% when pre-frail and frail individuals are added (73). Most of the resources spent on health care are concentrated in the frail elderly, who usually develop more severe clinical conditions (74). These represent on average 20 to 35% of the elderly population in contemporary societies (88). In the recent systematic revision present by Furtado and collaborators its possible to the prevalence of frailty and the most important is to observe the percentage of older individuals (pre-frail, n = 11.559) who can move to the frail condition. (74).

The economic impact of PF in the older populations is interrelated with the costs of care supported by several health systems in European countries (8). In Portugal, an average cost of 2.205,00 €/patient/year was reported versus a much higher value of 5.634,00 € in the case of severe health conditions including PF (75). In Germany, for example, similar results further provided evidence that older people with 4 or more positive FS components have a substantial increase in their health care costs (76).

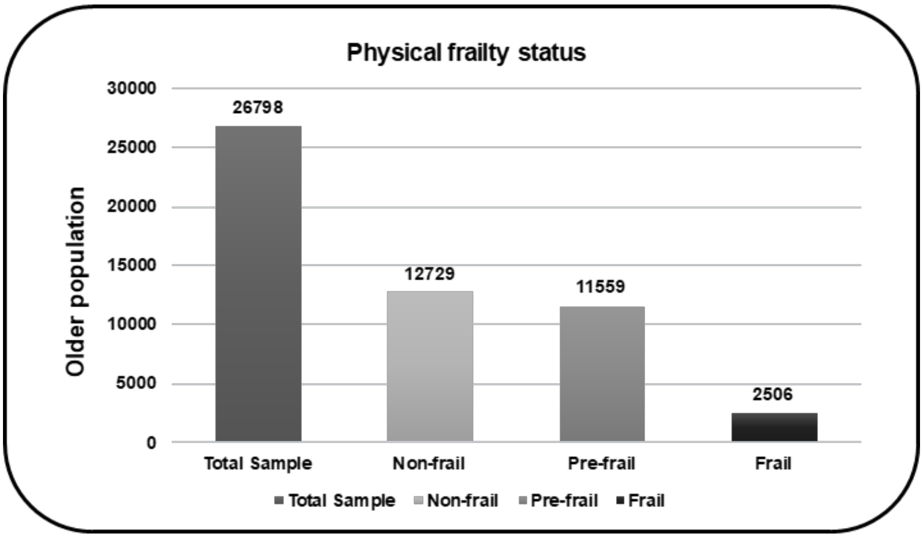

Figure 1.5 Prevalence of Physical Frailty based on epidemiological studies, in several countries adapted from systematic review study carried out by Furtado and colleagues, 2017.

In studies conducted with samples of elderly who live in institutionalized systems and who require social support and health care, the incidence of the frailty-trait seems to reach higher percentages, with higher prevalence in women, but with men dying earlier (77,78). In Portugal, the results of the first study recent published indicated that the prevalence of PF in elderly communities was 34.9% (n = 339 participants) and the incidence of PF among older (40.9%). women more frequent than in older men (32.5%) (79). This study also revealed that the PF in Portuguese elderly populations was associated with several psychosocial factors such as illiteracy, living within a family with some degree of dependence and living in unsuitable conditions. PF is considered by many authors as a 'phenotype' in a wide sense, since current research has identified other patterns associated with PF such as sarcopenia (80), severe decline in specialized cognitive functions (81), impairment of the immune and neuroendocrine systems (82,83) and the low cardiorespiratory reserves of muscular strength and endurance (84,85).

New studies involving a joint and multivariate analysis between PF and other global health indicators indicators, called frailty correlates, have also emerged (86,87). Some indicators that most correlate with frailty are: chronic cardiometabolic diseases makers (88); physical fitness (89,90); physical performance related to the decreased ability to perform everyday life activities (91); immunological and inflammatory parameters (82); the association between neuro-cognition, namely cognitive frailty (92,93); osteopenia and bone degeneration (94); sarcopenia and disturbance of the neuromuscular system (91); psychological well-being associated with mental health and other psychosocial factors, such as changes in emotional states and subjective well-being (95,96).

Recent findings report a direct relationship between frailty and negative changes in the neuroendocrine, immune and inflammatory systems (97,98). Imbalances in the neuroendocrine system appear to satisfactorily explain dementia, delirium, failures and cognitive absences, which may occur in individuals over 55 years of age (99). On the other hand, immunosenescence, characterized by the 'natural deterioration' of the immune system that arises with aging (5), is accelerated by the immunosuppressive effects of chronic psychological or biological stress (100), translating into autoimmune, infectious and degenerative diseases (14). All PF dimensions and their correlated domains have a 'feedback' relationship between them and can be explained by adverse biochemical events (2). When analyzed individually, biochemical markers (BM) have presented a weak relationship with the PF, so recent evidence reinforces the premise that certain BMs should be analyzed (101,102). BMs represent the 'biological passport' that allow an integrated understanding of adverse physiological events (103).

1.7.3 Impact of regular exercise on frail elders

An approach to the treatment, attenuation or reversal of the frail condition in older adults has gained some notoriety in recent years (19,20). Much has been discussed about the efficacy of different physical exercise programs as an adjunct therapy capable of promoting a positive impact not only on the independent components of frailty but on their correlated domains (104–106). Evidence indicates that PF-related and regular exercise research may be a 'key factor' in the study of these associations because of the important role played by PE in neuroendocrine, immune and hormonal modulation of BM (49,107). The aging process does not affect the immune and neuroendocrine system uniformly, and there is a high degree of individual variability that may be associated with confounding factors. These factors have the potential to either confound data interpretation or contribute to an interaction between different types of exercise and immune function, or both (105,108–110).

However, recently findings showed that participation in RE may induce a 'cascade' of cellular reactions, capable of promoting angiogenesis, neurogenesis and synaptogenesis, and further delay immunosenescence (105,111). In addition, there is proven positive action in improving the quality of life related to emotional states, psychological well-being and gains in autonomy to perform daily tasks (23). However, scientific evidence points to different types of exercise causing distinct and specific responses in the different physiological systems in this type of population (13).

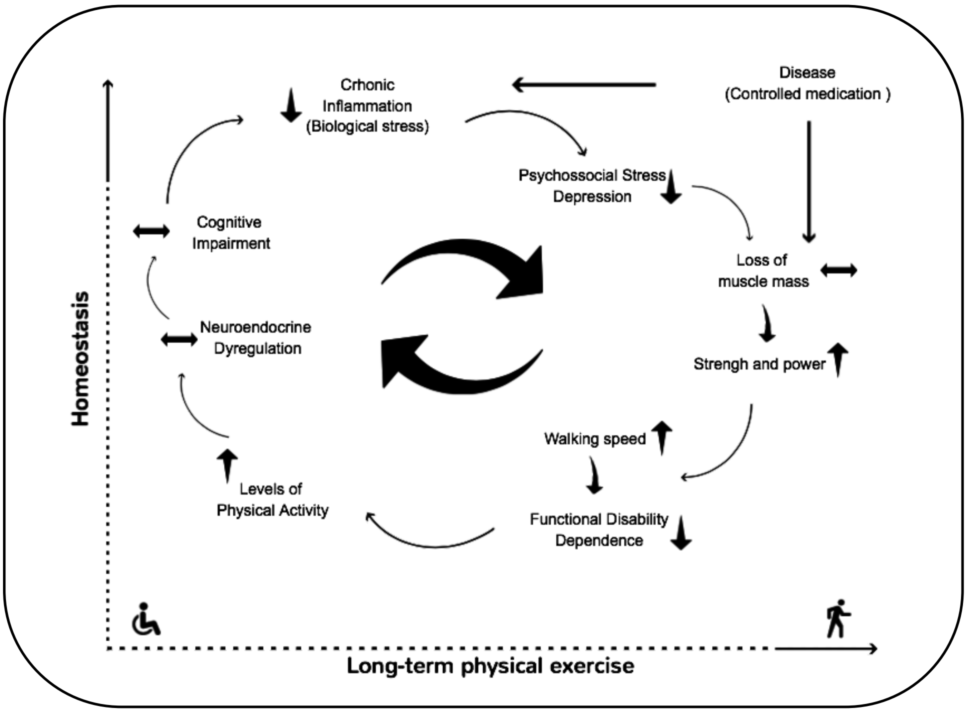

Figure 1.6 Hypothetical model of long term exercise-modulation effect to reverse physical frailty and stimulate changes in biopsychosocial correlates. Created from (112,113).

Current findings have demonstrated, for example, the beneficial effects of aerobic exercise on the increase of brain-derived neurotrophic factor (BDNF) in elderly people who practice regular exercise (83). BDNF is an important mediator of brain neuroplasticity, differentiation, neuronal growth, learning and memory (111). Its unregulated expression is related to diseases such as Parkinson's, Alzheimer's and mild cognitive impairment (MCI), this last one a clinical condition evidenced through cognitive testing (114). All these conditions or diseases can be diagnosed through easy-to-apply cognitive tests, that are also valid and capable of revealing a possible decline in executive function and memory, among others (115). However, MCI is often characterized as a condition or initial stage of more advanced cognitive impairments (116).

Recent findings consistently associate MCI with PF (114,117). Exercise can act as a positive mediator of cognitive functioning in individuals suffering from early dementia and mental disorders, these responses being attributed to a possible role of BDNF (92). Cognitive functions sensitive to early dementia and mental disorders shown to undergo positive changes in response to the effects of exercise were attributed to a possible neurogenic effect of BNDF (83). A possible regulatory effect of maintaining a satisfactory cognitive performance was also observed in studies with other markers such as testosterone and cortisol (Verdelho et al. 2011).

The efficacy of exercise in the prevention / attenuation of clinical manifestations of depression, stress and chronic anxiety, whose evidences are supported by biochemical mechanisms of a similar nature, was also shown (118). In addition, the evidence that associates physical and cognitive frailty with possible declines in the neuroendocrine system is increasingly robust. (103,117,119). A systematic review carried out by Hogervost et al. (2012) also found that different types of exercise may affect cognition and dementia risk to different levels; aerobic programs seem to be particularly effective while there is little evidence that flexibility exercises, such as yoga, can help cognition (120).

Dehydroepiandrosterone (DHEA), a sex hormone produced by the adrenal glands, appears as a strong predictor of PF (14). The reduction of DHEA, the decline of insulin-like growth factor (GH-IGF1), and testosterone, promote increased cortisol levels, which in turn increase immunosenescence, which is also related to cognitive decline, psychophysiological stress, cardiometabolic diseases and musculoskeletal disorders (13,33,121). This sequence of events counterproductive to the physiological system is also associated with the increased incidence of sarcopenia in the elderly, considered one of the central pathophysiological nuclei of PF (122). However, increased plasma DHEA concentration and cortisol / DHEA ratio balance are positive responses to moderate exercise (13,33).

Overweight/obesity in older people is also identified as a strong predictor of PF (80). Currently, researchers investigate the increased production of inflammatory cytokines in obese older patients associated with the risk of atherosclerosis and endothelial dysfunction (13); chronic inflammation (123); insulin resistance (124); and some mental disorders induced by the decrease of serotonin (125,126). The activation of powerful 'inflammatory cascades' caused by hormonal imbalance can also have serious consequences for the cardiorespiratory system (123). The term "inflammaging" is used to describe complex organic responses to various inflammatory stimuli mediated by high levels of pro-inflammatory cytokines (127), which appears to be triggered by chronic functional disorganization of the first line of immune defense (105,108,128).

The immune system of the mucosa, including the upper respiratory tract is considered the first barrier to colonization of pathogens (35,129). The reduction of episodes of upper respiratory tract infections (URTI) is related to the efficacy of these agents (13). The B lymphocytes, important components of the acquired and mucosal immunity and producers of immunoglobulins (including IgA), have their secretion affected by the immunosenescence process, which leads to an increase in the incidence of cardiorespiratory pathologies (130). Several studies suggested the practice of moderate intensity exercise as an agent for promoting improvements in IgA expression, indicated a reduction in the symptoms and incidence of URTI and a better immunological profile in well conditioned elderly individuals when compared to sedentary ones (105,131).

Studies examining the effects of moderate exercise for IgA expression were inconclusive as they did not find increased expression of important correlating biochemical markers such as interferon-gamma (IFN-γ) and salivary C-reactive protein (CRP), but point to important clues for the study of mechanisms adjacent to this process (132). Acute moderate exercise sessions have little impact on mucosal immunity, but prolonged and moderate/intense training may evoke decreases in sIgA secretion, compromising URTI (13). In addition to these measures in saliva, peripheral blood concentrations of inflammatory biomarkers like Interleukin-1 beta (IL-1β), Tumor Necrosis Factor (TNF-α) and Interleukin-6 (IL-6) have previously been found to be elevated in cases of mild cognitive impairment in comparison to healthy age-matched controls (133,134) Evidence shows that immunological and hormonal parameters are able to mediate the effects of exercise on mucosal immunity, psychological stress, cognitive improvement and risk of dementia in elderly who are regularly active (135) since regular exercise may provide an effective strategy in the treatment and prevention of associated disorders due to its anti-inflammatory benefits.

IFN-γ is a potent cytokine produced by T lymphocytes and Activated *“Natural Killers”* (NK) cells and exerts antiviral, antibacterial and anti-tumor effects (132,136). In a recent study on the mobilization of circulating NK cells and IFN-γ in response to exercise, the authors noted that the magnitude of the effort was a precisely controlled variable for desirable immune responses to occur (137). CPR, an important immune agent also quantified in this study, had its expression increased in acute response to exercise (138). But it seems to be the chronic moderate exercise that provides a homeostatic effect on the regulation of CRP, explained by the decrease in cytokine overproduction, improvements in endothelial function (137), decrease in insulin resistance, as well as a promising antioxidant effect (14,105).

Some authors have identified salivary alpha-amylase (α-amylase) as a potential marker of sympathetic activity and stress regulation associated with exercise (33). The α-amylase is an enzyme that catalyses the degradation of starch into maltose and can be important to host defence by inhibiting the adherence and growth of certain bacteria (139). It was already known for its' antibacterial effect, acting on the inhibition of adhesion, growth and proliferation of bacteria of the upper respiratory tract (35). However, chronic exercise responses of salivary α-amylase still need to be explored, as the existing literature has investigated the acute exercise-induced response in a more comprehensive way and used salivary cortisol as a preferred BM in most studies, that has similar and more recognized functions for evaluation of the response to biological stress (32,140,141).

Testosterone, the important sex steroid hormone is associated with musculoskeletal health, declines with aging and cognitive function loss, its levels reported to be diminished in patients with MCI, depression and chronic stress (121). Dehydroepiandrosterone (DHEA) is another steroid hormone involved in metabolism, produced mainly in the adrenal cortex, its functions linked with anti-glucocorticoid, anti-oxidant, anti-inflammatory and immunomodulatory effects (98). Recently, DHEA has been investigated for its relationship to mental and physical stress and also in psychological and behavioural disorders. The DHEA plasma concentration and the ratio Cortisol/DHEA have also been shown to increase with PA (123). Salivary markers may serve as potential non-invasive tools for evaluation of the relationship between the central nervous system and mucosal immunity following psychological and/or physical stress and how these may affect cognitive functions (32). Exercise could be a significant factor in ameliorating the deleterious effects of chronic stress but variables such as the type, intensity and frequency of exercise should be controlled and defined clearly in order to effectively reduce the stress burden.

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CHAPTER 2:

MATERIALS AND METHODS

Authors:

Guilherme Eustáquio Furtado

José Pedro Ferreira

Ana Maria Teixeira

2.1 Preliminary actions and ethics statement

This research protocol (RP) was integrated in the research project entitled "PRO-HMESCI: Hormonal mediation of exercise on cognition, stress and immunity", recently published (1). This RP was previously approved by the Faculty of Sport Sciences and Physical Education Ethical Committee - University of Coimbra (number reference: CE/FCDEF-UC/000202013). The RP takes into account the legal premises of the Portuguese Resolution [Art.º 4st; Law n. 12/2005, 1st series] on ethics in biomedical research with humans (2), and follows the guidelines for ethics in scientific experiments in exercise science research (3) and still, complied with the guidelines for research with human beings of the Helsinki Declaration (4).

The contact with the medical staff was established as one of the criteria to verify the eligibility of each subject to participate in the study and subsequently, to perform the exercise program. According to previous studies (1,5), the general procedures included: a) in the first visit, a presentation was made to all eligible participants and HSC staff, communicating the stages of this study; b) in the second visit, CHS or legal representative of participants was required to give a full informed consent (statement of responsibility) before beginning the research protocol, where the anonymization of data was performed.

2.2 Studies design (phases 1 and 2)

This research protocol was planned for approximately 13 months, involving a trained research team and it is built in different phases, according to the type of studies: cross-sectional and experimental (see Figure 2.1). The cross-sectional study (4 weeks' duration) consisted in the evaluation of older people (≥65 years old), living in different centres of heath care and social support (HCS), located in the city of Coimbra, Portugal. The participants were selected using a non-probalistic convenience sampling based on the geographical area of center region of Coimbra city. The experimental phase characterized as an intervention study with two different chair-based exercise programs, designed to assess the effect of strength/elastic band and multimodal interventions on biopsychological outcomes in frail e pre-frail individuals. Participants in these groups was attended a 45 minutes' exercise session, two-three times per week during 28 weeks and were extracted using the Physical Frailty status from the cross-sectional study design.

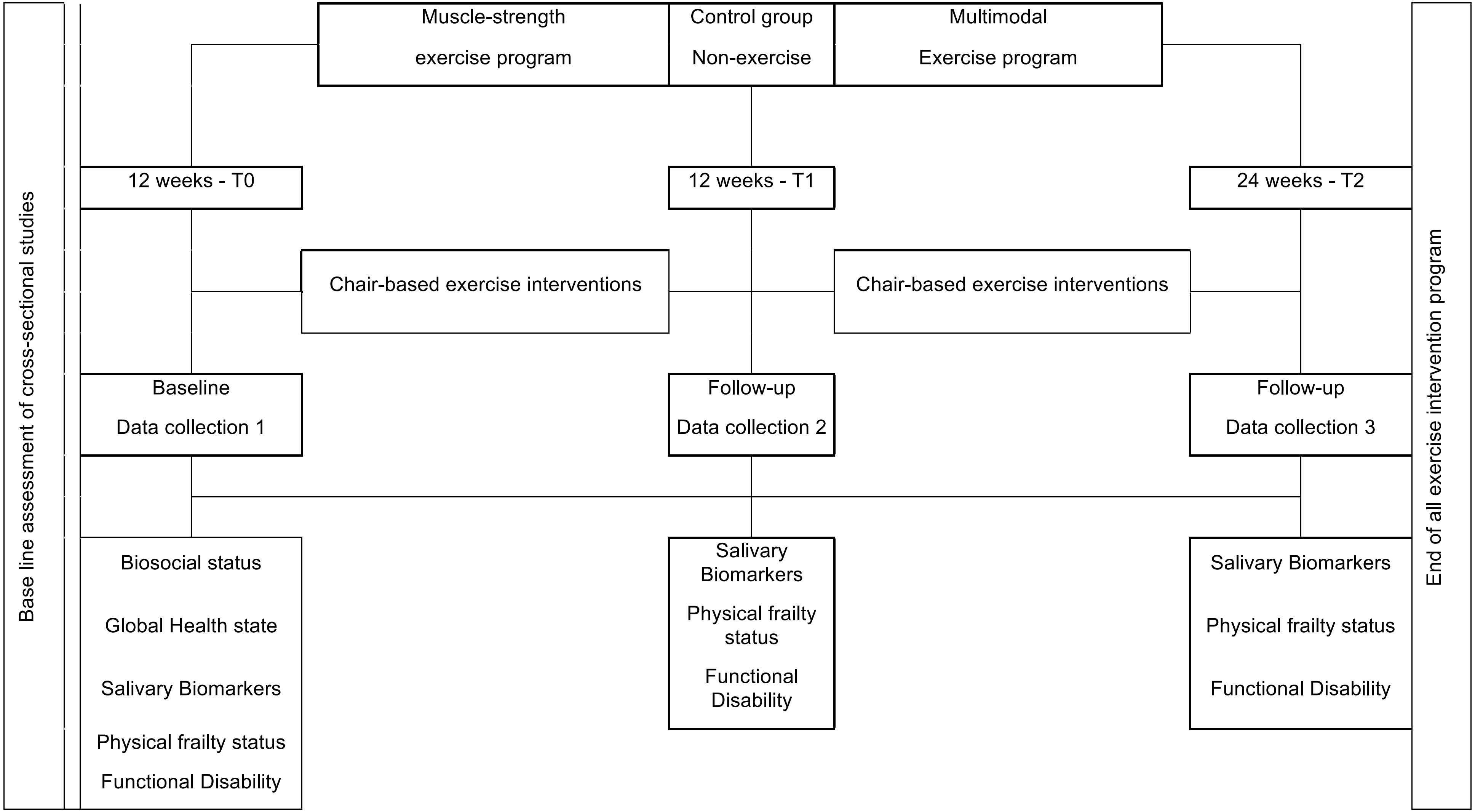

Figure 2.1 Timeline of the experimental study design .

2.3 Eligibility criteria

The description of the inclusion and exclusion criteria comprises the recruitment of the HCS and the elderly participants to take part of cross-sectional study and subsequent interest in participating in the different exercise programs.

i) inclusion criteria: a) ability to participate in a study with total duration of 12 months and encompassing three phases: cross-sectional study, intervention and detraining periods b) existence of an appropriate physical space to carry out the exercise sessions; c) required support of caregivers to assist with the elders' displacement to the exercise classes;

ii) Exclusion criteria: The following selection criteria for participants included was adopted to select the HCS participants: a) take a part in this study spontaneously; b) drug therapy and clinical condition controlled and updated (it must be stable and enable participation in the exercise classes as decided by local medical staff); c) not completing the '8-foot-up and go test' in the maximum time of 50 seconds. According to previous studies with samples of institutionalized elderly, scores above this value indicate severe disability/mobility dependence (6); d) no involvement in other structured exercise programs; e) no presence of any type of health condition that could prevent testing of functional autonomy such as severe or no controlled cardiopathy, hypertension, uncontrolled asthmatic bronchitis, and any musculoskeletal conditions that might prevent testing (i.e., osteoarthritis, recent fractures), mental disorder, hearing and vision impairment, morbid obesity, or the use of medications that could cause high attention impairment; f) do not have alcohol abuse; to have a high score on the comorbidity Index, indicating a life expectancy under 2 years (7).

2.4 Sample size estimation

Calculation of sample size (SS) is an essential stage in the proposal of a research study and is crucial to infer with confidence that SS calculated are reflective of underlying population parameters (8). For different combinations of power and effect size (ES), the SS for both cross-sectional and experimental studies were computed with G*Power 3.1.9.2 (9). G*Power is a free software program for a variety of statistical tests currently accepted by the scientific community (10). For the cross-sectional study, a total of 140 participants were enrolled for subsequently analysis according the Fried of PFS protocol. The sample size has been calculated according to the following assumptions: a 40% of incidence of frail condition of previous cross sectional studies using institutionalized samples, with an $\alpha < 0.05$ and $\beta = 0.80$. Assuming that 5% (n = 32) can be lost during the data collection for any reasons (i.e. death, non-cooperation, migration, chronic disease), 136 participants would be necessary.

However, for each cross-sectional study, the power and ES was reported, taking into account the adjustment of each evaluated dimension. In the experimental study the sample size (SS) estimation was performed by considering the comparison of physical performance between frail-subgroups in frail subjects between pre- and post multicomponent exercise intervention. The SS was seen to range between 5 and 44. Previous publications have reported high ES (Cohen's *d*) for a combination score of physical fitness tests, up to 1.08 (11). Assuming a minimum power of 0.8 as acceptable and that we may realistically but conservatively, expect the ES to be at least 0.7 [moderate to robust], the SS of the study should be 19 per group. Furthermore, assuming a dropout rate of 30% (12), the SS increases to 25 per arm, in total of a n = 75 participants.

2.5 Participants recruitment

In the first stage of recruitment, 10 eligible CSHS were randomly selected (see Figure 2.2). The primary recruitment strategy was based on information provided to the potential participants by the medical professionals from each CHS, combined with clinical primary outcomes information. The initial sample of cross-sectional study consisted of 305 institutionalized-dwelling individuals. Based on the medical staff recommendations, 52 individuals (14,6%) were excluded: i) severe clinical condition that does not allow one to get out of bed (n = 33); ii) morbid obesity (n = 8); iii) use of medications that could cause attention reduction (n=11).

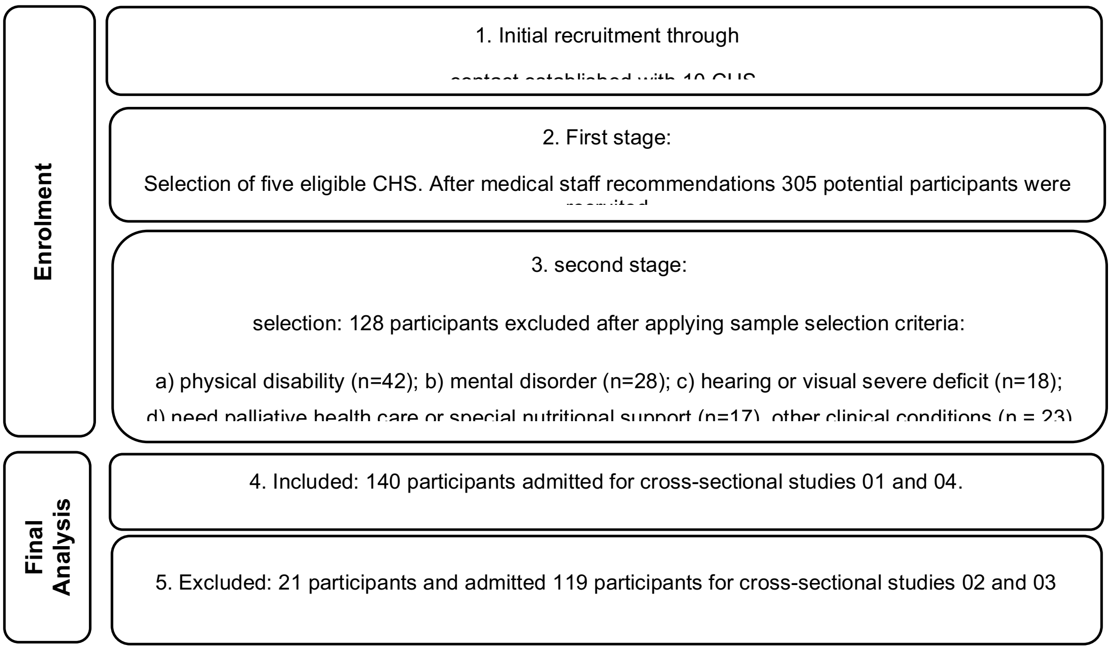

Figure 2.2 Flowchart of cross-sectional study design.

A total of 74 subjects failed to meet sample selection criteria as follows: i) physical impairment associated with musculoskeletal disorders and joint or muscle pain in the performance of tests (n = 34), ii) established diagnosis of early-stage dementia or other mental disorders (n = 9); iii) severe impairment of hearing or visual functions that made it impossible to perform all tests (n = 13); iv) need of palliative health care or special nutritional support, (n = 4); participants who dropped out when applying the tests (n = 14). In this phase, 39 participants also refused to participate a few minutes before data collection.

A total of 140 women were included in the cross-sectional studies 01 and 04. In studies 02, 03 and 04 119 participants were included, and because in the final analysis it was possible to identify poor data quality, dropouts, non-conclusion of psychometric rate scales and other issues, data of 21 participants were futher excluded. The Strengthening the Reporting of Observational Studies in Epidemiology Statement (STROBE) extension for trials has been used to design the cross-sectional study (13).

After defining the number of participants for the experimental studies, the Consolidated Standards of Reporting Trials statement extension (CONSORT) has been used to design the experimental study (14). To guarantee equal distribution [1:1:1] and the non-influence of the researchers in the assignment of the groups, a simple allocation technique, distributing the participants into 3 arms: chair-based multimodal exercise (CME), chair-based muscle-strength elastic band exercises (CSE) and non-exercise control group (GC_{ne}). Of the 75 participants selected for the experimental study, a total of 09 participants withdrew their willingness to participate before or immediately after the beginning of the study for different reasons and 3 participants were excluded from analyses due to low exercise adherence. None of the drop-outs left the intervention because of injuries or adverse responses to the intervention. Finally, a total of 59 participants of CME (n = 24), CSE (n = 18) and CG_{ne} (n =17) completed the 28 weeks' study (see Figure 2.3).

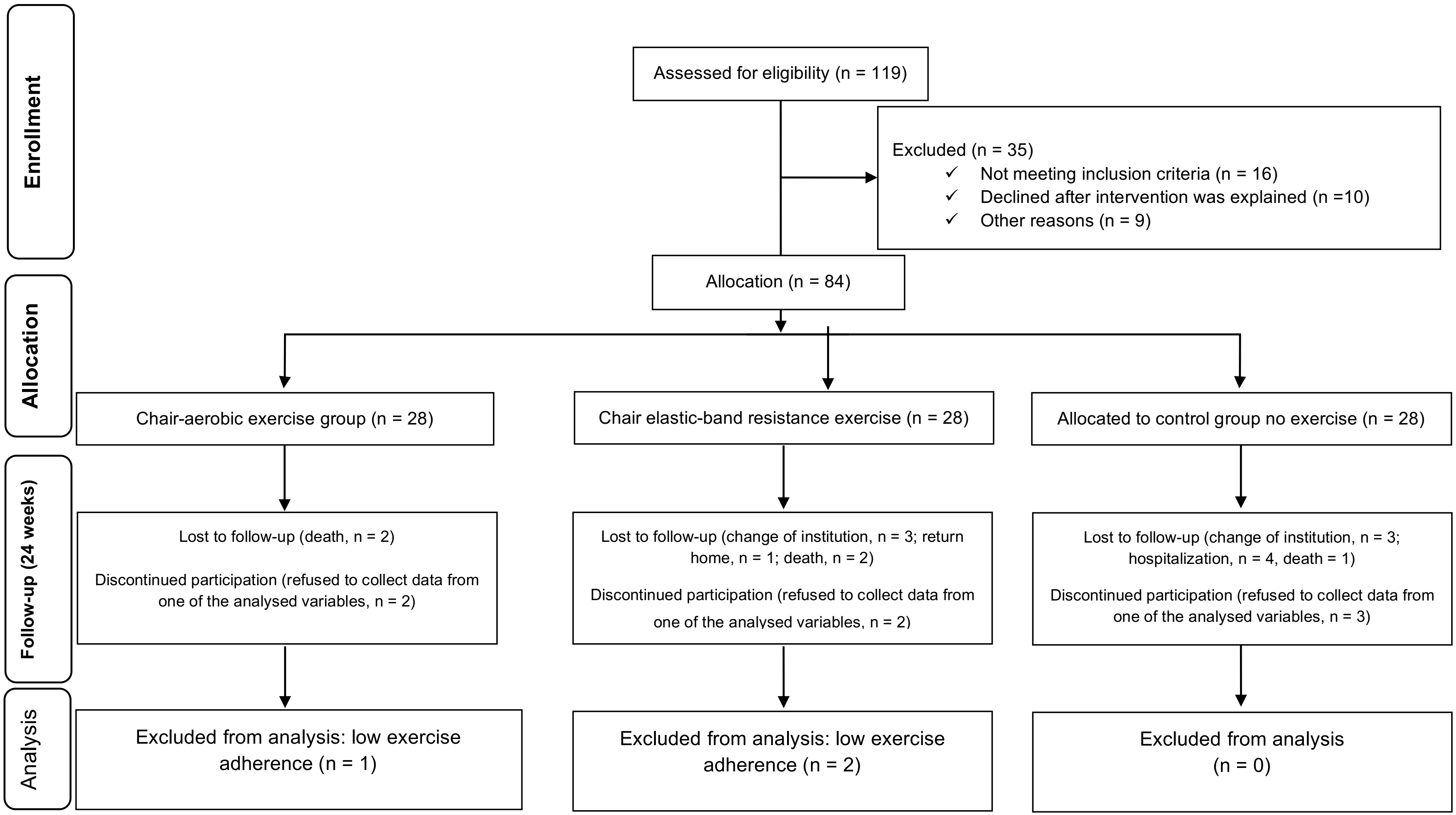

Figure 2.3 Flowchart of the intervention study design.

2.6 Data collection procedures

Firstly, the assessment of the cross-sectional study 01 and the extraction of participants for experimental study 02 were made. In the experimental design, 3-time points of data collection were applied. In agreement the research methods already described in a recent reports (1,5), all primary and secondary outcomes measures were collected at baseline following a specific order. Assessment measures were organized by the main investigator, applied by specialists and co-investigators of the research team and also, these were completed on different days respecting the motivation of the participants, interrupting the test, and continuing on another day if they felt tired or uncomfortable.

All baseline data collection was obtained between March and June 2015, during the morning (09:00 to 11:30 am). To minimize methodological inconsistencies, the same variable was always measured by the same member of the research team in all subjects. The quality of data was analysed in a pilot study and was reported for each physical measure through scores of internal consistency reliability (ICR). Table 2.1 and Table 2.2 presented the ICR scores for each variable in their respective dimension. The time-point for all outcomes measures were the first collected at baseline, after 14 and 28 weeks of exercise intervention period. Some variables of Biosocial and global health status were included just in the baseline assessment.

2.7 Primary outcomes

The physical frailty protocol characterizes as a primary outcome, however, biosocial, anthropometric and global health status were also considered.

2.7.1 Physical frailty protocol

Based on the scientific rationale explained by Fried and colleagues, a phenotype of frailty was proposed to include the several health domains and important co-variates associated to the frail condition (15). However, in the final characterization of the Fried's frailty Phenotype, taking into account the most important five elements in the construct which operationalized on five criteria to identify the Physical frailty construct, divide the population in non-frail, pre-frail and frailty older individuals. The prevalence of the independent components of PF was calculated, as well as the presence of each one of the five components of the Fried of PF criteria. The positive evaluation in one or two criteria classified the participants as pre-frail, in three or more as frail and as non-frail when the subject had none of the five PF components (15). The following five components of PF were assessed:

i) Weight Loss: assessed by self-reporting unintentional weight loss of four kilograms or more in the last six months, for both sexes. In addition, this measure was validated by medical records over one year assessed in the HCS; ii) Self-Reported Exhaustion: evaluated by negative concordance of questions number 7 (*"I felt that everything I did was an effort*") and 20 ("*I could not get "going"*), from the Centre of Epidemiologic Studies in Depression (CES-D) questionnaire (16). In the original study, Fried et. al (2001) explained that these were associations with the stage of exercise reached in graded exercise testing, as an indicator of VO_2 max and was predictive of cardiovascular disease; iii) weakness was analyzed using the handgrip strength test (HGT). This test uses a hand-held dynamometer (Lafayette Dynamometer, model 78010, United States) and strength is measured in kilograms. The subject holds the dynamometer in the hand to be tested, with the elbow by the side of the body. When ready, the subject squeezes the dynamometer with maximum isometric effort, which is maintained for 5 seconds. The best result of the two trials was used for scoring purposes (17). Participants who were unable to perform the HGT and those in the lowest 20% were categorized as positive. The cuttoff values for HGT ≥ 29 for male kg and ≥17 Kg for female were adopted; iv) slowness was measured using the 4.6 meters walking test (4.6-WT), which results are expressed in seconds and adjusted for gender and height. The best time of the two trials was used for final scoring. The cuttoff value of ≥ 7seconds for males and ≥6 seconds for females were adopted (18); v) low PA levels were assessed by the International Physical Activity Questionnaire (IPAQ) short version (19). The IPAQ short form asks about three specific types of activity undertaken in the three domains introduced above and time being sedentary. The specific types of activity that were assessed are walking, moderate-intensity activities and vigorous intensity activities; frequency (measured in days per week) and duration (time per day) are collected separately for each specific type of activity. The total volume and the number of day/sessions was included in the IPAQ analysis. There are three levels of PA suggested for classification: inactive, minimally active and a highly active. Participants classified with low levels of PA had a positive score for the FS condition (20).

Table 2.1 Reliability and validity measures of the three physical frailty components in a sample of n = 20 older women.

Frailty Phenotype outcomes	Unit	Internal consistency reliability
4,6 walking speed test	Seconds	0.80
IPAQ short version scale*	minutes per day	0.78
Hand Grip Test	kilos	0.84

Note: IPAQ = International Physical Activity Questionnaire.

2.7.2 Individual and Sociodemographic data

The following individual and sociodemographic data were assessed: i) Chronological age was assessed through the date at testing - date of birth and analyzed as a continuous variable. ii) Sex was classified in two categories, female or male; iii) Marital status was classified in four categories: single, married, widowed or divorced. iv) Level of education was classified according to the Portuguese educational system and analyzed as a continuous variable (21).

2.7.3 Anthropometric measures

The following anthropometric measurements were performed using following standardized procedures previous described (22): i) Body mass was determined using a portable scale (Seca®, model 770, Germany) with a precision of 0.1 kilograms; ii) Stature was determined using a portable stadiometer (Seca Bodymeter®, model 208, Germany) with a precision of 0.1 centimetres; ii) Body mass index (BMI) was calculated according to the usual formula [BMI = weight/height^2]; iii) Waist, arm and leg circumferences were measured using a retractable glass fibber tape measure (Hoechstmass-Rollfix®, Germany) with a precision of 0.1 centimetres.

Table 2.2 Reliability and validity measures of anthropometric indicators in a sample of n = 20 older women.

Anthropometric measurements	Unit	Internal consistency reliability
Stature	centimeters	0.87
Body mass	kilos	0.89
Waist circumference	centimeters	0.87
Hip circumference	centimeters	0.91

2.7.4 General health status

Overall general health indicators were evaluated through measures and instruments frequently used in epidemiological studies, due to their reliability and comparability with studies in other countries (23–29). The Charlson Comorbidity Index (CCI), Daily use medications (DUM), nutritional status, systolic (SBP) and diastolic blood pressure (DBP) were accessed in this study: i) CCI characterizes as a method of predicting mortality by classifying or weighting comorbid conditions. This instrument has been widely used by health researchers to measure burden of disease and has a weighted index based on 19 comorbid conditions. Its score can be combined/adjusted with age and gender to form a single index (continuous variable). One point for each additional 10 years is added to the initial score, that has been shown to predict one-year and 10-year mortality (7,30); ii) Daily medications used by the participants was assessed through question number six of the Mini Nutritional Assessment (MNA), that asks the participant if she takes more than 3 or less prescription drugs per day. Additionally, the number of medications-used was checked systematically through the institutional medical record of each participant, identifying and reporting polypharmacy (takes more than 3 prescription drugs per day) according to the Portuguese Classification System of Human Medicine (31); iii) Nutritional status was measured using the MNA. It consists of 18-item questionnaire that can be completed within 15 minutes and it includes four domains, namely anthropometric assessment, general health assessment, dietary assessment, and self-assessment of health and nutritional status. The maximum score is 30 points (pts), and classifies subjects as well-nourished (24 to 30 pts), having risk of malnutrition (17 to 23.5 pts) or as malnourished (score 17 pts and lower) (32); iv) To register SBP and DBP, the digital device OMRON (HEM-4011C-E®) model M1 Plus was used (33).

Table 2.3 Reliability and validity measures of global health indicators.

General health status	Present study	Original study
Mini nutritional assessment	0.74*	0.96¶
Rest Heart Rate	0.78**	NM
Systolic blood pressure	0.81**	NM
Diastolic blood pressure	0.80**	NM
Charlson comorbidity index	0.86**	1.2§
Medication use	NM	NM

Note: *The Kappa coefficient of study validation; ¶area under curve validation criteria; ** internal consistency reliability test applied in a sample of n = 20 older women (pilot study); §estimated relative risk of death calculated by hazard ratio, p<0.001; NA = not mentioned.

2.8 Secondary outcomes

Secondary measures comprised biochemical markers (blood and saliva samples), health psychological wellbeing (mood state, psychological well-being and self-perception), cognition status (global and specific areas) and physical functioning (functional disability and physical fitness related to health).

2.8.1 Salivary biomarkers analysis

The concentration of all salivary makers used were assessed by specific techniques, according to the manufacturer instructions for the differents kits used. (34). The collection times were always at the same time in the morning, in order to minimize the circadian effect seen with some of the markers under study (35). Saliva was collected by passive drool that consisted in the participant allowing saliva to collect on the floor of the mouth, then leaning forward and dribbles into a tube), for three minutes in high quality polypropylene vials to avoid problems with analyte retention or the introduction of contaminants that can interfere with the immunoassays. Prior to the saliva collection subjects will be asked to rinse their mouth with water to remove food residues 10 minutes before sample collection and to avoid: alcohol for 12 hours, dairy products for 20 minutes, foods with high sugar or acidity, or high caffeine content immediately before sample collection. All participants were instructed not to engage in extreme physical efforts in the 24 hours prior to the collection. The volumes measured, the flow rate calculated, and the samples stored at −20°Celsius until determination of the saliva markers proposed for this study. Immunoglobulin-A (IgA), testosterone (TT), lysozyme (Lys), cortisol (COR) and dehydroepiandrosterone (DHEA), interleukin-6 (IL-6) and interleukin-1β were analyzed by ELISA (34). Alpha-Amylase (α-amylase) was analysed by a kinetic-assay, according to standard procedures reported in previous studies (36). The reference values for all salivary markers were reported by the manufacturer and other relevant studies, in terms of sensitivity cut off value, absolute range in adults (34). In the case of α-amylase (37), IgA (38) and Lys (39), the reference values was obtained from other studies.

2.8.2 Blood biomarkers analysis

Venepuncture was used to collected blood samples by a registered nurse. The samples of blood were allocated into kEDTA and serum tubes. All participants were instructed not to engage in extreme physical efforts in the 24 hours prior to the collection. Determination of blood counts was done immediately after blood samples collection, using an automated haematology analyser Coulter AcT Diff [Beckman Coulter, USA]. The remaining blood were separated after centrifugation for the collection of plasma and serum and these stored in cryovials at −80°Celsus (C) until determination of the serum and plasma markers proposed for this study. The levels of the pro- and anti-inflammatory cytokines, such as interleukin-10 (IL-10), interferon gamma (IFN-γ), Tumour Necrosis Factor-alpha (TNF-α) and the neurotrophic factor Brain Derived Neurotrophic Factor (BDNF), were analyzed by ELISA kits according to the manufacturers' instructions [Invitrogen®, CA] (34). The cardiovascular risk marker C-reactive protein (CRP) was determined using the Horiba Medical Pentra C200 [Kyoto, Japan].

2.8.3 Physical fitness

The Senior Fitness Test battery developed by Rikli and Jones (1999) was used to access physical Fitness (PhFi). All PhFi tests were developed for adults aged over 60 years and are appropriate for both research and clinical purposes (40). Additionally, Tandem Stance Balance test (TSB) was used to evaluate static balance (Franchignoni, Tesio & Martino, 1998). Participants performed two repetitions for each physical test to familiarize themselves. For all the HrPf tests the best score of the two trials performed was used for final scoring purposes. When upper and lower members were tested in both sides (i.e. left and right) the best scoring side was the one considered for counting purposes.

The following PhFi measures were assessed: i) the lower body strength was determined with the '30 second's chair-and-stand test' (30s-CS), measuring the number of total full chair-stands that can be completed in 30 seconds with the arms folded across the chest; ii) The upper body strength was assessed with the '30 seconds arm-curl test' (30s-AC) that measures the total number of bicep curls that can be completed in 30 seconds, seated in a chair and holding a hand weight of 5 lbs (2.27 kg) for women. iii) For lower-body flexibility we used the 'chair sit-and-reach test' (CSR), from a sitting position at front of chair, with leg extended and hands reaching toward the toes, the number of inches (centimeters, + or -) between extended fingers and tip of toe were measured; iv) The upper-body flexibility (shoulder girdle) was measured using the 'back Stretch' test, that assesses the distance (centimeters, + or -) of approach between the middle fingers when one hand reaching over the shoulder and one up the middle of the back; v) Agility-dynamic balance test (ADB) was assessed using the eight-foot-up and go test, that assesses the time in seconds required for the participant to get up from a chair (seated position), walk as quickly as possible around either side of a cone placed 2,44 meters away from the chair, turn and sit back down in the seated position; vi) Aerobic resistance was measured through the "2-minutes step test" (2m-ST), that consisted of the number of full steps the subject completed in two minutes performing a stationary gait, with one hand resting on the wall and raising each knee to a midway point between the kneecap and iliac crest. Score is the number of times the right knee reaches the required height (Rikli,& Jones, 2013). vii)The TSB consists of the participant maintaining the standing position with open eyes and one foot in front of the opposite foot for a maximum of 30 seconds (43).

Table 2.4 Reliability and validity measures of physical fitness tests in a sample of n = 20 older woman.

Physical Fitness Tests	Unit	Original study*	Present study*	Range of Reference values*
30 second's chair-and-stand test	reps per time	0.87	0.89	4 - 15
30 seconds arm-curl test'	reps per time	0.83	0.90	8 to17
Chair sit-and-reach test'	centimeters	0.80	0.89	-1.0 - +4.0
Back Stretch' test	centimeters	0.79	0.84	-8.0 - +1.0
Eight-foot-up and go test	seconds	0.79	0.80	7.1 – 11.5
Two-minutes step test"	steps per time	0.91	0.78	44 - 101

Note: *test-retest reliability; **internal consistency reliability; NA = not applicable; *Original study (minimum and maximum values from old women

2.8.4 Functional disability (FD)

The indicators of FD were organized in a test battery following the approach of Tomes and colleagues (2009), that proposes objective and subjective measures to access disability (44). The following PhFi measures were assessed: i) Katz Index of independence (ADL) index was used to asses' daily function. The ADL ranks adequacy of performance in 6 functions such as bathing, dressing, toileting, transferring (using transport), continence, and feeding (45). Subjects are scored yes or no for independence in each of all functions described in the questionnaire and after adding up the points, individuals were ranked. Participants who scored for each function as dependent score 1 point and independent scored 0 points (46,47). ADL scale is most efficiently used among older adults in a variety of care settings, when baseline measurements, taken when the subject is well, are associated to periodic or subsequent measures (46). Unlike the Lawton Instrumental Activities of Daily Living Scale, this instrument has its recommended use for old individuals with an living institutionalized living (48); ii) Fear of falling was measured using the Tinetti Falls Efficacy Scale (FES), assessing the possibility of falling during the performance of 10 activities through the questions that encourage the individuals to give a punctuation to this subjective perception of confidence ability to perform daily living task to evolved stability, dynamic and static balance skills. Each question is rated from 1 point (very confidence) to 10 (not confidence) and the per question rating are added to generate a summary total score. The scores range from 10 to 100 points with a lower score indicating a high self-efficacy or little fear of falling (49).

Table 2.5 Reliability and validity measures for each Functional disability scale.

Functional Disability Scales	Original study		Portuguese version	
	Author	**score**	**Author**	**score**
Falls efficacy scale	Tinetti et al., 1990	0.71*	Melo, 2009	0.88*
Katz of Independence ADL	Katz et al.,	0.87*	Sequeira, 2007	0.92**

Note: ADL: activities of daily living; values of Pearson correlation with other physical functioning measures; scores of Cronbach alpha; *internal consistency reliability.

2.8.5 Psychological well-being

The assessment of Psychological Well-being (PwB) was organized in a test battery that comprised the most import three domains of psychological well-being and closely linked to older ages, comprising mood state, self-perception and subjective emotional well-being (50). In addition, the PWB tests were chosen because they had been validated in the Portuguese population and were also described in the concept of Psychological of frailty defined previously (51). The following measures of PWB were assessed:

i) Cognitive status: The Mini-Mental State Examination (MMSE) was used to assess cognitive state (52). MMSE assesses five areas of cognition status: orientation, immediate recall, attention and calculation, delayed recall, and language (53). The MMSE was used to classify participants by cognitive profile as a category variable, according to the following cut off values: severe cognitive impairment 1 to 9 points; moderate cognitive impairment 10 to 18; mild cognitive impairment 19 to 24 points and normal cognitive status 25 to 30 points (54). The propose was to measure cognitive functions sensitive to early dementia and age-related cognitive decline. These functions have in earlier interventions also shown to respond and be sensitive to the effects of exercise in the elderly populations (55,56);

ii) Mood states: Depression was assessed using the Center for Epidemiologic Studies for Depression (CES-D) scale reflecting major facets of this state. The 20-items are given on a four-point Likert scale, using to rate how often (older people) over the past week they experienced symptoms associated with depression, such as restless sleep, poor appetite, and feeling lonely. Scores range between 0 and 60 in which the highest scores correlate with more depressive symptoms for the last week (16). The Perceived Stress Scale (PSS) is the most widely used instrument for assessing the perception of stress. It is a measure of the level to which situations in one’s life are appraised as stressful. Items were designed to tap how unpredictable, uncontrollable, and overloaded respondents find their lives. The scale also includes a number of direct queries about current levels of experienced stress. Seven out of the 14-items is considered negative and seven as positive. Final scores can vary from 14 to 70 points, a higher score indicating greater feelings of stress (57);

iii) Self-perception: The Rosenberg Self-esteem Scale (RSES) analyses global self-worth. A 10-item scale that measures global self-worth by measuring both positive and negative feelings about the self. The scale is believed to be uni-dimensional. All items are answered using a 4-point Likert scale format ranging from strongly agree to strongly disagree. The sum of all 10-item scores gives results between 10 and 40 points, where higher values represent higher levels of self-esteem (58). The General Self-Efficacy Scale (GSES) was used to assess optimistic self-beliefs related to efficacy to cope with a variety of difficult demands in life. This is a 10-item scale and all items are answered using a 4-point Likert scale format ranging from strongly agree to strongly disagree. Responses sum up to a composite score with a range from 10 to 40 points, where higher values represent higher levels of GSES (59). The Attitudes to Aging Questionnaire (AAQ) was used to assess attitudes toward the ageing process as a personal experience from the perspective of older people. The 24-item scale (total scores range from 8 to 40 points) incorporates the concepts of both losses and gains with ageing. Factor analysis found three distinct subscales: Psychosocial Loss, Physical Change, and Psychological Growth. The AAQ contains 24 items and. The higher the score the more positive the attitude towards one's own ageing process (60);

iv) Emotional well-being: The Satisfaction With Life Scale (SWLS) measures global cognitive judgments of satisfaction with one's life. The SWLS is recommended as a complement to scales that focus on psychopathology or emotional well-being because it assesses an individuals' conscious evaluative judgment of his or her life by using the person's own criteria. The 5-item scale results in scores between one to 35 points, with higher values representing higher levels of life's satisfaction (58). The Happiness Face Scale (HFS) consisted of a graphical scheme where for each face is assigned one letter, in which the letter A (seven points) is considered the maximum and the letter G, the minimum (one point). This scale was commonly used to evaluate the positive facet of subjective well-being. The participant has to identify with one of the faces, depending on his/her state of happiness (61).

Table 2.6 Scores of internal consistency reliability for each psychometric rate scale.

Psychometric rate scales	Original study*		Portuguese version*	
	Author	**score**	**Author**	**score**
CES-D	Radloff, 1977	0.85	Gonçalves & Fagulha, 2000	0.89
Perceived Stress	Cohen et al., 1983	0.78	Mota-Cardoso et al., 2002	0.86
Rosenberg Self-esteem	Rosenberg, 1965	0.90	Ferreira & Fox, 2007	0.85
General Self-Efficacy	Schwarzer Jerusalem	0.86	Nunes et al., 1999	0.75
Attitudes to Aging	Laidlaw et al., 2007	0.86	Silva et al., 2013	0.67
Satisfaction with life	Dienner et al., 1985	0.83	Laranjeira, 2009	0.89
Happiness face scale	Andrew & Withey, 1976	NA	N.A.	078**
Mini-mental state exam	Folsten et al., 1975	NA	Morgado et al., 2010	0.71

Note: CES-D: Center of Epidemiologic Studies for Depression; *internal consistency reliability; **score calculated from the pilot study.

2.9 Pilot study

In the first phase of the study, some initial procedures were adopted that are described in the following lines. As previously mentioned, a pilot data collection was carried out in the first four weeks, aiming at analysing the quality of data for each physical-functional fitness measures. At the same time, interviews, psychometrics scales, cognitive and functional tests were applied to check the subject's conditions and evaluate the methods of application of the study (1). In addition, an exploratory exercise-based intervention study was carried out, using the data of 14 weeks of the chair yoga-type flexibility intervention, characterized as a third arm of the complete study protocol in which this research project was inserted. The complete description of chair yoga method was presented in the next topic. Previously, a four weeks of exercise sessions was conducted with an exercise session per week aimed to test the chair-based method, subjective perceived exertion (PSE) of the participants and the use of heart rate monitors of the participants. The experimental-exercise classes had a duration of 30 minutes (pre-training, easy-level PSE = 4-5).

2.10 Description of exercise programs

The initial approach to the development of the exercises programs included the complete description of both programs, defining the types of exercise for each program, conducting literature review using key-terms related to the topics, consulting with other group class exercise experts and preparing of the final version of the different types of chair-based exercise program activities. The development of the chair-based exercise (CBE) group classes was conducted by specialists in exercise prescription for older populations. In first order, the method consisted of integrating the main guidelines of exercise prescription recommended by the American College of Sport Medicine Science (ACSM) for older adults (62–65) as well as recent guidelines for exercise prescription in groups, with the support of a chair were incorporated (66). In the CBE music was will not used during the sessions, since the objective was to test the influence of exercise in some mental health parameters and therapy of music alone (67), or combined with physical exercise can positively influence cognition parameters (68). All exercise programs have the similar characteristics in terms of systematization (i.e. number of weeks and sessions, time of session) but, different specificities (i.e. volume intensity, type of exercises). An instructor-to-participant ratio of 1:12 was adopted.

2.10.1 Chair-based exercise method

The CBE consists of systematized and gradual exercises performed with a chair for support that guarantees the individual's stability during the session, respecting individual limitations without discouraging individuals to reach beyond their limits (69). The CBE protocol was shown to be a suitable and appropriate method of exercise for inactive older adults (70). This method, combined with other exercise methods can vary in intensity from vigorous chair aerobic or resistance exercise designed to provide muscle conditioning and benefits for healthy adults to movement that concentrates in maintaining a basic level function for older-frail participants (70). Recent studies have demonstrated the effectiveness of multicomponent, yoga type flexibility and muscle-strength elastic band exercises programs combined with chair support in promoting beneficial changes on older individuals' general health status (56,70,71).

2.10.2 Multimodal exercise program

In order to establish a progressive endurance training program aimed to improve the walking-speed capacity, balance and other correlate motor skills, specific exercises were performed with a determined number of exercises, repetitions, sets/circuits, and other variables involved in this type of exercise program. Multimodal or multicomponent exercise (ME) programms encompassing conventional progressive strength-resistance training, flexibility, weight-bearing exercise and/or balance exercises have shown a good evidence to reduce risk factors for falls and fracture as well improve motor skills (63). This form of designing exercise program denotes an effective method to increase multiple musculoskeletal and functional performance measures in older adults with risk factors for falls and/or low bone mineral density (72).

According to ACSM based-evidence guidelines ME exercises is classified as a degree C (medium-low evidency) (73). However, recent studies have increasingly confirmed the efficacy of this type of program for the development of physical fitness and improvement of some cognitive abilities, especially in physically frail individuals or older populations with lower levels of physical activity (72,74,75).

Table 2.7 Overview of single session multimodal exercises program.

Multimodal exercise group class	**Total time: 50 minutes**				
Phase 1 warming-up:	5 minutes				
Mobilization and dynamic flexibility exercises	sets*	reps	Cadence	Rest	PSE
Sequence of joint and full body mobilization exercises	2	10	1:2	20”	1-3
Phase 2 main workout Multimodal circuit-training protocol exercises	35 minutes				
1. Walk around the gym-room during 2-3 minutes.	2-4	8-16	1:2	20-30”	3-5
2. Chair-based sit and reach + easy skipping	2-4	8-16	1:2	20-30”	3-5
3. Chair-based sit and reach + arms coordination	2-4	8-16	1:2	20-30”	3-5
4. Chair-based leg extension and overhead reach	2-4	8-16	1:2	20-30”	3-5
5. Mini-circuit coordination, balance, quickness, agility	2-4	8-16	1:2	20-30”	3-5
6. Chair-based skipping + standing rear leg extension	2-4	8-16	1:2	20-30”	3-5
7. Chair-based middle skipping + arms coordination	2-4	8-16	1:2	20-30”	3-5
8. Chair-based power skipping	2-4	8-16	1:2	20-30”	3-5
9. Walk around the gym-room during 2-3 minutes.	2-4	8-16	1:2	60-120”	3-5
Phase 3 cool-down: Full body relaxation exercises	5 minutes				
Sequence of joint and static stretching exercises	1	10	2:1	10”	1-2

Complementary to the ACSM guidelines, the CME was an used integrated exercises method, suggested by National Academy of Sport Medicine (NASM), in the form of physical fitness programs periodization (76). The NASM of optimum performance training model (OPT), is the way of describing how one should progress (as the PhiFi capacity improves) (stabilization, strength and power) and their respective 5 sub-phases. Each exercise session was performed with a pre-determined number of exercises (7-10), repetitions (6-12), sets (2-4), rhythm of execution (1:2) and active rest in the siting position between sets (20-30) seconds and active rest between circuits (90-180 seconds). Each session was conducted using a functional-circuit training protocol, that consisted in completing one set of each exercise in a full range of motion following two-three minutes of walking around the gym-room (77). When one circuit of exercises was complete, one begins the first exercise again for the next cycle. The exercise-types of body-weight strength, walking time route to work handedness, changes in direction, static and dynamic balance, coordination as well exercises with accessories (i.e. cones, floor makers) were included. During the first 14 weeks, the body weight workout executed in the set and reach position and simple walking exercises around the gym room were used to develop stabilization. In the lasting 14 weeks, the increase of exercise intensity was induced by inclusion of more difficult and complex exercises and challenges sequences, aimed to improve endurance and specific motor skills (i.e. time reaction, balance, coordination).

Exercise-intensity was indirectly calculated using the Karvonen´s formula to predict target heart rate (HR), with maximal (max) HR calculated using a specific formula for older population [HR_{max}= 207 (beats per minute, bpm) - 0.7 x chronological age] (78) and was monitored using heart rate monitors (Polar, RCX5®) randomly distributed among participants. A low to moderate intensity effort around 50-75% of maximum heart rate zone (HRz_{max}) values was attained as recommended by the ACSM (79). Additionally, intensity was measured through the modified BORG scale of perceived exertion (PSE), that consists of an arbitrary scale ranging from 0 to 10 points, with identical intervals and with reference to the quality of effort: (0) nothing at all; (1) very weak; (2) weak; (3) moderate; (4) somewhat strong; (5-6) strong; (7-9) very strong; (10) very, very strong (almost maximal). Each exercise class was divided into three parts: 5 minutes of warm-up and body mobilization (PSE = 1-3, HRz_{max} = 50-55%); 35 minutes of multimodal circuit exercises (PSE 3-6, HRz_{max} = 56-85%) and finally 5 minutes of stretching exercises targeted to encourage cool down (PSE 1-2, HRz_{max} = 45-50%).

2.10.3 Elastic-band muscle-strength exercise program

To create a progressive chair elastic-band muscle resistance exercise program (CSE), specific exercises were performed with a determined number of repetitions, time of rest and other variables evolved in this type of training. Elastic band (EB) is an alternative to traditional muscle strength exercises devices which reduces the risk of injury, is cheap and easily accessible (80), and allows individuals to perform a range of ergonomic movements and adjust the training intensity based on the rate of perceived exertion (81). According the ACSM evidence-based statement position, the systematic muscle-strength exercise has a evidence category A (73). Elastic Band are relatively inexpensive and provide a practical form of training that could be considered in programs designed for older adults with mobility limitations (82). A type of resistance exercises with dumbbells as well as EB system showed increased same electromyography amplitude and perceived loading with increasing resistance (83), Consequently, this type of training is increasingly indicated for populations that are in clinical and special conditions (84,85).

Table 2.8 Overview of single session chair-muscle strengh exercises program.

Chair muscle-strength exercise group class	Total time: 50 minutes				
	5 minutes				
Phase 1 Warming-up: Body mobilization and dynamic flexibility exercises	**sets***	**reps**	**Cadence**	**Rest**	**PSE**
	2	6	1:2	20”	1-3
Phase 2 Muscle-Strengthening Activity: Elastic-band exercises compound (bi-sets) protocol	35 minutes				
Sequence of exercise*					
1. Front squat (stand or chair)	2-3	10-15	2:3	30-45”	4-6
2. Unilateral hip flexion with chair	2-3	10-15	2:3	30-45”	4-6
3. Bench over Row (with flexion)	2-3	10-15	2:3	30-45”	4-6
4. Chest Press (stand or chair)	2-3	10-15	2:3	30-45”	4-6
5. Standing reverse Fly	2-3	10-15	2:3	30-45”	4-6
6. Spine Twist extension arm (oblique's)	2-3	10-15	2:3	30-45”	4-6
7. Shoulder Press/twist arm front position	2-3	10-15	2:3	30-45”	4-6
8. Frontal total raiser	2-3	10-15	2:3	30-45”	4-6
9. Biceps arm curl (stand or chair)	2-3	10-15	2:3	30-45”	4-6
10. Overhead Triceps extension	2-3	10-15	2:3	30-45”	4-6
Phase 3 cool-down: Body mobilization and static flexibility exercises	5 minutes				
	1	10	2:1	10”	1-2

A descriptive evaluation survey study aimed to developed a systematic exercise program for older adults using EB, involving 11 exercise professional experts and 20 older participants concluded that the EB program feasible, was manageable, and could be helpful to their health promotion (86). In our exercise program, the first three levels of the Thera Band elastic system (yellow, green and red color) were used [Thera Band®, Akron, Ohio, US] (87). An specific exercises were performed with a determined number of exercises (4-8), sets (2-3); repetitions (12-15), a cadence of repetitions execution in 2 seconds concentric and 3 seconds eccentric (2:3) and a passive rest in the sit position between sets (30-45 seconds). The details information regarding control of exercise-type, repetitions and other variables involved in the program varying across the time, respecting the different phases of training, as possible to show in Table 2.8 above. The macrocycle of CSE was also design based on OPT model by NASM (76).

Intensity was measured through the OMINI perceived extension scale (PSE), that consists of an arbitrary scale ranging from 0 to 10 points, with identical intervals and with reference to the quality of effort: (0) extremely easy; (1-2) easy; (3-5) somewhat easy, (6-7) somewhat-hard; (8) hard; (9-10) extremely-hard (88). During the first 14 weeks of periodization, participants developed their stabilization and endurance strength training program using an intensity somewhat easy (PSE = 3-5). To this effect, the level one (yellow colour) of EB were used. In the last 14 weeks, participants were encouraged to develop their resistance strength level increasing their intensity load perception somewhat to hard (PSE = 6-7), induced by changing the elastic-band levels to 2 and 3 (red and green colour).

The methodical organization of all CSE exercise sessions following a bi-set strength-exercise protocol, that consisted in completed two exercises involving the major muscle groups consecutively followed a rest period, performed in a full range of motion. In terms of control of effort during the CSE program, the goal of was to keep the intensity of the exercise activities between 1 to 7 in PSE levels. It was expected that the relationship with the real effort would be 55-80% of maximum heart-rate (64). For safety reasons, the participants of CSE were using heart rate monitors. The session was divided into three parts: 5 minutes of warm-up exercises for general body mobilization (PSE 1 to 3, HRz_{max} = 45-55%), 35 minutes of strength elastic-band exercises in PSE 4 to 7 (HRz_{max} = 56-75%) and finally, 5 minutes of cool-down stage, through easy-walking and static flexibility exercises for ´breath´ control, PSE 1 to 2 (HRz_{max} = 45-50%).

2.10.4 Yoga type flexibility

The creation of the chair-based yoga (CY) was based on the essential philosophy of Hatha Yoga and its āsanas, focusing on the flexibility benefits provided by them (89). The introduction of āsanas was made through a sequence of movements combined with breathing (90). This method allows the modification of postures itself and of how to "enter" and “leave" the postures, which simplifies working with limiting conditions in group classes with various levels of physical ability and can be reviewed according to the participant’s evolution (91). In this intervention program, exercises sequence was prepared cautiously and reviewed according to the participant’s evolution aiming to easily achieve moderate intensities in classes.

Participants of CY (n = 20) maintained a frequency of two-three times weekly. Each session had a maximum duration of 50 min divided into three parts: i) 10 min of warm-up, with standing or sitting exercises of joint mobilization and exercises to promote respiratory body awareness; ii) the standing or sitting practice of āsanas and postures sequences, with the duration of 30 min; iii) 10 min to cool down and relaxation, through sitting or lying respiratory body awareness exercises, localized massages, exercises for muscle relief and meditation and vocalization. Additionally, the methods of design of the exercise programs include the ACSM guidelines for stretching exercises prescriptions for older populations (79) (Table 2.9). The global exercise intensity was measured with heart rate monitors and it was expected that the real effort would 50-75% of maximum heart-rate (PSE = 4-6), the values recommended by the ACSM.

Table 2.9 Overview of single session chair-yoga type flexibility exercise program.

Chair yoga exercise group class	**Total time: 50 minutes**				
Phase 1 Warming-up: Joint mobilization and respiratory body awareness exercises	5 minutes				
	sets*	**reps**	**Cadence**	**Rest**	**PSE**
	1	10	**	**	1-3
Phase 2: Asanas exercise routine	30 minutes				
1. Seated Forward Bend" (*Paschimottanasana*)					4-5
2. "Butterfly" (*Baddha Konasana*)					4-5
3. "Seated Spinal Twist" (*Ardha Matsyendrasana*)					4-5
4. "Cow face pose" (*Gomukhasana*)					4-5
5. "Cat" (*Cakravakasana*)					4-5
6. "Child's Pose" (*Balasana*)					4-5
7. "Snake" *(Bhujangasana*)					4-5
8. "Child's Pose with arms extended" (*Utthita Balasana*)					4-5
9. "Side Bending Stretch" (*Tiryaka Tadasana*)					4-5
10. "Dorsal Torsion" (*Kati Chakrasana*)					4-5
Phase 3 cool-down: Body mobilization and static flexibility exercises	5 minutes				
	1	10	2:1	10"	1-2

Note: SoSp= Standing or sitting position **Cadence according breathing and rest in transition periods

2.10.5 Non-exercise control group

This group did not participate in any physical exercise intervention during the development of both exercise programs. However, they maintained their normal routines, which included a monthly agenda of artistic, cultural and other activities offered by the institutions.

2.10.6 Exercise engagement and masking

Exercise sessions were offered two-three times/week, during 24 weeks, in a total of 74 sessions. Entries for each participant were recorded in a specific data sheet and the percentage of exercise adherence to group classes was calculated individually through the total sum of participation and reported as the total percentage. When a participant has two consecutive absences, she was contacted to return to the exercise group classes. According to recent systematic review, many factors influenced the adherence to exercise in the elderly involved in a long term exercise program (12). Adherence rates were generally higher in supervised programs involving older participants, fluctuating between 58 to 86% (12). Based on this information, an adherence to the exercise program of 65%, was established as minimum for each participant to be included in the study. The physical exercise instructor did not not take part in data collection procedures. Precaution was taken to avoid interaction between individuals of the two exercing groups by staggering the classes schedule. Each team of teachers conducted the classes in their respective chair-exercise program, so that no possible influences would occur.

2.11 General statistical procedures

First of all, it is important to point out that the statistical analyzes used in this study were systematized for two study types: i) cross-sectional studies, which are epidemiological characteristics and therefore use statistical methods inherent to this area of knowledge; ii) intervention study design with exercise and controls, which used basically the repeated measures as a statistical method, depending on the intervention over time. The rigor in the statistical treatment of data produced in this type of study is justified when seeking accuracy and precision in the measurements (92). The sampling procedure used requires that the data analysis procedure considered in the calculation estimates the data weighting, either by the losses and / or the effect of the study design, to generate more accurate estimates of the studied phenomena (9). In this sense, it is quite obvious that the starting point is an exploration of the data, in order to verify its normality. From this first step, we determined that the most consistent was to report results and use of parametric and/or non-parametric statistical analysis, according to the nature of the data, and not taking into account the unsubstantiated premise that it is only the sample size that will determine the statistics to be used. The statistical direction used for each type of study is described above, depending on its design (see

Table 2.10).

Table 2.10 Statistical analysis presented in each study of PhD thesis.

Statistical analyses	Studies										
	1	2	3	4	5	6	7	8	9	10	11
Normality (Shapiro-Wilk or Kolmogorov)			x	x	x	x	x	x	x	x	x
Mean (standard deviation)	x	x	x	x	x	x	x	x	x	x	x
Median (1st and 3rd quartile)				x	x	x	x	x			
Correlation (Pearson or Spearman)			x	x	x	x	x	x			
Multiple regression analysis				x	x	x	x	x			
ROC analysis				x	x			x			
Collinearity (Nagelkerke R square test)				x	x	x	x	x			
Quantitative Comparison of T-student										x	x
Quantitative Comparison of ANOVA				x	x	x	x	x	x		
Qualitative comparison of Kruskal-Wallis				x	x	x	x	x			
Qualitative comparison of Chi-square				x	x	x	x	x			
Qualitative comparison of McNemar									x		
Bonferroni Post-Hoc test									x	x	x
Cochrane's Q Post-Hoc test									x		
Effect size of Eta-square									x		
Effect size of Cohens' d			x							x	x
Effect size of Phi									x		
Confidence intervals (CI:95%)				x	x	x	x	x	x	x	x
Chi-square	x										
Cochran's Q	x										
Higgin I	x										
squared (I^2)	x										
Tau square tests (T^2)	x										

It is important to mention that the preliminary study 01 used the meta-analysis (MA) as the statistical treatment. MA is a statistical technique current in several areas of health research, whereby all data from all available studies of something are combined, at times regardless of the quality of the data. The method is used by researchers to get a highest amount of statistical information, at times without worrying about distortion of the results (93). The standard MA treatment includes the calculation of the magnitude of effect of the differences (e.g. between treatments or time-points) or or magnitude of correlations (if applicable), using statistical tests such as tests of heterogeneity, effect size, publication bias and sub-group analysis (94). The details inherent to specific statistical procedures for all studies can be found in each article. To conduct the statistical analyzes, two programs were used: SPPS Package and R - Statistical Analysis Program. The Comprehensive Meta-Analyses Statistical Program was used to performed MA statistical treatment.

2.11.1 Cross sectional studies

The non-normality distribution observed in some study variables after the Shapiro-Wilk test statistical treatment, induced us to report them in the form of median, first and third quartiles, since this form is considered the most logical and rational by statistical specialists. However, the measures represented by their mean, standard deviation were used when the data were presented normality, as a described in each study. The comparison of the frailty subgroups according to the variables of interest for each study followed the assumption of normality. For the normal variables were used the repeated measures ANOVA or, if applicable, the non-parametric equivalent (Kruskal-Wallis test). The analysis of correlations between variables followed a similar rational. For the normal data we used the Pearson correlation analysis and for the non-normal distribution data we used the non-parametric (Sperman) equivalent test.

Regarding the use of multivariate analyses, which were a common endpoint for all cross-sectional studies, very specific assumptions were followed according to the interest for each group of variables in the different studies. Linear, multiple or logistic regression models were used, as well as some specific statistical resources for this type of analysis, based on other (empirical or statistical) assumptions, such as stepwise regression methods (which extract from the regression model those variables that don’t explain much the variance of the dependent variable over the independent (i.e. studies 3,4 and 6) or, for example, the hierarchical regression model (i.e. study 4), which takes into account the assumption that 'theoretically', a given dependent variable will explain better than the other variables introduced in the model the variance on the independent variable and this way, this variable must be introduced into the model separately.

In addition, a logistic regression following the Receiver Operating Curve (ROC) as an attractive statistical solution was used in the analysis of data in studies 01, 03 and 06. ROC is a graphical plot that illustrates the diagnostic ability of the binary classifier system when its discrimination threshold is varied. The type of statistical treatment is frequently used in epidemiological of health to choose the most appropriate cut-off for a specific test. This type of statistics, despite being used in a permissive way in cross-sectional studies, does not indicate prediction of factors contrary to what some studies point out. The real power of prediction when using this type of analysis is in Cohort studies or longitudinal studies (95). However, ROC analysis can be used to explore cross-sectional population data and estimate some statistical outcomes trough models performance assessment.

2.11.2 Intervention studies

In the exercise-based intervention studies we also used the principle of data assumption as the first statistical procedure to be taken into account. However, the use of logarithmic conversion or conversion to z-score, was a solution to better and more clearly treat some biological data that accounted for inter- and intra-individual variability but very likely for this type of studies and above all for some variables such as functional fitness (96). This way, we were allowed to use parametric comparative statistics to analyse the effect of exercise over time (T-test or repeated ANOVA measures). In order to demonstrate the results of exercise modulation on variables of different dimensions (i.e. psychological, biological, physiological), some principles described by Batterham and Hopkins (2006) and his colleagues were followed, which make it clear that the significance value often does not indicate what is clinically or biologically relevant to understand the real impact of exercise effect (97). For this effect, measurements of the effect size were used. In addition to the ES calculation, the Delta scores, which indicate the percentage of the change, were reported so that the joint analysis of these measures of magnitude of the effect, taken together, led to a more reasonable interpretation.

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SECTION II

Preliminary study: systematic reviews and a pilot study of exercise-intervention

CHAPTER 3 (STUDY 1):

PHYSICAL FRAILTY AND COGNITIVE STATUS OVER-60 AGE POPULATIONS: A SYSTEMATIC REVIEW WITH META-ANALYSIS**

Authors:

Guilherme Eustáquio Furtado

Adriana Caldo

Taís Rieping

Edith Filaire

Eef Hogervorst

Ana Maria Teixeira

José Pedro Ferreira

Furtado GE, Caldo A, Rieping T, Filaire E, Hogervorst E, Teixeira, AM, et al. Physical Frailty and cognitive status over-60 age populations: a systematic review with meta-analysis. Archives of Gerontology and Geriatrics [Internet]. 2018 Sep 1 [cited 2018 Jul 22];78:240–8. Available from: https://www.sciencedirect.com/science/article/pii/S0167494318301377 ; **Impact fator: 2.241.

3.1 Abstract

The aim of this meta-analysis was to analyse the magnitude of the effect-size of the cognitive status of populations over 60 years of age, when comparing nonfrail versus pre-frail and nonfrail versus frail subgroups. A systematic review of prospective studies published from 2000 to 2017 was completed in Medline, B-on, Ebsco, Ebsco Health, Scielo, ERIC, LILACS and Sport discus databases and observational, cohort and cross-sectional studies were selected. The Mini-Mental State Examination to screening cognitive status and the Fried phenotype for assess physical frailty state was used as clinical outcomes. After applying additional search criteria, 14 manuscripts (26798 old participants) were selected from an initial universe of 1681 identified. When comparing the scores of cognitive status of the participants who were non-frail (n = 12729, 47.4%) versus pre-frail (n = 11559, 43.2%) and non-frail versus frail (n = 2452, 9.4%) subgroups, significant statistical differences were found for both comparisons (M±SD =0.60, 95%CI: 0.50-0.62, p<0.001 and M±SD = 3.43, 95%CI: 2.26-4.60, p<0.001, respectively). It is clear that poor cognitive function is strongly closed associated with pre-frailty and frailty subgroups in older populations around the world.

Key-words: Frail older adults, geriatric assessment, mild cognitive impairment, mini-mental state exam.

3.2 Introduction

Increasing functional health status in older adults across the life has been given more attention in the last decade (WHO 2012), including both cognitive and physical functioning. Cognitive status refers to all fundamental mental skills that regulate humans' lifestyles, such as instrumental daily life activities and complex behaviours (Carlson et al. 2009). An older age has been shown to be a risk factor for early dementia and age-related cognitive decline in specific areas, such as episodic memory (Misiak et al. 2013), with a third to half of the older adults in Europe complaining of cognitive impairment (CI), a possible precursor of early dementia (Verdelho et al. 2011). Recently, studies have found that older people with lower physical function, called the Physical Frailty syndrome (PFS), were more likely to develop CI (Gray et al. 2013; Buchman & Bennett 2013). However, conversely, individuals with IC can also enter a spiral of early physical-functional decline, e.g. through engaging in less activity because they feel less secure and/or because a common co-factor (e.g. dementia pathology) driving both CI and apraxia (the inability to perform learned activities and routines) (Panza et al. 2015; Brigola et al. 2015; Ruan et al. 2015) .

PF is thought to be highly prevalent in old age, particularly in those with low education and those of low socioeconomic status (Guessous et al. 2014). According to Fried's model, the phenotype of clinical PF is characterized by a critical mass of three or more "core frail components" which are: i) weight loss>10 lbs in past year, ii) weak grip strength (lowest quintile), iii) exhaustion (by self-report), iv) slow gait speed (lowest quintile) and v) low physical activity (lowest quintile) (Fried et al. 2001). Likewise, Ensrud in 2007 identified the physical frailty phenotype as having the following components: i) diminished levels of physical activity ii) unintentional weight loss, iii) self-rated fatigue, as also identified by impaired hand grip strength and low performance in gait speed (Ensrud et al. 2007). While these criteria have mainly physical components, Campbell and Bucher (1997) measured PF by incorporating specific physical and cognitive tests, comprising i) grip strength, ii) chair stand, iii) sub-maximal treadmill performance, iv) 6 min walking test, v) static Balance Test, vi) body mass index (to assess weight loss), vii) arm muscle area (to assess sarcopenia, the muscle loss associated with frailty) but also viii) Mini-Mental State Examination (MMSE) to assess cognitive impairment (Marshal F. Folstein et al. 1975; Campbell & Buchner 1997). However, because of its ease of application, the Fried model has been widely disseminated in several studies around the world (Theou et al. 2015). For instance, according to some criteria, mental or cognitive impairment is a crucial factor for PF and this would need to be assessed using objective instruments (Panza et al. 2015).

On the other hand, PF may also be an early indicator for possible later dementia (Gray et al. 2013). One study showed that at post-mortem, Alzheimer Disease brain pathology was associated with PF both in people with and without dementia (Buchman et al. 2013). Epidemiological studies demonstrate the interconnection between physical frailty and cognitive performance. However, longitudinal studies show this relationship and the emergence of cognitive changes, cognitive impairment and dementia to be associated with an increased risk of frailty status in older populations. Some systematic reviews have been carried out in order to clarify this association (Panza et al. 2015; Brigola et al. 2015; Ruan et al. 2015). However, a recent review of cross-sectional data used meta-analysis, comparing the means scores of MMSE among pre-frail and frail sub-groups, but omitted the non frail group data (Furtado, Guilherme Eustáquio, Teixeira, Ana Maria, Ferreira 2017). The present paper, in order to complement this systematic review with metanalysis (SM) and to clarify the magnitude of effect size in mean cognitive status investigated frail, pre frail and non frail subgroups using the Fried of Physical Frailty Protocol.

3.3 Methods

This work followed a pre-determined and published protocol available in PROSPERO 2017: number registration CRD42017057360 (Furtado, Adriana Caldo, et al. 2017). The search was conducted in English language (published or in press) in the following databases: Medline, B-on, Ebsco, Ebsco Health, Scielo, ERIC, LILACS and Sportdiscus databases, with access made between December of 2016 and July of 2017, using the advanced meta-search option in which original articles of epidemiological studies of cross-sectional, observational, cohort and population-based published between 2000-2017. Key Medical Subject Headings (MeSH) and search indexed descriptors were used to refine the data search (Huang et al. 2011): ((("frail elderly" [MeSH Terms] OR "frail" [MeSH Terms]) AND "cognition" [MeSH Terms]) OR ([mild cognitive impairment]] AND "frail older adults" [MeSH Terms]) OR "frail older adults" [MeSH Terms] AND "[mini-mental State examination or MMSE]". Studies done in the last 17 years, with samples of people over 60 years of age of both genders, who were not hospitalized samples were selected. The data source strategy included also additional terms related to indexed descriptors such as 'Fried criteria', 'Fried Phenotype of Frailty' and 'Fried Phenotype'.

3.4 Central criteria of selected studies

The search was further limited by selecting articles including the Fried's model to assess frailty status and Mini-Mental State Examination (MMSE) to assess cognitive status. The PF Phenotype was developed by Linda Fried and collaborators (Fried et al. 2001). After consecutive studies on older adults samples, they identified five dimensions which translated into five criteria to operationalize PFS. Weight loss was assessed by self-reporting, targeting unintentional weight loss of four kilograms or more in the last six months or a loss of 5% of total body weight in the three months prior to the assessment date. Self report exhaustion was evaluated by negative concordance of questions number 7 and 20 of the Centre of Epidemiologic Studies in Depression scale. Weakness was analyzed using the handgrip strength test, adjusted for gender/body mass index. Slowness was measured using the 4.6 meters walking test, which results are expressed in seconds and adjusted for gender/height. Low PA levels were assessed using the Minnesota Questionnaire - short version. The positive evaluation in one or two negative criteria classified the participants as pre-frail, in three or more as frail and as non-frail or robust, when the subject had none of the FS five criteria (Fried et al. 2001).

The MMSE is an instrument composed by 30 questions, and is able to assess the cognitive profile based on the evaluation of six areas of cognition: orientation, immediate recall, attention, calculation, delayed recall, and language (Mungas 1991; Han et al. 2014). It is a continuous score, ranging from 0 to 30 points (pts) and according to the criteria established in several studies, the following cut-off values that classify individuals (categorical scores) on cognitive profiles are: a) severe cognitive impairment (from 1 to 9 pts); b) moderate cognitive impairment (10 to 18 pts) mild cognitive impairment (19 to 24 pts), d) normal cognitive status (25 pts and above) (M F Folstein et al. 1975).

3.5 Exclusion criteria

The exclusion criteria of the present study comprised the elimination of all articles that did not meet the initial selection criteria (include both MMSE and PF), had poorly defined dimensions, did not report MSSE scores as mean and standard deviation, examination of middle-aged adults was omitted. Extended or congress abstracts, systematic reviews, book chapters, letters to editor, short surveys, study protocols, and interventional studies were also excluded.

3.6 Data Extraction

The initial search to create the present study was carried out by two independent research assistants, who were trained in SM methods. Each research assistant performed the independent-blindly search and at the end of the work, the principal research was conducted a short briefing to assess the level of agreement of the search procedures. All titles and abstracts of identified articles were screened and the full-text articles were assessed for potential inclusion by the principal investigator and any conflicts that arose were reviewed until an agreement was reached. For the final selection of the articles we included all based-population studies, according to the FS subgroups non-frail, pre-frail and frail (as a categorical variable) as well as compare the mean scores of the MMSE results (as a continuous variable), according to the aforementioned subgroups.

3.7 Quality Assessment (QA)

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement for the organization of this study was followed(Panic et al. 2013). PRISMA describes the four stages (identification, screening, eligibility, final selection) needed to perform the search and selection of manuscripts under a SM, and feature the graphic option to draw a flowchart (Liberati et al. 2009). At the same time, the PRISMA presents the PICOS acronym ('patient, problem or population', 'intervention', 'comparison, control or comparison', 'outcomes'), which directs the refinement of the systematic search, making the process more effective (Panic et al. 2013). In addition to this method, we chose to use the Strengthening Reporting of Observational studies in Epidemiology (STROBE) Positioning Statement, that the characterization of each assessed item has been described in detail elsewhere (Malta et al. 2010).

This method consists of a checklist comprising 22 items, which characterizes a manuscript based on the quality assessment that it presents. In this study, we used a STROBE combined model of study designs, which is specifically assesses observational, epidemiological, population-based, cross-sectional or cohort studies (Abeysena 2011). After applying the above criteria we attributed to the total score of the 22 items a value of 100%. The purpose of this procedure was not to use an established cut-off point to enter/or not enter the meta-analysis. Instead, the percentage value was used to identify studies in which low quality assessment could interfere with the results of the SM.

3.8 Statistical Analysis

The results are expressed by calculating the values of the standardized mean and standard deviation (M±SD) differences in MMSE scores when comparing the subgroups of NFvsPF and NFvsF, as well as their respective variance, confidence intervals (CI:95%), the magnitude of the effect size and levels of statistical significance, which was set at $p \leq 0.05$ (Batterham & Hopkins 2006). The global M±SD of the studies included in this review were calculated based on the random effects model, including the assumption of heterogeneity of the studies and their participants. The risk of publication bias was assessed by the method of visual inspection method of the scatter plot generated by the Egger's intercept test (Egger et al. 1997). This graphic assumes a format of an 'inverted funnel plot' inserted by a midline, with analogue display of points representing the studies included in the graphical analysis (Sterne et al. 2001). Heterogeneity was measured using the Chi square, Cochran's Q, the Higgin I squared (I^2) and Tau square tests (T^2), assuming that a $T^2 > 1$ suggests presence of substantial statistical heterogeneity. In terms of I^2 test analysis, the percentage of the variance attributed to the heterogeneity of the study, ranges from low ($25\% < I^2 < 50\%$) to high ($I^2 > 75\%$)(Egger et al. 1997). If the Q test is statistically significant (set at $p < 0.05$) there is also evidence of heterogeneity. The SM was performed using the statistical program Comprehensive Meta-Analysis - Version 3.0 (Bax et al. 2007).

3.9 Results

3.9.1 Data search

Figure 3.1 shows the paths covered for final studies selection that were later included in the meta-analysis. The initial search identified 1681 potentially eligible papers. After excluding articles following a review of titles and abstracts, replication and others reasons, such as systematic reviews and intervention studies, 149 full-text articles were examined in the screening stage. After applying the central criteria to the studies, 56 papers were advanced for the eligibility phase. From the eligibility stage, criteria such as presentation of MMSE scores as a categorical variable and treating the physical frailty as a continuous variable, as well as studies carried out with the same database, were the most common reason for papers exclusion. In total, 20 studies were included after quality analysis and six studies were excluded (see Table 3.1).

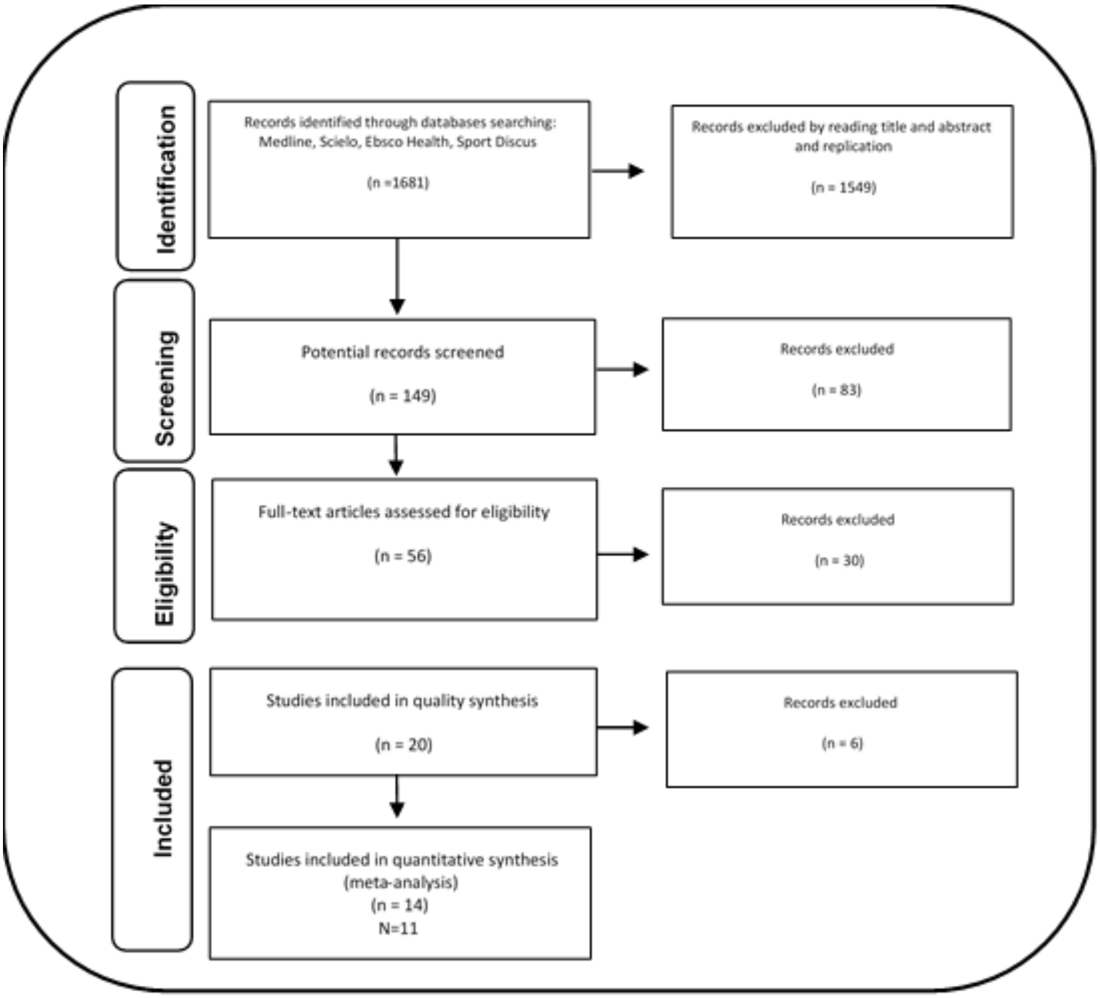

Figure 3.1 Flow diagram of studies selection according PRISMA guidelines (Panic et al., 2013).

3.9.2 Characteristics of studies and participants

Table 3.1 shows the 14 epidemiological studies were included for data quantitative meta-analysis. From the total of 22 items, the overall mean of included studies was 92%. The Table 3.2 showed the general characteristics of all studies included. A total of 14 studies included for final data analysis have a total sample of 26798 participants which came from 11 different countries, with mean and their respective standard deviation of ages varying between 61.8 (1.4) to 87.5 (5.4) years old. Overall, the sample included 12729 (47.4%) non-frail, 11559 pre-frail (43.2%) and 2452 (9.4%) frail individuals.

Table 3.1 Quality assessment scores of selected studies based on the STROBE check-list.

Items (paper sessions)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**100%**	**22**
1. (Abizanda *et al.*, 2013)	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	95%	21
2. (Alencar *et al.*, 2013)	0	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	86%	19
3. (Avila-Funes *et al.*, 2009)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	100%	22
4. (Furtado *et al.*, 2017)	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	95%	21
5a. (Han, Lee and Kim, 2014)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	100%	22
5b. Han, Lee and Kim, 2014)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	100%	22
6. (Jacobs *et al.*, 2011)	0	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	91%	20
7. (Kiely *et al.,* 2009)	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	95%	21
8. (Robertson *et al.*, 2014)	0	1	1	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	1	1	1	86%	19
9. (Samper-Ternent *et al.*, 2008)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	95%	21
11. (Al-Kuwaiti, *et al.*, 2015)	0	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	91%	20
12. (Macuco *et al.*, 2012)	0	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	86%	19
13. (Ottenbacher *et al.*, 2009)	0	1	1	1	1	1	1	0	0	1	1	1	0	1	1	1	1	1	1	1	1	1	82%	18
14. (Yassuda *et al.*, 2012)	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	1	1	1	0	1	82%	18
15. (Tay *et al.*, 2016)	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	1	91%	20
Median of total scores																							**92%**	**20**

A total of 10 studies had samples from both genders (Han et al. 2014; Avila-Funes et al. 2009; Robertson et al. 2014; Abizanda et al. 2013; Tay et al. 2016; Yassuda et al. 2012; Ottenbacher et al. 2009; Al-Kuwaiti et al. 2015; Macuco et al. 2012; Kiely et al. 2009), but only the study carried out by Sook-Han and colleagues presented a separate analysis performed by gender (Han et al. 2014). Three studies included female participants (Furtado, Adriana Caldo, et al. 2017; Alencar et al. 2013; Samper-Ternent et al. 2008) and one study included only older men (Jacobs et al. 2011). Four types of epidemiological studies were found: Three longitudinal (Avila-Funes et al. 2009; Samper-Ternent et al. 2008; Ottenbacher et al. 2009), four cohort (Tay et al. 2016; Alencar et al. 2013; Abizanda et al. 2013; Jacobs et al. 2011), six cross-sectional (Yassuda et al. 2012; Furtado, Adriana Caldo, et al. 2017; Macuco et al. 2012; Robertson et al. 2014; Han et al. 2014; Al-Kuwaiti et al. 2015) and one observational study (Kiely et al. 2009). Study designs and full details are summarized in Table 3.2. The cognitive status measured by MMSE was assumed as the central outcome in 11 studies (Alencar et al. 2013; Han et al. 2014; Jacobs et al. 2011; Avila-Funes et al. 2009; Robertson et al. 2014; Yassuda et al. 2012; Ottenbacher et al. 2009; Al-Kuwaiti et al. 2015; Kiely et al. 2009; Macuco et al. 2012; Samper-Ternent et al. 2008) and as a co-variate in three studies (Furtado, Adriana Caldo, et al. 2017; Tay et al. 2016; Abizanda et al. 2013).

All of the included papers used a version of Fried's model and their respective five components were used to create frail sub-groups. However, the study conducted by Laura Tay and collaborators (Tay et al. 2016) did not have the three frailty subgroups and the main investigator decided to introduce it only in the statistical analyses that compared the non-frail versus frail individuals. When looking to the mean scores of cognitive performance in the PF subgroups and taking into account the cut-off values of the cognitive status by MMSE, In all studies the frail subgroup was classified as having cognitive impairment (MMSE lower 24 pts), expect for studies carried out in France (Avila-Funes et al. 2009), United States (Kiely et al. 2009) and Ireland (Robertson et al. 2014). In the pre-frail subgroup, a total of 7 studies (USA, South Korea, Brazil, Portugal, Mexico and United Arab Emirates) also presented the same cut-of values to classified participants as a cognitive impairment (Yassuda et al. 2012; Furtado, Patrício, et al. 2017; Ottenbacher et al. 2009; Alencar et al. 2013; Han et al. 2014; Al-Kuwaiti et al. 2015; Macuco et al. 2012).

Table 3.2 Characteristics of select studies following the PICOS statement (Panic *et al.*, 2013).

Author's study	Country of Samples population	Sex	Age (M±SD)	Study Method	Frailty Subgroups samples distribution (100%)			Mini-mental scores by Frailty subgroups (M±SD)			Central outcomes	Main goal
					Non-frail n (%)	Pre-frail n (%)	Frail n (%)	Non-frail	Pre-frail	Frail		
						n = 993						
1. Abizanza et al. (2013)	Albacete, Spain	M/F	79,4±6,4	Cohort	168 (16.9%)	482 (48.5%)	286 (22.8%)	26.61 (3.23)	24.92 (4.91)	22.31 (5.52)	Physical Frailty, morality, disability and activities of daily living	To analyse whether frailty implies increased risk of death and incident disability.
						n = 160						
2. Alencar et al. (2013)	Belo Horizonte, Brazil	F	78,37±7,2	Cohort	47 (23.7)	112 (54.1)	48 (23.2)	24.02 (4.03)	21.11 (5.99)	17.02 (5.43)	Physical Frailty, cognitive status, hospitalization and death	Evaluate associations between frailty status and cognitive decline as well as the incidence of cognitive impairment over 12-month period.
						n = 6030						
3. Ávila-Funes et al. (2009)	3 cities, France	M/F	74,1±5,2	Longitudinal	2738 (45.4)	2871 (47.6)	421 (7)	27.51 (1.93)	27.42 (1.93)	26.91 (2.01)	Physical Frailty, mortality incidence, disability and cognitive profile	To determine whether adding cognitive impairment to frailty improves its predictive validity for adverse health outcomes.
						n = 4294						
4a. Sook-Han et al. (2014)	25 cities, South	M	68,1±5,4	Cross-sectional	2200 (51.2)	1719 (40.3)	375 (8.7)	26.10 (2.93)	24.42 (3.21)	21.53 (5.11)	Physical Frailty and cognitive abilities	To analyse Association between frailty and cognitive disorder in community people.
						n = 6094						
4b. Sook-Han et al. (2014)	25 cities, South Korea	F	64,8±3,72	Cross-sectional	2593 (42.5)	2894 (47.4)	607 (10.1)	23.81 (3.92)	21.73 (4.54)	18.61 (5.72)	Physical Frailty and cognitive abilities	To analyse association between frailty and cognitive disorder
						n = 834						
5. Jacobs et al. (2011)	Jerusalem, Israel	M	87,5±5,4	Cohort	206 (24.5)	470 (56)	164 (19.5)	28.21 (2.34)	27.01 (2.72)	22.22 (6.12)	Physical Frailty and cognitive status	To examine the association between frailty and cognitive impairment and the impact on 5-years survival
						n = 760						
6. Kiely et al. (2008)	Boston, United States	M/F	78,1±5,4	Observational	389 (51.2) 20 (20.2)	295 (38.8) ------	76 (10) 79 (79.8)	27.31 (2.53)	26.78 (2.72)	25.39 (3.21)	Physical Frailty, falls, disability and hospitalization.	To validate two established frailty indexes and compare their ability to predict adverse outcomes

(Continuation…)

7. Robertson et al. (2014)	Dublin, Ireland	M/F	61,8±1,4	Cross-Sectional	n = 4349			28.88 (1.52)	28.41 (1.82)	27.63 (2.23)	Physical Frailty and cognitive abilities	To explore the relationship between cognitive function and physical frailty syndrome.
					3115 (71.6)	1144 (26.3)	90 (2.1)					
8. Samper-Ternent et al. (2008)	Texas, United States	F	75,2±5,8	Longitudinal	n = 1370			26.11 (2.97)	25.41 (3.22)	24.81 (3.05)	Physical Frailty and cognitive profile	Examine the association between frailty status and change in cognitive function over time
					684 (49.9)	626 (45.7)	60 (4.4)					
9. Al-Kuwaiti et al. (2015)	United Arab Emirates, Abudabi	M/F	65,6± 6,2	Cross-Sectional	n = 151			24.72 (1.52)	23.71 (2.64)	19.73 (3.88)	Physical Frailty	To determine the prevalence and correlates of frailty
					75 (46.9)	53 (33.1)	23 (14.4)					
10. Macuco et al. (2012)	São Paulo, Brazil	M/F	72,3±5,8	Cross-Sectional	n = 384			24.56 (2.77)	23.63 (3.72)	20.52 (5.54)	Physical Frailty and cognitive status	To examine the association between frailty and cognitive functioning
					142 (36.9)	211 (54.9)	31 (8.2)					
11. Ottenöacfter et al. (2009)	Texas, United Status	M/F	74.03±6.4	Longitudinal	n = 777			21.71 (3.88)	21.87 (41.10)	19.14 (5.63)	Physical Frailty and cognitive performance.	We examined the prevalence of frailty and explored the correlates associated with disability and morbidity
					191 (24.5)	425 (54.6)	161 (20.9)					
12. Yassuda et al. (2012)	Sao Paulo, Brazil	M/F	72.3±5.8	Cross-Sectional	n = 384			24.66 (3.78)	23.68 (3.76)	20.50 (5.55)	Physical Frailty and cognitive function.	To explore the relationship between cognitive function and frailty.
					142 (36.9)	211 (54.9)	31 (8.2)					
13. Furtado et al. (2017)	Coimbra, Portugal	F	81.96±7.9	Cross-Sectional	n = 119			23.75 (3.98)	21.58 (4.84)	18.11 (5.17)	Physical Frailty and physical fitness	To explore the relationship between physical frailty and physical fitness
					19 (15.9)	n = 46 (38.7)	n = 54 (45.4)					
14. Tay et al. (2016)	Singapore, Southeast Asia.	M/F	76.6±6.7	Cohort	n = 99			16.72 (3.76)	---	19.03 (5.11)	Physical Frailty and cognitive status	To examine the independent and combined effects of inflammation and endocrine dysregulation on baseline frailty status and frailty progression at one year

3.9.3 Magnitude of effect size

Regarding the central hypothesis of this SM, we attempted to assess whether the frailty subgroups, non-frail versus pre-frail (NFvsPF) and non-frail *versus* frail (NFvsF) differed in mean and standard deviation scores for cognitive performance. The results showed that the global effects of MMSE mean and standard deviation differences were statistically significant for both NFvsPF (M±SD = 0.60, 95%CI: 0.50-0.62, p<0.001) and NFvsF (M±SD = 3.43, 95%CI: 2.26-4.60, p<0.001) comparisons (see Figure 3.2). The results of Z-values test scores showed that we may reject the null hypothesis as the frail subgroups-effect was not associated with cognitive performance) in both comparisons (NFvsPF, Z = 18.31 and NFvsF, Z = 5.73).

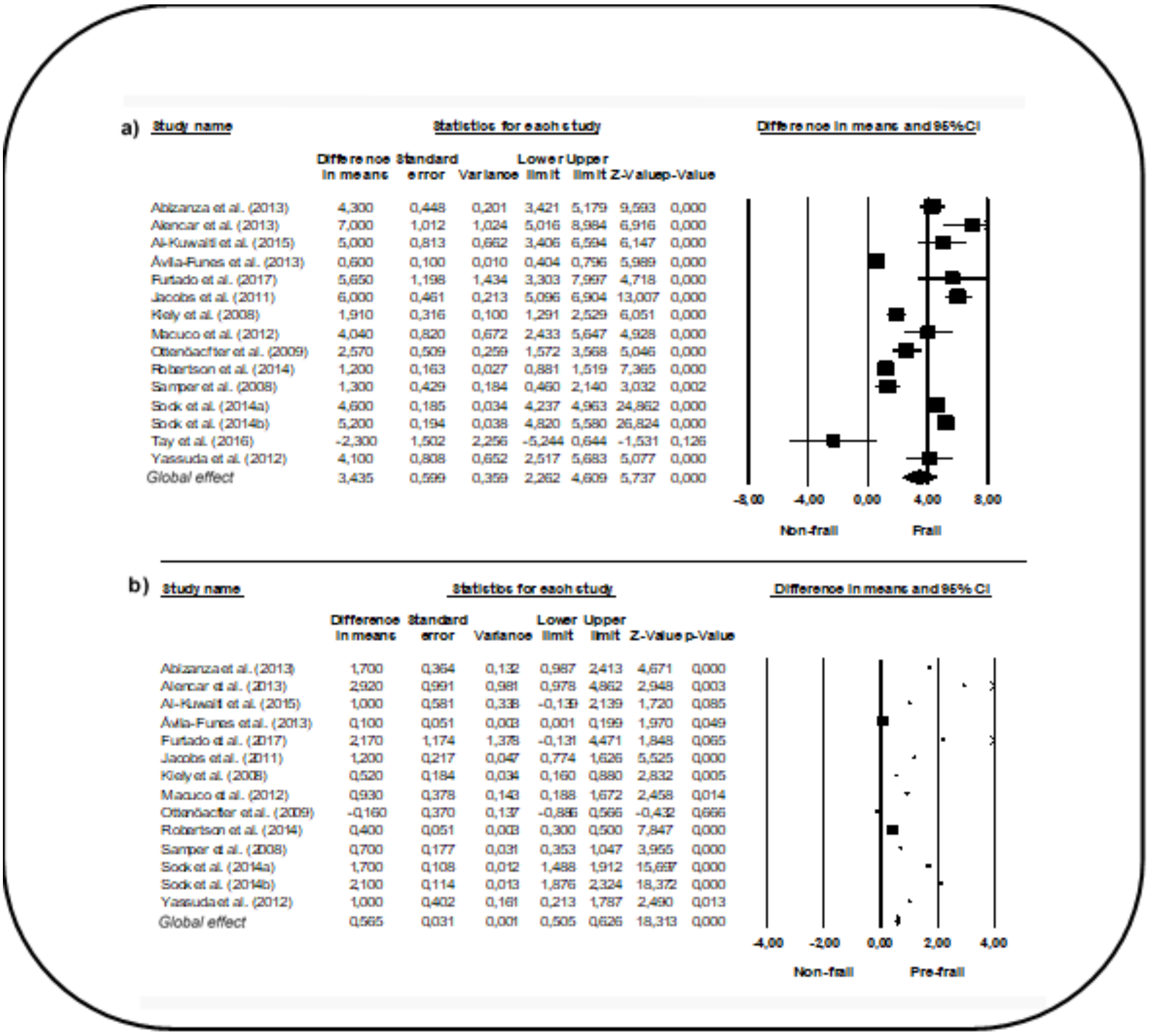

Figure 3.2 Descriptive statistic of each study and global results of meta-analysis. (a) Non-frail versus frail, (b) Non-frail versus pre-frail.

3.9.4 Homogeneity effects

To determine whether the observed variation fell within the interval assigned to the error of the studies sample and to test the null hypothesis according to which all the studies involved in this SM share a magnitude of common effects, the Cochran`s Q test (Q) was used. If all studies share the same magnitude of effects, the expected value of Q would be equal to the degrees of freedom, i.e., the number of studies minus 1. The value obtained from Q test for both comparisons were 857.820, with 14 degree of freedom (NFvsF) and 417.520, with 13 degree of freedom (NFvsPF). In both comparisons the values were statistical significant (p <0.001) accepting the alternative hypothesis, i.e., the true magnitude of the effect varies from study to study.

The statistics of I^2 corresponded to the ratio of the real heterogeneity of the total variation of the observed effects, that is, it tells us what proportion (percentage) of the observed variance reflects the differences in the true magnitude of the effect rather than in the error of the sample(Dinnes et al. 2005). The obtained value of I^2 = 98.368 (NFvsF) and 96.886 (NFvsPF) which means that about 98.40% of the variance reflects the true effects. The Tau squared (T^2) values correspond to the variance of the true effect sizes among studies which were in the current SRM, 4.92 (NFvsF) and 0.54 (NFvsPF).

3.9.5 Publication Bias

To assess hypothetical publication bias, we initially performed the visual inspection of the funnel plot, suggesting low evidence for publication bias. However, we used Egger intercept test and standard deviation (SD), Confidence interval (CI):95% and degree of freedom (df) to test the null hypothesis according to which the intercept is equal to zero (see Figure 3.3). The result for NFvsF intercept comparison was 5.05 (SE = 2.96, CI:95% = -1.27-11.38, t = 1.72, df = 13 and p = 0.10) and for NFvsPF comparison the intercept comparison was 3.34 (SE = 2.05, CI:95% = -1.12-7.81, t = 1.63, df = 12 and p = 0.12). In the both comparisons the p value was not significant, indicating no strong evidence for publication bias.

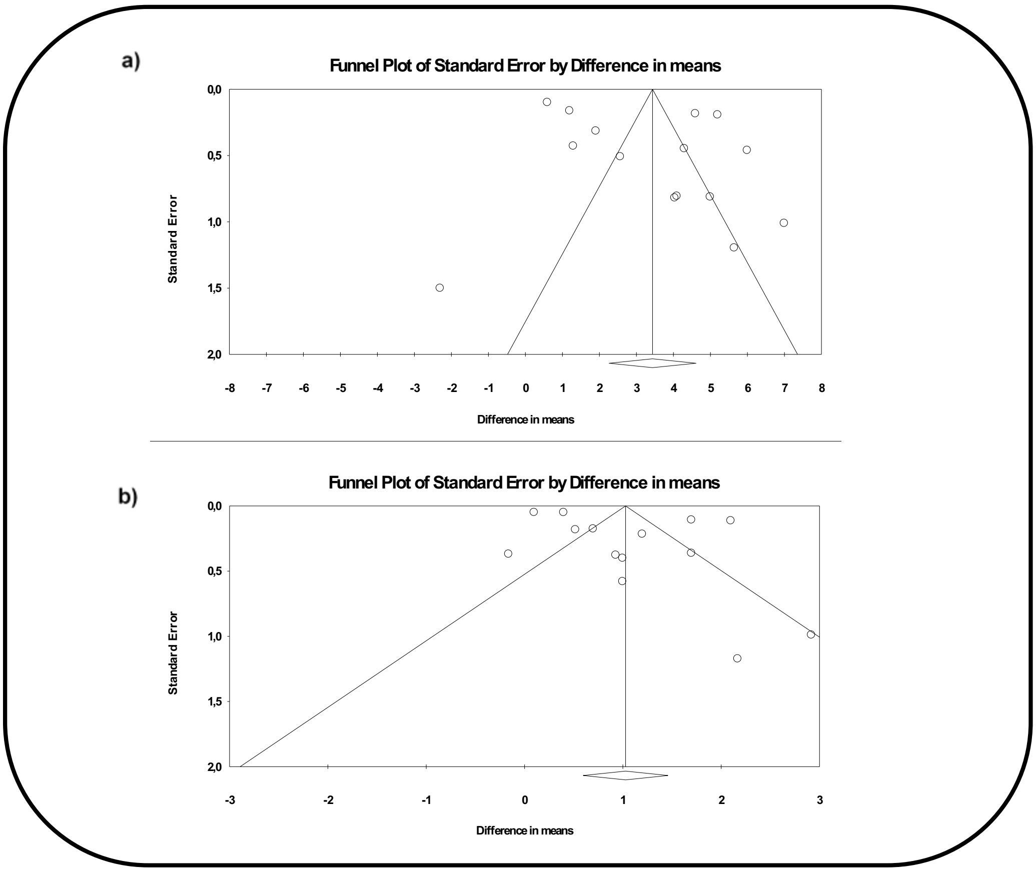

Figure 3.3 Visual Funnel plot inspection associated to Egger's test. (a) Non-frail versus frail, (b) Non-frail versus pre-frail.

3.10 Discussion

3.10.1 Frailty, age and gender

Regarding PF and sex differences, the older literature points to a similar association between physical frailty and cognitive decline in both male and female older adults (Han et al. 2014). It is perhaps for this reason that many authors did not present the statistical analyses stratified for sex. However, findings in recent studies that used other PF screen tools are unanimous in revealing a higher incidence of PF in older women when compared to older men (Chang & Lin 2015; Theou et al. 2015; Theou et al. 2011). Older men (with or without cognitive decline) have physical frailty associated with a higher incidence of mortality when compared to older women and such results were corroborated in 3 studies selected for this SM (Avila-Funes et al. 2009; Abizanda et al. 2015; Jacobs et al. 2011). In the present study, similar to occurred in a previous study (Furtado, Guilherme Eustáquio, Teixeira, Ana Maria, Ferreira 2017), it was not possible to explore sex-differences, since only the study carried out in South Korea presented statistical analysis by gender (Han et al. 2014).

In fact, sex is one of the variables which influence may help us to explain the high heterogeneity found in this meta-analyses (Sterne et al. 2001; Egger et al. 1997). Frailty linked to cognitive decline is identified in the literature as having a strong relationship with advanced age, although this phenotypes may be able to manifest itself early as well. In the present SM the results showed that only studies carried out in Portugal (Furtado, Patrício, et al. 2017) (81.96±7.91) and Singapore (Tay et al. 2016) (76.6±7.03) with a higher mean age showed more cognitive decline and similar distribution in the PF subgroups. Contrariwise, the studies conducted in South Korea (Han et al. 2014) and United Arab Emirates (Al-Kuwaiti et al. 2015) presented the same frailty and cognitive characteristics but had lower mean ages for cognitive scores. Factors such as education, public policies to adopt an active and healthy lifestyle during the course of life and different eating habits from country to country may interfere and could be identified in a more in depth meta-analysis.

3.10.2 Frailty, cognition performance and assessments

PF assessment is used to identify older populations at risk for adverse aging-related health indicators (Mohler et al. 2014). Recent reviews recognized more than 25 types of frailty screening tools among which the Fried´s and colleagues set is the most widely used (de Vries et al. 2011; Sieliwonczyk et al. 2014; Schwenk et al. 2014). The PF comprises five components and this screen tool has been confirmed associated with subsequent health outcomes in a succession of studies drawn from a range of diverse older populations (Brigola et al. 2015; Bouillon et al. 2013). However, Fried´s model, which comprises physical frailty, had a strong interrelationship with cognitive state as assessed by MMSE (Yassuda et al. 2012; Alencar et al. 2013; Han et al. 2014; Robertson et al. 2014). As the MMSE assesses several cognitive domains, it might be useful to determine which individual experienced cognitive deficits are most significantly associated with frailty scores (Mungas 1991). However, MMSE total score (rather than isolated cognitive ability screen tools) showed to be a better predictor of physical frailty scores (Abizanda et al. 2013; Avila-Funes et al. 2009). As the Fried construct seems to be the most used protocol for assessing the frailty phenotype, MMSE is the most widely used tool for assessing cognitive status, thus increasing the level of comparability with other studies (Vella Azzopardi et al. 2018).

3.10.3 Frailty subgroups and cognitive decline

The pattern of decreased cognitive performance in the comparisons of non-frail versus pre-frail and frail subgroups was found in all studies included in this meta-analysis, except in those carried out in Singapore (Tay et al. 2016), that showed higher MMSE values, i.e. better cognitive results in the frail subgroup. In the other comparisons, the mean differences in MMSE scores were always statistical significant. The results were recently confirmed when also comparing pre-frail and non-frail subgroups (Furtado, Guilherme Eustáquio, Teixeira, Ana Maria, Ferreira 2017). Various studies have confirmed the existence of cognitive decline in pre-frail and frail subgroups. However, according to our latest review of literature, this is the first study to statistically show the magnitude of the mean differences.

The strong evidence of communal physio-pathological chains is based on the occurrence of both physical frailty and decreased cognitive function involved in the same biopsychological systems (Gale et al. 2013). Recent findings suggest a severe loss of muscle (sarcopenia) and bone (osteopenia) mass as a common nutritional impairment in this population, causing cellular and molecular damage, reducing homeostatic reserves caused by mechanisms that are regulated by complex neuronal maintenance and repair networks (Chang et al. 2016). Cognitive Frailty, as it is known today, has become of major concern for public health, as a result of the increased incidence of many types of dementia (Panza et al. 2015), since it is characterized as a phenotype that represents large expenditures to health care systems (Macklai et al. 2013).

3.10.4 Study limitations

To the best of our comprehension this is the first analyses to systematically examine the interaction between physical frailty and cognition performance in the elderly population. Despite the high methodological quality of the studies included, this work has some limitations. It was not possible to perform a gender analysis, since only one of all the studies included presented the results according to the sex of the participants. The different criteria for the evaluation of frailty phenotype adopted by some researchers did not allow us to include more studies. Our results signify the importance of implementation of public policies to develop and improve non-pharmacological treatments (i.e. physical activity plus nutritional support) when evaluating physical impairments and their associations with cognitive decline to be used as a basis for health professionals decision-making.

3.11 Conclusion

Worse of physical frailty condition improves the predictive validity of the accepted currently definition of cognitive impairment, characterize as a low score of mini-mental cognitive test. The accuracy in the evaluation of cognitive functioning may help to well-define and characterize frailty associated to cognitive decline in older persons. This would be useful in expecting aging policies needs and to provide appropriate services to encourage an active life style, aiming to large prevent the premature health decline effects in the old populations.

3.12 References

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CHAPTER 4 (STUDY 2):

EXERCISE-BASED INTERVENTIONS AS A CO-ADJUVANT TREATMENT OF FRAILTY SYNDROME IN OLDER ADULTS: A SYSTEMATIC REVIEW OF REVIEWS

Authors:

Guilherme Eustáquio Furtado

Rubens Letieri

Adriana Caldo

Maryam Farhang

Eef Hogervrost

Ana Maria Teixeira

José Pedro Ferreira

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4.1 Abstract

Background: Regular exercise has been shown to have positive effects on several factors related to FS (e.g. improve immunity, cognitive abilities, improve psychosocial domains), because of its potential effect of biopsychological outcomes modulation **Goals:** To combine considerable information concerning the benefit of exercise through a systematic review of existing systematic reviews on the frailty status exercise scientific literature. **Methods:** the RS followed a pre-determined and published protocol available in PROSPERO 2018. The search was conducted in English language, in the following Ebsco, Ebsco Health, Scielo, ERIC, LILACS, Medline (PubMed), Web of science and SportDiscus data bases. The entry was made between the months of December 2017 and February 2018, using the advanced meta-search option, aiming to detecting existing SR and metanalysis of exercise-based intervention published between 2000-2017. The terms of 'physical exercise', elderly-frail and systematic review (and analogues) were used. The strength of evidence of each article was assessed and the respective score atrabuted, trough the AMSTAR-2 (A MeaSurement Tool to Assess Systematic Reviews) A narrative and descriptive findings are reported. **Results:** In total, 19 studies were including after quality synthesis analisys. The quality of evidence was completed according AMSTAR-2 checklist revealed a mean (standard deviation) score of 11,2 (±2,3) with a range of 8-16 points, suggests moderate quality of the systematic reviews. In general, findings demonstrate an overall positive benefit of long term multicomponent exercise-based intervention in the attenuation and reversing frailty status and have a substantial impact in their correlates outcomes, especially in the physical-functioning status. **Conclusions:** A trend towards better results in old participants classified as pre or moderate frail, and who underwent programs lasting more than 22 weeks, with an average weekly frequency of 2-3 times a week and with session time exceeding 45 minutes was found. For other forms of exercise, the evidence is inconclusive due to the low number of studies. Despite some limitations, more high-quality studies that use metanalysis statistical treatment are needed to clary the real effect on the specific group of variables.

Key-words: Exercise, Frail older adults, systematic reviews

4.2 Introduction

According studies in recent years, in the last year's exercise-based interventions have been considered a preferable alternative for treating condition of frailty (1). Frailty syndrome is a complex ageing expression determined by ontogenetic and phylogenetic factors (2). Chronic stress has been shown to have immuno-suppressive effects that accelerate immunosenescence and cause cumulative disorders in many physiological systems, resulting in the frailty state (3). Environmental factors such as malnutrition and negative psychological adjustment events across life also contribute to manifesting frailty earlier (4). Several forms of manifestation and classifications frailty exist (5). Fried et al. (2001) have developed a construct whose bases are sarcopenia, negative energy balance and inactivity, called physical frailty (PF) status (6). Recently some studies have identified that cognitive of frailty, for example, may be separated into subtypes distinct physical frailty (PF) (7). This implies that cognitive frailty syndrome, a novel age-related concept (8), is a form of pathological brain-aging and a precursor to neurodegenerative processes, that is characterized by concurrent PF and potentially reversible cognitive impairment (1).

Despite the different subtypes of frailty, there is a consensus that sedentary life style proves to be a powerful condition linked to PF (9). Regular exercise has been shown to have positive effects to several factors related to PF (e.g. improved immunity, cognitive abilities and psychosocial indicators), because its potential effect in the modulation of biopsychosocial indicators (10). For this reason, a large number of the intervention studies with exercise in old individuals, opted to investigate variables of physical, biological and behavior factors (11). This factors share commonalities that can be explained by studying the simultaneous exercise modulation effect on some of these variables (12).

Evidence shows that immunological and hormonal parameters are able to mediate the effects of exercise on mucosal immunity, psychological stress, cognitive improvement and risk of dementia in elderly who are regularly active (13). In fact, regular exercise may provide an effective strategy in the treatment and prevention of associated disorders owing to its anti-inflammatory benefits (14). Regular exercise has also been shown to diminish the level of stress and anxiety and the risk of psychological diseases and emotional decline in the elderly (15). Currently, there is conflicting evidence concerning the efficacy and practicality of different types of exercises interventions to decrease PF. For this reason, some review articles written in the last decade, aimed at presented a robust evidence that supporting the use of exercise as a coadjutant treatment to reverse the frailty status (16–18).

In this sense, the current research was designed to summarize the recent robust evidence and analyzing the impact of regular exercise in the decrease of the several factors associated with frailty. We started from the premise that there were already some revisions made of great quality, this systematic review (SR) of previous systematic reviews articles (SRofR) updates the previuos one and offers a more open view of the best 'state of the art' on this topic.

4.3 Methods

The method used to perform this systematic review study protocol was based on the Cochrane approach, organized by Smith and colleagues (19). This approach is suggested to appraises and summarizes research findings from separate papers of SR papers to discuss the different results to help provide clinical decision makers with relevant scientific evidence. Sources and searching, review selection, quality assessment, presentation of results and implications of practice research are the recommended foci for conducting this type of study.

4.3.1 Data sources

This work followed a pre-determined and published protocol available in PROSPERO 2018, number registration CRD42018088782 (20). The search was conducted in English language in the following data bases: Ebsco, Ebsco Health, Scielo, ERIC, LILACS, Medline (PubMed), Web of science and SportDiscus, though the University of Coimbra on line remote control access (21). The entry was made between the months of December 2017 and February 2018, using the advanced meta-search option, aiming at detecting existing SR and metanalysis of exercise-based interventions published between 2000-2017.

4.3.2 Inclusion and exclusion criteria

Generally, the following two inclusion criteria were taken into account for further evaluation and selection of a paper: a) a paper a defined as a SR and/or SR following metanalysis; b) the use of any systematic regular physical exercise or analogous coadjutant treatment interventions (i.e. tai-chi), aimed at treating frailty or modulating overall frailty correlated outcomes; RS papers that included randomized controlled trials (RCT) or non RCT-type studies; Exclusion criteria included: a) withdrawal of comprehensive, scoping and literature review type paper where the authors do not presented a discussion in the narrative way b) withdrawal of papers where the coadjutant treatment does not fit into the concept of physical exercise or where no therapeutic exercise was adopted.

4.3.3 Main search criteria

The search was developed taking into account the PICOS approach (22). **P**articipants included frail male and female adults aged 65 years and older, classified according to the standardized methods for evaluating frailty with criteria accepted by the scientific specialists (23). **I**ntervention include any types of systematic physical exercise, comprising aerobic, resistance and strength-muscle, yoga, Pilates, flexibility/balance and other similar types, therapeutic exercise, chair-based, combined, and multicomponent exercises programs. **C**omparison largely addressed supervised or unsupervised exercise interventions, experiments with or without control group, comparison of different exercise programs with randomized and non-randomized trials design. The duration, frequency and adherence to the exercise could be varied. **O**utcomes included physical, functional and mental health changes, such as musculoskeletal, body composition and cardiometabolic functions. They also included improvement in physical fitness and frailty outcomes measures; improvments in psychosocial, psychological wellbeing and quality of life domains. The exercise-based interventions also tested the impact of neurocognitive functions and specific cognitive abilities. Blood count and saliva samples were analyzed for alterations in stress and sex steroids hormones, cytokines, neuroendocrine, immune, pro- and anti-inflammatory biochemical makers.

4.3.4 Search strategy

The strategy was developed by a first author in discussion with the reviewer specialist and author's research team. Firstly, a meeting was held with three exercise experts aiming to define the key search terms. Secondly, the data extraction was carried out by two independent exercise specialists, who communicated only in the initial phase of refinement of the search methods. It was recommended to the first author to exclude the articles by reading the title, abstract and finally, reading the manuscript in its integral form, in this order. At the end of the searches, a concordance analysis of the two searches was performed by the first author and reported as a percentage. The Medical Subject Headings (MeSH) indexed descriptors were used to refine the data search and Table 4.1 summarizes the key-terms were used (24). Additionally, analogues terms of eligible primary terms were identified and used according to decision of the members of research specialist in physical exercise.

Table 4.1 Summary of adopted descriptors for meta-data search**.**

Physical exercise
…OR exercise or exercise training OR exercise therapy OR aerobic exercise or aerobic training OR circuit-based exercises OR circuit training OR muscle strength exercises OR muscle strength training or resistance training OR Weight-Lifting exercise program OR muscle stretching exercises OR balance exercises OR flexibility exercises OR multimodal exercise OR multicomponent exercise or combined exercise OR physical activity OR physical fitness programs. AND
Frail Elderly
…OR frail elders OR frail older adults OR frail older populations OR frailty syndrome OR frailty phenotype OR physical frailty OR frailty outcomes OR frailty status OR frailty state. AND
Systematic review
…OR review OR metanalysis.

4.3.5 Quality of evidence Assessment (QEA)

The strength of evidence of each article was assessed trough the AMSTAR-2 (**A** **M**ea**S**urement **T**ool to **A**ssess **S**ystematic **R**eviews). AMSTAR-2 is a validated instrument that assesses the attributes of the best available evidence in systematic reviews (19). Based on online calculator, queries the papers estimating 16 items and attributing a final result classification based on quantitative (0 to 16 points) and qualitative (low, moderate and high quality) approaches. According to relevance that require insight on the quality of the SR methodology, AMSTAR-2 helps to minimized errors and bias checklist (25). Each paper included in the eligibility phase was assessed using this tool (for more details see: https://amstar.ca/Amstar_Checklist.php).

4.4 Results

4.4.1 Data search

The initial search recognized 753 potentially eligible papers in the identification stage, however, 726 were excluded after reading titles and abstracts, and identifying replications. A total of 27 full-text articles were examined in the screening stage. After reading the article completely, 21 papers advanced for the eligibility stage (see Figure 4.1). In total, 19 studies were including after quality synthesis stage. The QEA realized according AMSTAR-2 checklist revealed a mean (± standard deviation) score of 11.2 ± 2.3 with a range of 8-16 points (see Table 4.2). A total of 3 studies was obtained high scores (strong evidence), varying between 14 to 16 points (26–28) and one study presented a poor score, classified as a critical evidence (29). Descriptive findings are provided because pooled effects were not calculated.

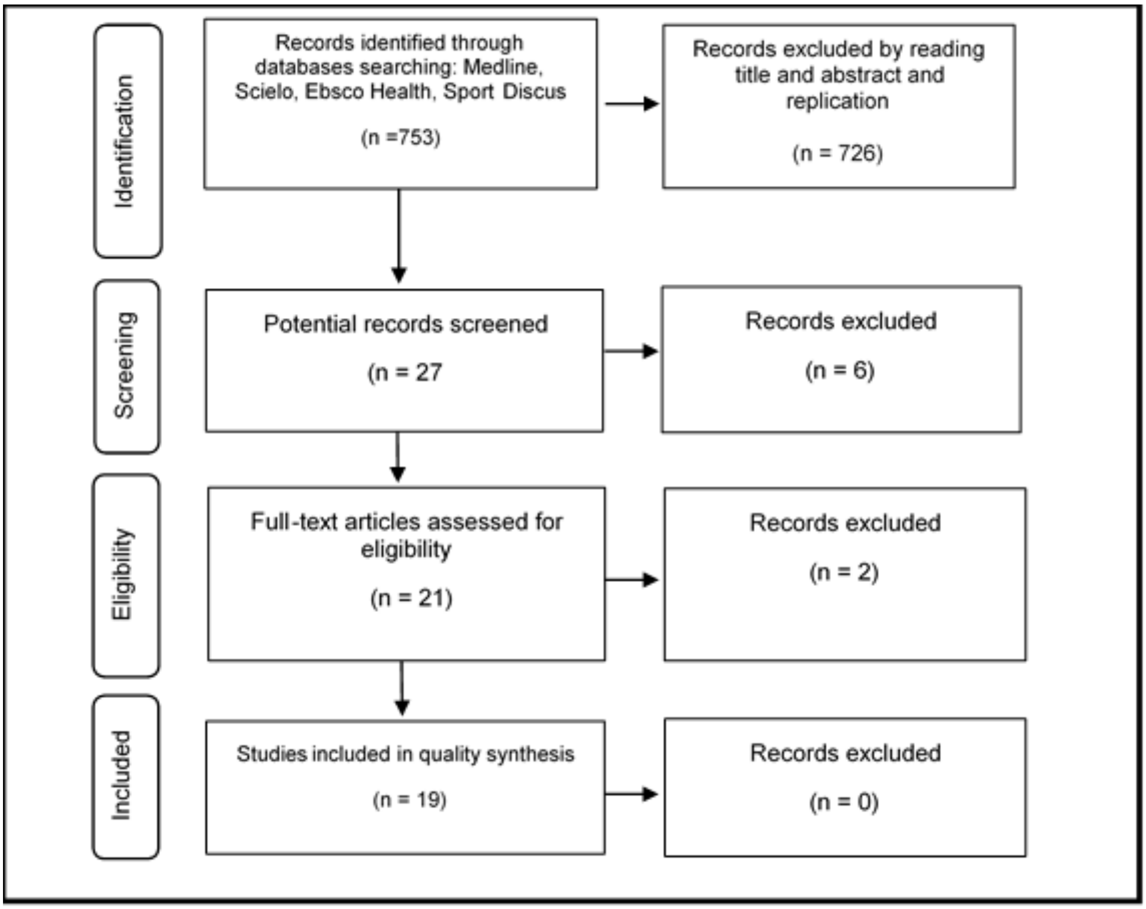

Figure 4.1 Flow diagram of studies selection according PRISMA guidelines (30).

4.4.2 General characteristics of SR studies

As can be seen in Table 4.3, in general, all the authors included only RCT-type studies in their respective SR articles. Overall, out of 18 studies, 4 articles performed metanalysis (16,26–28), 13 studies did not advance to any statistical treatment, chosing the narrative way using qualitative and categorical results presentation (29,31–42), and one article chose to use an alternative statistical comparison treatment for calculating the degree of exercise effect eviendence (pre- and post-exercise) measuring Cohens' *d* effect size (43). The number of articles included in all papers ranged from 4 to 47 papers. However, these numbers are relative and not absolute, because when analysing all the articles included in the presented SRofR, we found that there were several studies that were in more than one revision. The number of data bases assessed, the form of data access and the date range for the articles search is quite varied, but it does not appear to be directly proportional to the number of articles included in each review.

A total of six studies presented an open date search not delimiting an initial date of interval, only defining the final year (26,28,33,36,39,42). The remaining authors closed the date of the search in a range that includes approximately 10-15 years. Observing all included SR, the number of participants varied between 9 to 1338. But these numbers are relative, for the same reasons we mentioned above. The study variable included in each SR study was depend on the interest of the respective authors and the main goals of studies. Analysing each SR, it was very clear that the option of performing a SR following meta-analysis (SRM) or just a SR also interferes with the selection of variables. The option of running a SRM, for example, requires the select of a limited number of variables since the authors interest is to present a solid evidence (16,26–28), while the objectives of SR, in generally, is to presented the topic of interest with several correlated sub-themes (29,31,32,34,37,40,41); or offered a large comprehensive review on the main theme (27,33,38,42). Despite the particular objectives of different authors, the variables included in each SR study can be classified into the following categories, current is called by gerontology and gerontology specialists as frailty correlated dimensions (44–46):

i) Psychosocial determinants: cognitive status, mood states, depression, quality of life, social engagement and caregiver burden;

ii) health determinants: vitality, perceived health status, self-reported pain, tendinitis, admission to hospital or long care;

iii) physical-functional fitness and physical frailty status: gait speed, upper and lower muscle strength, endurance capacity, upper and lower flexibility; aerobic resistance; levels of physical activity.

iv) motor skills: static and dynamic balance, coordinator, reaction time, mobility and neurological tests;

v) Physical functioning (related to disability): independent and instrumental activities of daily life, falls incidence, risk of falls and fear of falling;

vi) Body composition and anthropometry: nutritional status (ratio of calories intake), changes in body weight and composition; circumferences and BMI;

vii) biochemical makers: inflammatory cytokines, blood counts, bone and muscle damage biomarkers and insulin resistance indicators;

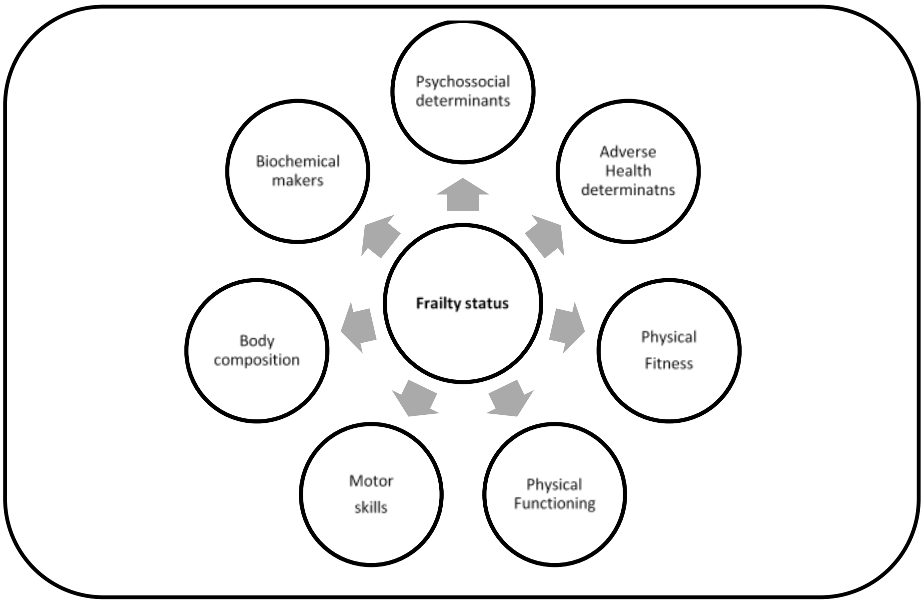

Figure 4.2 Categorization of the variables emerged from the 18 systematic reviews studies.

4.4.3 Scope of studies and participants

Overall, all SR studies used physical-functional fitness, physical frailty and/or motor skills as the first outcome, that included the physical frailty outcomes, which was in agreement with the central objectives of each SR. Almost all reviews included in their studies measures of indirect functional physical function using questionnaires and psychometric scales. Only 3 authors were included in their reviews studies with biochemical makers as a central indicator, especially variables of pro and anti-inflammatory system and insulin resistance (29,33,42). The study participants' ages included in each review range from 60 to 90 years of age. However, a specific group of studies have samples older than 70 years (28,31–35,40,47). In all studies, male and female old frail and pre-frail participants were included, only one study included pre-frail participants (27). Even though in all SR the authors labelled their participants as frail status, the frailty assessment used in the studies cited in each review were substantially varied. However, all the authors assumed that they included studies whose measures can be classified as valid (as in the case of the protocol of Fried, Tinetti or the Edmonton Frailty Scale) or non-standard measures, such as the ability to climb stairs, activities of daily life and falls risk scales, physical fitness tests and others (Table 4.3)

Table 4.2 Summary table of general scope of systematic reviews studies.

Author's study	Review Characteristics	Methods of studies included	Search Strategy	Studies included	Total of participants (range)	Main results
1. Chin et al. (2008)	A systematic review (without metanalysis) exercise interventions to generated impact on physical functioning outcomes	RCTs studies	PubMed, EMBASE, EMtree (via EMBASE.COM) (in and CENTRAL (in the Cochrane Library) data bases were searched between 1995 and 2007 in English language	20	20 to 551	This systematic review suggests that older adults with different levels of abilities can improve their functional performance by regular exercise training.
2. Theou et al., (2011)	An comprehensive systematic review of exercise interventions for frail older people, that examines how frailty is assessed and does not focus only on one specific outcome measure	RCTs studies	Medline, Embase, Psycinfo (Scholars Portal), Cinahl (OVID & EBSCO; 1982-), Scopus, Ageline, Eric (ProQuest), and SportDiscus (EBSCO) data bases, were searched up to February 1, 2009 in English language	47	13 to 188	Multicomponent training program interventions, of long duration (≥5months), performed 3x per week, for 30–45 minutes per session, generally had superior outcomes than other exercise programs
3.Weening-Dijksterhuis et al., (2011)	A systematic review (without metanalysis) aimed to test the power effect size of interventions studies with several types of planned exercise	RCTs studies	Medline, PubMed, Cochrane, and CINAHL data bases, using MESH terms data bases in English language, published between and published between 1955-2008.	27	20 to 981	The conclusion is that there is firm evidence for training effects on physical fitness, functional performance, activity of daily living performance, and quality-of-life.
4. Cadore et al., (2013)	The systematic review (without metanalysis) was focus on supervised exercise programs that improved muscle strength, balance, and gait ability and decreased the risk of falls.	RCTs studies	Scielo, Science Citation Index, Medline, Scopus, Sport Discus, and Science Direct data bases data bases in English language and published between 1990-2012.	20	9 to 684	The multi-component exercise composed by strength, endurance and balance training seems to be the best strategy to improve rate of falls, gait ability, balance, and strength performance in physically frail older adults
5. Clegg et al. (2012)	The systematic review following metanalysis on specific primary and secondary outcomes previously selected.	RCTs and cluster RCTs studies	AMED, CINAHL, Cochrane Library, EMBASE, PSYCHINFO and PedRO data bases in English language, published between 1950-2010.	6	94 to 243	Home-based exercise interventions may improve disability in older people with moderate, but not severe frailty status. Home-based exercises are a potentially simple, safe and widely applicable intervention to prevent dependency decline for frail older people.
6. Bibas et al. (2014)	The systematic review (without metanalysis) was focus on Randomized clinical trials that tested one or more therapeutic interventions in a population of frail older adults	RCTs studies	PubMed, using Mesh and Tiab terms data base, was searched in English language, up to 2014.	38	17 to 1665	Exercise training interventions succeeded in improving PPTs, although it regress to the pre-intervention state once exercise discontinued. Home-based exercises were safe/effective and appeared to help counteract the regression. Moderate-intensity programs achieved superior results for muscle mass and function. Individuals with moderate frailty derived greater benefits.
7. Nash (2012)	The systematic review (without metanalysis) was focused on Randomized controlled trials reporting physical outcomes in frail older people	RCTs studies	Medline, Embase, AMED, PEDro, The Cochrane Library, British Nursing Index and PsychINFO between 1995 and 2010.	13	30 to 682	Exercise and some physical activity programmers, particularly moderate intensity and multi-component, are safe and can improve strength and function in the majority of frail, except highly frail with multiple comorbidities. Limited evidence on transferability of improvements into everyday life, and sustainability could not be determined.

8. Gine-Garrida et al (2014)	Systematic review following metanalysis to determine the efficacy of exercise-based interventions on improving performance-based measures of physical function and markers of physical frailty in frail older people.	RCTs studies	MEDLINE, The Cochrane Library, PEDro, and CINAHL, up to April 2013.	19	21 to 138	Exercise has some benefits in frail older people, although uncertainty still exists with regard to which exercise characteristics (type, frequency, duration) are most effective.
9. Daniels et al (2008)	Systematic review to assess the content, the methodological quality and the effectiveness of intervention studies for the prevention of disability in physically frail elderly.	RCTs studies	PubMed, the Cochrane (CENTRAL), CINAHL, and hand-searching, in English, Dutch and German up to 2007.	10	46 to 188	There is an indication that relatively long-lasting and high-intensive multicomponente exercise programs have a positive effect on ADL and IADL disability for moderate physically frail elders.
10. Chou et al (2012)	Systematic review following metanalysis to determine the effect of exercise on the physical function, activities of daily living (ADLs), and quality of life (QOL) of the frail older adults.	RCTs studies	PubMed, MEDLINE, EMBASE, the Chinese Electronic Periodical Service, CINAHL, and the Cochrane Library, between 2001 and 2010.	8	30 to 311	Exercise is beneficial to increase gait speed, improve balance, and improve performance in ADLs in the frail older adults.
11. Liberman et al (2017)	Systematic review to report the most recent literature regarding the effects of physical exercise on muscle strength, body composition, physical functioning and inflammation in older adults	RCTs and CCTs studies	PubMed and Web of Science in 2015 or 2016 in English.	34	19 to 127	Exercise has moderate-to-large effects on muscle strength, body composition, physical functioning and inflammation in older adults. Future studies should focus on the influence of specific exercise modalities and target the frail population more.
12. Dedeyne et al (2017)	A systematic review aimed to determine the effect of multi-domain compared to mono-domain interventions on frailty status and score, cognition, muscle mass, strength and power, functional and social outcomes in (pre)frail elderly (65 years).	RCTs studies	PubMed, EMBASE, CINAHL, PEDro, CENTRAL, Cochrane Central, and by citation search, author search, and reference lists up to 2016, in English, Dutch, French, or German	12	31 to 246	Overall, multi-domain interventions tended to be more effective than mono-domain interventions on frailty status or score, muscle mass and strength, and physical functioning. Results were inconclusive for cognitive, functional, and social outcomes. Physical exercise seems to play an essential role in the multi-domain intervention, whereby additional interventions can lead to further improvement
13. Arantes et al (2009)	A systematic review of the literature on physical therapy interventions and their effect on frail community-dwelling elders	CTs, CCTs, RCTs studies	Medline, Embase, PEDro, SciELO, LILACS and Cochrane Library until June 2008	15	11 to 243	There is little evidence of the effect of physical therapy intervention on frail community-dwelling elders; thus, it is not possible to reach a consensus or conclusion on the effectiveness of the therapeutic regimens proposed for this complex syndrome.
14. Frost et al (2017)	A systematic review following metanalysis aimed to synthesize randomized controlled trials evaluating home and community-based health promotion interventions for older people with mild/pre-frailty	RCTs and crossover studies	MEDLINE, MEDLINE, EMBASE, Scopus, Social Science Citation Index, Science Citation Index Expanded, Cochrane, Cochrane Central, Cochrane Effective Practice and Organization, NHS Health Economic Evaluation Database, Cochrane Methodology Register, Cochrane Groups, Database of Abstracts of Reviews of Effects, PsycINFO; Cumulative Index to Nursing and Allied Health Literature, Evidence for Policy and Practice Information Centre Register of Health Promotion and Public Health Research (Bibliomap), Sociological	7	18 to 103	Interventions of exercise in groups showed mixed effects on functioning (no effects on self-reported functioning); positive effects on performance-based functioning.

			Abstracts, Social Care Online, and Applied Social Sciences Index and Abstracts, between 1990 and 2016, in English.			
15. Lopez et al (2017)	A systematic review of the effect of resistance training (RT) alone or combined with multimodal exercise intervention on muscle hypertrophy, maximal strength, power output, functional performance, and falls incidence in physically frail elderly	RCTs studies	MEDLINE, Cochrane CENTRAL, PEDro, and SportDiscus from 2005 to January 2017.	16	24 to 616	Frequency of 1–6 sessions per week, training volume of 1–3 sets of 6–15 repetitions and intensity of 30–70%1-RM promoted significant enhancements on muscle strength, muscle power, and functional outcomes. Therefore, we suggest that supervised and controlled RT represents an effective intervention in frailty treatment.
16. Schechtman and Ory (2001)	This article uses covariate-adjusted preplanned meta-analyses of the effect of exercise on quality of life (QOL) outcomes.	RCTs studies	All medical data base provided by Cooperative Studies of Intervention Techniques - Washington University in St. Louis	4*	100 to 1323	Results indicate that exercise produced a small but significant improvement in the emotional health component of QOL, trended toward an improved social component, and did not effect perceptions of general health; exercise-related joint and muscle stresses did not increase bodily pain; and QOL improvements were independent of changes in physical functioning.
17. De Labra et al (2015)	A systematic review to examine the exercise interventions to manage frailty in older people	RCTs studies	PubMed, Web of Science, and Cochrane Central Register of Controlled Trials from 2003 to 2015, in English.	9	24 to 243	Results suggested that frail older adults seemed to benefit from exercise interventions, although the optimal program remains unclear. More studies of this topic and with frail populations are needed to select the most favorable exercise program
18. Apostolo et al (2017)	A systematic review to summarize the best available evidence regarding the effectiveness of interventions for preventing frailty progression in older adults	RCTs studies	CINAHL, MEDLINE, Scopus, Embase, Cochrane Central Register of Controlled Trials and SciELO. ProQuest Theses and Dissertations, Open-Grey, Banco de teses da CAPES (www.capes.gov.br) and Dissertation Abstracts Online (e-Thos), in English, Portuguese, Spanish, Italian and Dutch, from January 2001 to November 2015.	21	24 to 1338	Mixed results regarding the effectiveness, however, there is clear evidence on the usefulness of such interventions in carefully chosen evidence-based circumstances, both for frailty itself and for secondary outcomes, supporting clinical investment of resources in frailty intervention.

Notes: * The data was extracted from data base of 4 sites (cities), that managing a public health based community exercise intervention.

4.4.4 Exercise interventions characteristics and outcomes

In general, findings demonstrate an overall positive benefit of exercise-based interventions in the attenuation and (or) reverse of frailty, and have a substantial impact in their correlates outcomes. Considering all the interventions found in the different systematic review studies, we can attribute two classifications that are based on the following approaches according to: i) the place where the exercise interventions were carried out (community centres, gym centres, naturalistic style, home based and aquatic exercises programs); ii) use (or not) of some integrated technologies or advices for mediating exercise programs (e.g. Wii-fit, assistance device and tele-monitoring and vibration platform); iii) exercise-type associated to physical fitness component, single-component (e.g. flexibility, balance, coordination, muscle strength, aerobic walking or cycling) or multicomponent (e.g. aerobic plus strength, balance, aerobic and strength, repetitive performance of ADL tasks, reaction time plus resistance, functional training and environment adaption exercises. There is a type of exercises, which in a more contemporary way, can be called body and mind activities (e.g. Pilates, Tai-chi and Yoga). A large part of these interventions take the form of exercise group class, except the category that used integrated technologies.

There was significant variability regarding duration, frequency, type and intensity of commonly prescribed exercise programs. A general trend toward improved outcomes was noted when exercise was conducted in a moderate-supervised multicomponent (composed by strength, endurance and balance) exercise-type intervention (32–35,37,40). The SR comprised in this review also show a trend towards better results in old participants classified as pre or moderate frail, and who underwent programs lasting more than 22 weeks, with average weekly frequency of 2-3 times a week and with session time exceeding 45 minutes (31,33–35,37,38,40).

Some SR reported that many of the studies examined failed to meet the designation of physical exercise, whereas others reported well-defined, if disparate, exercise parameters. One study, for example, was not very clear when including studies that used exercise and physical therapy treatment, abruptly increasing the risk of bias in interpreting findings, which is already great, since the variability of interventions is considerable (39). Systematic reviews that included studies using some form of integrated technology considered the modulating effect of physical exercise when using this resource (27,39,42).

Table 4.3 Characteristics of systematic reviews studies according the PICOS statement and quality of evidence score.

Author (year)	Main goals	Characteristics of participants	Type of intervention	Frail criteria	Comparison	Variables	Evidence quality (total score)
1. Paw et al. (2008)	To analyse the systematic physical exercise modulation-effect on physical performance	Male and female with a variable degree of frailty status participants, age range from 77 – 88 years old living in community and health care facilities	Multi-component exercises programs (mixed strength, balance and endurance); Tai-chi and resistance training program	The author's study use the main outcomes of physical-functional fitness status to stratified older frail-population	Supervised group class exercise and group class plus home-based exercise, frequency of 2-3 times per week (one study = 4-5 times), 45 to 60 minutes of time session and time of intervention ranged from 10 weeks to 28 months.	The gait performance was used time-up and go, chair rising and stairs climbing tests; the balance performance was measured by the tandem and semi-tandem tests, Berg balance scale, one leg stand test, 10-seconds parallel and POMA tests; timed Up and Go test for gait performance;	Moderate (12 points)
2. Theou et al. (2011)	To examine the effectiveness of current exercise interventions for the management of frailty status.	Pre-frail and frail men and woman, age of 71 – 90 years old living in community, hospital and health care facilities.	Multi-component exercises and resistance training program	Only 3 studies utilized one of the validated operational definitions of frailty (Fried, and Tinetti protocol)	Supervised group class exercise, frequency of 2-3 times per week, 30 to 90 minutes of time session and 1 to 18 months of time duration	Psychosocial determinants (quality of life, cognitive functions, quality of life, ADL disability and falls). Physical health (physical activity, cardiorespiratory, muscle function, motor skills, flexibility and balance); Adverse health outcomes (body composition, biochemical, neurological and nutritional status)	Moderate (13 points)
3. Weening-Dijksterhuis et al., (2011)	To performed a state of art on exercise-training outcomes influencing functional fitness, activity of daily living, and quality- of-life	Institutionalized (living in a long-term care facilities and nursing homes) pre-frail and frail older people (age, + 70 years old.	Balance, aerobic, flexibility and strength exercises programs, combined and, functional training exercises.	The author's study use the main outcomes of physical functioning (ADL scale and physical fitness) to stratified older frail-population	Supervised group class exercise, frequency of 2-3 times per week, 45 to 60 minutes of time session and 1 to 18 months of time duration	ADL Performance, quality-of-life, operationalized as Depression, Vitality, and Perceived Health and physical fitness (endurance, balance, strength, flexibility and coordination).	Moderate (11 points)
4. Cadore et al. (2013)	To recommend training strategies that improve the functional capacity in physically frail older adults.	Pre-frail, frail and moderate-frail men and woman, age of 70 – 90 years old living in community, hospital and health care facilities.	Strength, endurance and balance training, and multi-component exercises program	11 studies classified their participants using valid protocol and 9 studies consider history of injurious falls, illness-induced functional decline and sarcopenic condition as an effective screen of frailty.	Supervised progressive group class exercise program, frequency of 1-3 times per week, 5 to 60 minutes of time session and 1 to 48 weeks of time duration.	Berg balance scale, one leg stand test, and clinical test of sensory interaction and balance) Timed Up and Go test for gait performance, the strength measurements were done using the one repetition maximum test (1RM) and isokinetic and isometric dynamometry. Data on incidence of falls	Moderate (10 points)
5. Clegg et al. (2012)	To evaluate whether home-based exercise interventions improve outcomes for frail older people.	Male and female participants with the median age was 83 years (range 78 - 88)	Home based exercise (supervised and non supervised) and a mix of home-based and group-based exercise (included if the home-based component)	Two trials used an operationalised, non-validated frailty model to select and stratify participants. Four trials did not use an operationalised frailty model but reported inclusion criteria or baseline characteristics.	Modal treatment frequency was three times per week (range 3-21 sessions per week). Treatment duration was 6 months (mean 28 weeks, range 6 weeks - 18 months).	Measures of mobility, health-related quality of life indices, self-Report questionnaire and measures of activities of daily living. Secondary outcomes measures were muscle strength, balance, depression, bone strength and adverse outcomes including falls and admission to hospital or long-term care.	Moderate (16 points)

6. Bibas et al, 2014	To test one or more therapeutic interventions in a population of frail older adults	Men and women Frail and pre-frail at baseline, age over 60 years.	Exercise training, nutritional supplementation, combined exercise plus nutritional Supplementation, pharmaceutical agents, multi-dimensional programs, and home-based trial	34 studies classified their participants using valid frailty protocol and 4 studies consider inability to descend stairs, to live in residence and sarcopenic condition as an effective screen of frailty.	Dietary counselling, balanced diet, milk protein, ricotta cheese, amino acids supplementation, nurse visits, education small groups, symbiotic, estrogens, androgens, testogel, DHEA, rhGH, Supervised group class exercise and group class plus home-based exercise program, frequency of 2-5 times per week.	Timed Up and Go test for gait performance, the strength one repetition maximum test (1RM), isokinetic and isometric dynamometry, insulin resistance, inflammatory cytokines, incidence of falls, quality of life, disabilities, death or hospitalization, frailty status, change in body weight and its composition (muscle mass and fat mass) was assessed by validated methods.	Moderate (8 points)
7. Nash, 2012	To investigate the effectiveness, sustainability and adverse effects of exercise interventions on muscle strength and physical performance in frail older people.	Male and female participants with the range age of 77 – 86, and frail	Multi-component exercises programs (mixed strength, balance and endurance); adapted Tai-chi, Hydrotherapy, PRT, and ADL tasks program	All studies classified their participants using a minimum of one valid frailty protocol	Group and individual classes exercise, and group class plus home-based exercise program, frequency of 1-7 times per week, with 30-75min session/duration, and 3 -52 weeks program	Strength, flexibility, balance, TUG, walking speed, 2-min step test and PPT, mobility, health-related quality of life indices, self-Report questionnaire, FS-36 and measures of activities of daily living.	Moderate (12 points)
8. Gine-Garrida et al (2014)	To determine the efficacy of exercise-based interventions on improving performance-based measures of physical function and markers of physical frailty in frail older people.	Men and women defined as frail according to standardized criteria, age over 65 years.	Strength, endurance, balance, flexibility and stretching training, and supervised group training, home based physiotherapy, multifactorial interdisciplinary intervention, home based exercises program	All studies classified their participants using a minimum of one valid frailty protocol	Group and individual exercise, functional training, home-based exercise and physiotherapy program, frequency of 2-7 times per week, with 8-90min session/duration, and 10 - 48 weeks program	Physical function such as mobility, gait, muscular strength, balance, endurance, and disability in ADL. Falls, incidence of fractures, tendinitis, or muscular soreness; health-related quality of life; symptoms of depression; hospitalization; and death.	Moderate (14 points)
9. Daniels et al (2008)	To assess the content, the methodological quality and the effectiveness of intervention studies for the prevention of disability in physically frail elderly	Men and women defined as frail according to standardized criteria, aged 76 to 83	Nutritional status and intervention. Exercise program, Single-Component, strength, multi-component, and both nutritional and exercise	All studies classified their participants using a minimum of one valid frailty protocol	Multicomponent exercise for 10 weeks to 18 months' duration; Home exercising independently and provided monthly phone calls. Additional support by telephone	Physical measures (e.g. weight gain, strength, mobility, oxygen uptake, physical fitness, physical activity and balance; daily life activities, disabilities, diverse frailty outcomes	Moderate (12 points)
10. Chou et al (2012)	To determine the effect of exercise on the physical function, activities of daily living (ADLs), and quality of life (QOL) of the frail older adults.	Man and Women defined as a frail participant with ages ranging from 75.3 to 86.8 years	Exercise-training single or multiple, including flexibility, low- or intensive resistance, aerobic, coordination, balance, and Tai-Chi; repetitive performance of ADLs; and task-oriented or gait train	At least one of the Adapted Fried of Physical Frailty Index, Speechley and Tinetti's criteria, and the EFS, depressed mood, , dependence on assistance in performing ADLs, fall rate, and poor nutritional status	Supervision either exercised in facilities or in communities, or home-based. 60- to 90-minute sessions, repeated daily or weekly for 3 to 12 months.	Timed Up & Go (TUG) test, gait speed, or Berg Balance Scale (BBS), performance in ADLs evaluated by the validated questionnaire or reliability inventory, and QOL evaluated by the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36).	Moderate (14 points)

11. Liberman et al (2017)	To report the most recent literature regarding the effects of physical exercise on muscle strength, body composition, physical functioning and inflammation in older adults.	Man and Women aged at least 65 years	Resistance training ranging (moderate to high intensity), aerobic training (cycling and walking), combined resistance training and aerobic training, other types of exercises including whole body vibration, exercise with horses, Pilates and Huber training, tai chi, soccer training and balance training	Different types of frailty screen and frailty related to sarcopenia	The participants exercised 50- to 60-minute/sessions, 2 to 5x/week for 12 to 60 weeks.	Outcome focused on biochemical makers of inflammation status, muscle strength, body composition or physical functioning	Moderate (12 points)
12. Dedeyne et al (2017)	To determine the effect of multi-domain compared to mono-domain interventions on frailty status/score, cognition, muscle mass, strength and power, functional and social outcomes in (pre)frail	Men and Women aged at least 65 years, classified as (pre)frail	Stretching exercises, to increase strength, balance. Resistance training, functional tasks, proprioception, aerobic exercises.	All participants defined as (pre)frail by an operationalized frailty definition.	The participants exercised 45- to 90-minute/sessions, 2 to 3x/week for 3 to 9 months	Primary outcomes including one or more of the following: frailty status or score, muscle mass, strength or power, physical functioning, and cognitive or social outcomes	Moderate (10 points)
13. Arantes et al (2009)	To carry out a systematic review of the literature on physical therapy interventions and their effect on frail community-dwelling elders.	Men and Women aged at least 65 years, classified as frail	7 types of interventions 1) muscle strengthening; 2) exercises for muscle strengthening, balance, coordination, flexibility, reaction time and aerobic training; 3) functional training; 4) physical therapy; 5) at-home physical therapy; 6) environment adaptation and prescription of assistive device; 7) water exercise	All studies classified their participants using a minimum of one valid frailty protocol	The participants exercised 2 to 3x/week for 10 to 27 weeks.	Muscle-strengthening, balance, coordination, flexibility, reaction time and aerobic training and water exercise.	Moderate (10 points)
14. Frost et al (2017)	To synthesize randomized controlled trials (RCTs) evaluating home and community-based health promotion interventions for older people with mild/pre-frailty	Men and Women over 65 years with mild/pre-frailty	Balance, Strength, , speed, walking, Power, Flexibility and resistance training, Wii fit and seated exercise, tele monitoring and home exercises.	Mild frailty identified through a validated frailty scale which contained an intermediate classification between frail and robust	Supervised exercises, monthly sessions, tele monitoring, and home-based exercise, frequency 2-3x/weeks, for 45 to 60minutes, for 10 to 48 weeks	Self reported functioning, performance based-physical functioning, gait speed, balance, time-up and go and muscle-strength tests.	Moderate (15 points)

15. Lopez et al (2017)	To know the effect of resistance training (RT) alone or combined with multimodal exercise intervention on muscle hypertrophy, maximal strength, power output, functional performance, and falls incidence in physically frail elderly	Men and Women over 65 years and older and defined as frail according to standardized criteria	Multimodal and Resistance training	All studies classified their participants using a minimum of one valid frailty protocol	Supervised progressive exercises, 1-6x /weeks, for 8 to 48 weeks. Resistance training increased individually, and sets varying to 1 of 8-15reps, 2 of 6-12 reps, and 3 of 8-10reps.	Muscle mass, muscle strength, functional capacity, and falls incidence. Specifically muscle hypertrophy, maximal strength, gait speed, timed up and go (TUG) test, sit-to-stand test, Short Physical Performance Battery (SPPB) scores	Moderate (12 points)
16. Schechtman and Ory (2001)	To evaluate the effect of exercise on quality of life (QOL)	Men and Women at least age 65	Resistance, balance, flexibility, and endurance exercise. Tai chi and educational session.		Supervised groups (large or small) exercise program, home exercise frequency of 1-6 times per week, 15 to 60 minutes of time session and 15 to 24 weeks of time duration.	Falls and falls-related injuries, strength, aerobic capacity, gait speed, balance, functional mobility and measures of activities of daily living, general health perception, emotional, pain, and social scales.	Critical Low Quality (10 points)
17. De Labra et al (2015)	To examine the exercise interventions to manage frailty in older people	Men and Women with a mean age of 82.5 ± 4.3 years old, defined as frail	Multicomponent, functional, walking, balance, resistance, and home exercise training.	Defined with a clear operational definition/measurement valid frailty protocol.	Exercise frequency of 1-5 times per week, 20 to 90 minutes of time session and 12 to 48 weeks of time duration. Resistance training increased individually, and sets varying to 1-2 of 6-8 reps, and 3 of 8reps	Frailty status and/or physical capacity and/or functional capacity, muscle strength, incidence of falls, balance and body composition.	Moderate (11 points)
18. Apostolo et al (2017)	To summarize the best available evidence regarding the effectiveness of interventions for preventing frailty progression in older adults	Older adults aged 65 and over, explicitly identified as pre-frail or frail	Multicomponent, functional, resistance, and home exercise training.	All studies classified their participants using a minimum of one valid protocol	Supervised groups (large or small) exercise program, home exercise frequency of 1-6 times per week, 15 to 60 minutes of time session and 15 to 24 weeks of time duration.	Cognition status, quality of life, activities of daily living, caregiver burden, functional capacity, depression and other mental health-related outcomes, self-perceived health and social engagement;	Moderate (11 points)

Two independent reviews selected studies that contained one arm of the RCT design controlling combined or multi-domain treatment (e.g. exercise plus especial diet, exercise plus hormonal therapy or cognitive training) (29,36). The author of these reviews revealed that both treatments combined with exercise had a unclear results when compared to exercise treatment alone, since the number of studies was relatively small (29,31,33,34,36). Only one review points to consistent positive results in the quality of life associated to substantial improvements on motor competence in physically frail older adults (32).

4.5 Discussion

To our knowledge, this SR of existing frailty-related, exercise-specific SR is the first of its kind to combine outcomes associated with any type of exercise-based interventions aiming to treat, attenuate or reverse frailty in older adults. Other SRofR papers regarding the exercise effect have been recently developed and served as a guideline for us to carry out this study (25,48). This type of approach in the treatment of information about the 'state of the art' already produced in the area of exercise (or any area of knowledge) on a specific topic seems to be a very attractive way of gathering information from highly explored themes (49).

The overall quality evidence of the included SR studies was moderate, limiting our ability to draw decisive conclusions about specific elements of results. However, it seems that the low scores of QEA were related to the type of SR, since the reviews articles that opted for a SRM show more solid evidence regarding the results presented (16,26–28), according AMSTAR guidelines. Notwithstanding the satisfactory results achieved by these reviews in the QEA, it is worth noting that even following the meta-analysis statistical treatment, some articles present a very small number of studies, which raises doubts as to the validity and weight of the evidence (28). The evidence presented in this review considerably supports a multitude of general health benefits from exercise on frail individuals, even though the mean value of the QAE of the studies classified as moderate. In fact, it seems to have been a characteristic of the different articles not to delimit only a specific and restricted sub-topic related to frailty, but the option for selecting several sub-themes decreases the possibility of performing a RSM (50). However, we must also take into account the main characteristic of intervention studies with exercise carried out with older populations, which, in general, take a multidimensional approach as a way to selected study variables (33). In addition, the number of RS (or comprehensive) included in our study is much higher than the number of RS with meta-analysis articles, an important factor that seems to limit a more solid conclusion.

Observing that most of the included SR considered only RCT studies, we can increase the degree of consistency of our hypothesis, that considers the benefits of regular exercise in the frail elderly. Considering the real nature of the findings and the reasonable evidence found in the SR studies, we can assume that, that the multi-component exercise seems to promote more satisfactory results. Looking at the SR studies it is noted that a classification for this type of program does not always consider its real concept. The ACSM defined multi-component exercise as exercise-type program whose main characteristics usually including muscle-strength, flexibility, balance and walking and balance exercises in the same session, aim to prevent falls, improve lower muscle-strength and static-dynamic balance (51). Perhaps, for some exercise programs classified as multi-component by the different studies, the term integrated exercise program would be the most appropriate.

Among the other type of interventions, the only convincingly effective intervention to improve physical fitness performance and other global health makers were muscle-strength exercises (38). The SR looing at home-based as a exercise programs exposed that this type of exercise-mediation intervention may improve disability in older people with moderate, but not severe frailty status (26,28). These results corroborate the findings reported within the different SR studies, which identify that supervised exercise had a greater impact when compared to unsupervised programs. This may be attributed to superior attention from the health care provider and the control of the actual exercise-dose may be better in supervised settings where effort, technique, motivation and volume are better controlled, thereby enabling greater impact of exercise effects (48).

This type of SR has demonstrated the importance of long-term exercise and moderate intensity to achieve impact in a large number of global health variables on pre-frail and frail individuals. Some important concepts do not appear to be associated in different studies, such as the concept of exercise periodization and alteration of stimuli over time (in order to test different benefits), which are variables to be considered in long-term programs. This results also reveal a very important finding. Few studies included in the SR papers have tested the effects of exercise on the physical frailty independent components, especially low levels of physical activity domain, which are currently the dimensions most associated to frailty status (52). However, this SR offers important clues to understand the real impact of exercise on this type of population, as well as to important information for the elaboration of useful exercise programs that contribute to better results and help attenuate the frail condition.

4.6 Conclusion

The increasing incidence of physical frail individuals warrants a crucial need to define public health interventions that improve general health, focussed on physical fitness status. Despite some limitations, such as the exclusion of SR that contained exercise but did not cleary defined the frail status of the subjects and other revisions that included studies with others therapies associated with exercise, the general results showed that structured exercise training has a positive impact on frail older adults (especially pre-frail) and should be used for the management of frailty. The multi-component exercise program seems to be the one that have the most positive impact on this type of population. For other forms of exercise, the evidence is inconclusive due to the low number of studies and evidences. More high-quality studies that use metanalysis statistical treatment are needed to clarity the real effect on specific groups of variables.

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CHAPTER 5 (STUDY 3):

EFFECTS OF A CHAIR-YOGA EXERCISES ON STRESS HORMONE LEVELS, DAILY LIFE ACTIVITIES, FALLS AND PHYSICAL FITNESS IN INSTITUTIONALIZED OLDER ADULTS**

Authors:

Guilherme Eustáquio Furtado

Mateus Uba Chupel

Humberto Moreira Carvalho

Nelba Reis Souza

José Pedro Ferreira

Ana Maria Teixeira

**Furtado GE, Uba-Chupel M, Carvalho HM, Souza NR, Ferreira JPP, Teixeira AM, et al. Effects of a chair-yoga exercises on stress hormone levels, daily life activities, falls and physical fitness in institutionalized older adults. Complementary Therapies in Clinical Practice [Internet]. 2016 May [cited 2016 Jun 13];0(0):144–56. Available from: http://linkinghub.elsevier.com/retrieve/pii/S174438811630041X; Impact factor: 1.701.

5.1 Abstract

The aim of this study was to assess the changes mediated by exercise on activities of daily life and falls (autonomy), physical fitness, salivary cortisol and alpha amylase in older adults living in social care givers centers. Methods: 35 women (83.81 ± 6.6 years old) were divided into two groups: chair-yoga exercises (CY, n=20) and control group (CG, n=15). All subjects were evaluated before and after 14-weeks of intervention. CY was involved in classes two times per week, while the GC did not participate in any exercise. Results: Fear of falling decreased in both groups, cortisol increased and alpha-amylase decreased in the CG. No significant changes occurred in physical fitness outcomes. Conclusion: Chair-yoga practice was able to maintain the PF scores and stress hormone levels, but was not able to improve the subject's perception on the ability to perform the instrumental activities of daily life.

KEY-WORDS: Older adults, yoga, exercise, physical fitness, cortisol, alpha-amylase.

5.2 Introduction

Ageing is characterized by deregulation of multiple physiological systems with deleterious effects on physical health and functional autonomy in older adults [1], [2]. Biological chronic stress has been shown to have immuno-suppressive effects and to induce a physical-frail state [3]. The gradual deterioration in the skeletal muscle system seems to be the central mechanism for decreased independency in activities of daily life (IADL) and physical fitness (PF) indicators [4]. The autonomy in the elderly can be characterized as the ability of the individual to perform IADL while demonstrating a satisfactory PF condition, without eminent risk of falling [5], [6]. Functional impairment, especially when it is generated by the consequences of falls, increases public health spending to treat patients with later sequels [7]. For this reason, recent aging-autonomy models propose an integrated approach, whose major intervention mechanics are to assesses eminent risk of falls and improve PF over time [8].

Even non injurious falls are disabling with strong associations with activity constraint, isolation, deconditioning, increased fear of falling again and depression [7]. Associated with factors such as multi-comorbidity and polypharmacy, an increased risk of falls can further increase older adult's vulnerability [9]. In this sense, to check for possible associations between hormonal parameters related to stress and psychosocial and stressful constraints seems to be a prudent direction [10], [11].

Cortisol (sCOR) is an essential hormone in the regulation of the biological stress response, but recently salivary alpha-amylase (sAA) has also emerged as a novel biomarker for evaluating stress [12]. These neuroendocrine markers play an important role in establishing the bodily reaction to stress and regulation of the autonomic function [13]. Stress responsiveness is primarily regulated by two neuroendocrine axes: the hypothalamic-pituitary-adrenocortical (HPA) and sympathetic adrenomedullary systems [14]. The HPA axis is a complex neuroendocrine stress system involved in bio-behavioral adjustments to confrontational stimuli and change [12]. Because saliva collection is a non-invasive method and for being accurate salivary biomarkers for detection of autonomic activity [15], sCOR and sAA received more attention lately in respect to their relationship with physical exercise [10]. However, results from chronic exercise on neuroendocrine modulation in the older populations are scarce [11]. In the few studies that address exercise in the elderly and biological stress, the use of diverse methodologies strip the accuracy of the inference of the results [16]. The premise that preserving an adequate state of physical independence in advanced age is related to satisfactory PF seems to be widely accepted (Fraga et al., 2011; Matta et al., 2013; Pernambuco et al., 2013).

For this reason, a physical exercise routine can be a complementary form of muscle damage prevention through the improvement of HrPf [19]–[21]. The American College of Sport Medicine (ACSM) makes it clear in their own guidelines when it refers that ten minutes of flexibility training a day, twice a week, will aid in the prevention of falls by improving balance [22]. But the recommendations on flexibility training are controversial since this type of training by itself does not seem to be enough to promote the functional benefits required by older people to maintain an adequate level of PF [23]. Among the various forms of exercise that could be practiced by older persons, yoga has been recommended as it could mitigate the deleterious effects of aging on flexibility [21], [24]. According to the literature, the benefits of regular yoga practice include improvements in balance, coordination, strength and flexibility [19], [25]. In older people with physical limitations to perform the full practice of yoga, adaptations may be made and an exercise program supported by a chair can be developed [21], [24].

To date, few publications on the effect of yoga in elderly have been published [23]. In a recent systematic review [19], the studies that tested the effects of yoga, mainly looked at variables such as strength, flexibility and cardiovascular resistance [25], psychosocial factors such as depression and anxiety [26], and biomarkers able to assess oxidative stress and lipid profile [27]. Studies involving athletes were also used to assess the acute effects of exercise on biological stress [28]. In a recent systematic review [19], Questions regarding whether biological levels of stress are associated with PF, fear of falling and psychosocial factors, as well as if the practice of yoga is able to change these parameters in the older person remain unanswered. Towards this purpose, the aim of this study was to evaluate the effects of a chair-based yoga exercise program on stress hormone levels, ADL, fear of falling and PF in institutionalized older adults.

5.3 Methods

Participants were older women living in social and health care support centres (SHC), located in the city of Coimbra, Portugal. All participants (or responsible) were required to give a full informed consent before beginning the research project. The study protocol was approved by Faculty of Sport Sciences and Physical Education Ethical Committee - University of Coimbra [Ref.: CE/FCDEF-UC/000202013]; it respects the Portuguese Resolution (Art.º 4st; Law n. 12/2005, 1st series) on ethics in research with humans [29], follows the guidelines for ethics in scientific experiments in exercise science research [30] and complies with the guidelines for research with human beings of the Helsinki Declaration [31]

5.3.1 Design of the study

This study was planned for approximately 20 weeks and was built in 3 different stages, as described below: Phase 1 (2 weeks) consisted in the evaluation of the participants before chair-based yoga exercise program. Phase 2 was an intervention study with implementation. Phase 3 (2 weeks) consisted in the evaluation of the participants after the 14 weeks of exercise. All the tests were applied before and after the exercise intervention in all groups. To minimize difference in procedures the same evaluators performed the data collection both at baseline and follow-up assessments.

5.3.2 Participants

According to a recent systematic review (08 studies, sample average of 09 participants) previous studies on exercise interventions have shown small effect size in psychobiological outcomes in similar populations [16]. For this reason, a minimum sample of 15 participants per group was recruited, sufficient to identify possible beneficial effects taking into account the size of the effect size (d = 0.50, strong effect size, power = 0.80) established [32]. Additionally, another 7 participants were recruited (30% of 15 participants) in order to prevent dropout of the study sample [33]. In total, 58 participants from a Center for social and health care support were selected from a convenience sample. After applying the inclusion and exclusion criteria and after dropout the final sample consisted of 35 female participants (age = 83.81 ± 6.6years old). The participants were allocated into two groups: chair-based yoga type flexibility exercise group (CY, n=20) and non-exercising control group, (CG, n=15).

5.3.3 Sample selection criteria

Baseline assessment tasks included measures of biosocial and global health status, which associated with the medical staff report, formed the basis for determining the selections sample criteria's in the study. The inclusion conditions for the older participants stipulated in first order were: Being female participant aged over 60 years; drug therapy controlled and updated; If the participant present clinical condition or comorbidity, it must be stable and enable participation in yoga classes as decided by local medical staff. The exclusion criteria were: not completing or withdrawing from the '8-foot-up and go test' (FGT) in the maximum time of 50 seconds, since scores above this value indicate severe mobility dependence [34]; involvement in other structured exercise program; presence of severe cardiopathy, uncontrolled hypertension or asthmatic bronchitis, musculoskeletal dysfunctions that prevented the physical testes (i.e. osteoarthritis, recent fractures), mental disorder, hearing and vision impairment, morbid obesity or the use of medications that significantly impair attention.

5.3.4 Masking

To minimize differences in assessment procedures the same evaluators performed the collection data at both baseline and follow-up measures. The psychometric scales were applied by independent assistant that establish contact with the participants without made references to the exercise program. The instructor of the exercise sessions did not take part in the data collection procedures. Precaution was taken to avoid interaction of CY exercises between individuals of the two groups by staggering the classes' schedule.

5.3.5 Assessments

5.3.6 Activities of daily life and falls

The Lawton Instrumental Activities of Daily Living (IADL) questionnaire was used. The questionnaire is used for identifying how a person is carrying out daily activities at the present time and for identifying improvement or deterioration over time in 8 domains [35]. A summary score ranges from 9 (low function, dependent) to 20 points, for 'high function' independent [36]. Tinetti Falls Efficacy Scale (FES) was used. The FES contains questions concerning the possibility of falling during the performance of 10 activities [37]. FES is represented on a 10-item analog scale and accordingly, the lower the score the greater the confidence, resulting in a high self-efficacy and reduced fear of falling when performing the 10 activities described in the questionnaire [38].

5.3.7 Physical tests assessment

The Senior Fitness Test battery (Rikli; Jones 2013) was used to assess PF. The lower body strength was determined with the '30 second's chair-and-stand test' (30s-CS), measuring the number of total stands completed in 30 seconds. The upper body strength was determined with the '30 seconds arm-curl test' (30s-AC) that measures the total number of arm curls executed in that time. To assess lower-body flexibility the 'chair sit-and-reach test' (CSR) was used measuring the distance in centimeters, (cm) of overlap or between the tips of the middle fingers when the arms are reaching up in the middle of the back as far as possible. To assess agility and dynamic balance the FGT was used, assessing the time needed for the participant to get up from the chair, walk as quickly as possible around either side of a cone placed 2.44 cm away and to sit back down in the chair. Each physical test has its respective cutoff value, however, the final scores were used as a continuous variable form.

5.3.8 Biochemical markers

Saliva will be collected by passive drool (method for collecting whole saliva), which provides the purest sample and making possible future testing. The individuals will salivate without any orofacial movement into high quality polypropylene vials to avoid problems with analyte retention or the introduction of contaminants that can interfere with the immunoassays. Collection was always at the same time of the morning in order to minimize the circadian effect of the markers used. After collection, the saliva containing tubes were store at -20ºC until analysis, then defrosted and centrifuged in order to collect the saliva sample [40]. The determination of the sAA was done by kinetic assay (Salimetrics, UK) and concentration of sCOR was determinate by competitive ELISA (Salimetrics, UK), according to the manufacturer instructions [41].

5.3.9 Chair-based yoga exercise program

The creation of the chair based CY was based on the essential philosophy of Hatha Yoga and its āsanas, focusing on the flexibility benefits provided by them [19]. Music was not used during the sessions, since it could exert influence on neurocognitive aspects [42], [43]. Exercise intensity was controlled using heart rate monitors (Polar, RCX5) randomly distributed between participants during the exercise program and monitored a low to moderate intensity effort, reaching intensities around 50-75% of maximum heart-rate values as recommended by the ACSM [22]. For safety reasons, exercise intensity was indirectly calculated using the Karvonen´s formula to predict target heart rate (HR), but with maximal (max) HR being calculated using [HR_{max}= 207 (beats per minute) - 0.7 x chronological age] for older people [44]. For this study, the sequences of exercises were prepared cautiously and reviewed according to the participants evolution [45], aiming to achieve moderate intensities in classes.

5.3.10 Exercise Adherence

Classes were offered 2-3 times/week, during 14 weeks, in a total of 32 sessions. The percentage of exercise adherence to group classes was calculated individually through the total sum of participation. When a participant had two consecutive absences, she was contacted to return to the group classes. An adherence to the exercise program between of 65% - 75% [46], was established as minimum for each participant to be included in the study.

5.4 Data analysis

The Kolmogorov-Smirnov and visual inspection was done to check the distribution of data. For an elderly population, it should be noted that the intra-individual variability of the data becomes a major research challenge, with regard to homogeneity. Thus dependent variables were log-transformed before analysis to reduce non-uniformity of error as a recurring feature on data from biological nature, except FES and IADL which were based on Likert scales [47]. Descriptive statistics were summarized as average, standard deviation, range and association between variables was done using the Spearman Correlations Rank Test. The magnitude of correlations was classified following the standards: trivial [$r \leq 0.1 - 0.3$]; moderate [$r < 0.3 - 0.5$]; strong [$r < 0.5 - 0.7$], robust [$r < 0.7 - 0.9$] [48]. Comparison between groups was accomplished using *t*-test for two independent samples. The *T*-paired test accessed differences between variables pre and post exercise and percent changes were calculated. The between-subject standard deviation for each dependent variable was used to convert the log-transformed changes of HrPf indicators into standardized [Cohen effect size (ES)] changes in the mean. The smallest standardized change was assumed to be 0.20 [49]. The statistical analysis was made with SPSS 20.0 (*Statistical Package for Social Sciences, IBM*), and $p \leq 0.05$ used as the level of significance.

5.5 Results

Table 5.1 shows the characterization of the sample. No statistically significant differences between the CG and CYG groups were found, in other words, they were homogeneous for all variables at the beginning of the study.

Table 5.1 Characteristics of experimental and control groups at baseline and comparison between groups by Two-independent samples.

Variables	Chair Yoga/Flexibility (n=20)	Control group non-exercising (n=15)	*p*	*d*
	M±SD	M±SD		
Salivary Cortisol (ug/mL)[a]	00.57(00.23)	00.65(00.19)	.488	0.09
Salivary Alpha Amylase (U/mL)	76.16(41.13)	67.98(54.60)	.496	0.16
Chair sit-and-reach test (cm)	18.90(10.48)	16.90(10.72)	.924	0.18
30s Arm-curl test (per time)[a]	11.45(04.10)	08.67(04.70)	.091	0.63
30s chair-and-stand test (per time)	09.20(03.75)	07.40(02.84)	.590	0.48
8-foot up and-go test (seconds)	20.36(16.22)	17.10(11.90)	.827	0.22
Falls Efficacy Scale (#)	27.85(21.63)	40.87 (22.76)	.804	0.58
Lawton of IADL scale (#)	20.15(04.13)	22.01(05.12)	.601	0.11

Notes: ** $p \leq 0.01$; * $p \leq 0.05$, comparisons between groups based on t-statistic; [a] logarithm transformed; M±SD = means (standard deviation); d = Cohens effect size; IADL: Activities of Daily life

Preliminary, associations between the variables studied at baseline were tested: IADL was inversely and moderately correlated with the 8f-UGT (*r* = -.347, *p* < .01), 30s-AC (*r* = -.361; *p* < .01), 2m-ST (*r* = -.343; *p* < .01); FES moderately correlated with the 30s-CS (*r* = .336; *p* < .01) and sCOR showed a moderate and inverse correlation with CSR (*r* = -.431; *p* < .01). There were no correlations between the levels of sAA and any of the other parameters assessed. When comparing the results obtained before and after the 14-weeks chair yoga exercise program (Table 5.2) FES values decreased in both groups. The percent change for the CYG is dimmed to be possible beneficial (-36%; *p* = .04). However, the FES change in the CG was -45% (*p* = .002). In both groups a large magnitude of effect size (*d* = 0.60 and *d* = 1.03 respectively) was identified. A trend towards an increase in the values of the IADL scale in the CYG group (*p* = .055) was also found with a magnitude of effect size considered as moderate (*d*= .36). No changes in the IADL score were detected for the GC.

Levels of sCOR increased significantly only in GC (+14%; *p* = .050) with a moderate magnitude of effect size (*d* = .39), whereas in the YG no significant changes in this hormone concentration occurred. The results also showed a significant decrease of sAA levels in the CG, with a substantial percentage of change and large magnitude of effect size (-47%, *p* = 0.24; *d* = .78). The HrPf indicators (2m-ST, 8f-UGT, 30s-AC and 30s-CS) did not change in both groups.

Table 5.2 Comparison between pre and post exercise intervention values.

	Chair Yoga/Flexibility (n=20)					**Control group non-exercising (n=15)**				
	Pre	Post				Pre	Post			
	M±SD	M±SD	*p*	Δ%	*d*	M±SD	M±SD	*p*	Δ%	*d*
Cortisol	00.57(00.23)	00.62(00.16)	.158	+9	0.25	00.65(00.19)	00.73(00.22)	.050	+14	0.39
Alpha Amylase	76.16(41.13)	70.54(43.46)	.701	-7	0.13	67.98(54.60)	36.32(15.31)	.024	-47	0.78
Chair sit-and-reach	18.90(10.48)	21.01(13.02)	.398	+11	0.17	16.90(10.72)	16.30(10.46)	.883	-4	0.05
30s Arm-curl	11.45(04.10)	10.95(03.33)	.542	-4	0.13	08.67(04.70)	08.06(03.78)	.929	-7	0.14
30s chair-and-stand	09.02(03.75)	09.30(04.24)	.937	+1	0.06	07.40(02.84)	06.20(03.91)	.128	-16	0.35
8-foot up and-go	20.36(16.22)	18.90(12.17)	.989	-7	0.10	17.10(11.90)	14.02(05.75)	.484	-18	0.32
FES Scale	27.85(21.63)	17.90(08.08)	.042*	-36	0.60	40.87 (22.76)	22.46(10.44)	.002**	-45	1.03
Lawton of IADL	20.15(04.13)	21.55(03.59)	.055	+7	0.36	22.01(05.12)	22.33(04.28)	.783	+2	0.06

Notes: ** *p*≤0.01; * *p*≤0.05, comparisons between groups based on t-statistic; [a] logarithm transformed; M±SD = means (standard deviation); d = Cohens effect size; IADL: Activities of Daily life

5.6 Discussion

The objectives of this study were to assess the effects of a structured program of CY in an older population on: physical fitness, which takes place as a set of global health-related measures (Nelson et al., 2007); on functional autonomy, which in this study was evaluated through subjective analysis instruments for activities of daily living, (Graf, 2008); on the fear of falling (Morgan et al., 2013); and on biomarkers related to autonomic system function and biological stress, representing a promising line of studies in older populations [11].

The results of this study revealed significant changes or 'benefit possible' on FES when baseline values where compared to the ones after 14 weeks of exercise intervention with CY. However, this change could not be attributed to exercise only, since the CG also presented the same changes. It is possible that the change from winter to spring, might have also influenced the results obtained. However, two new correlations between FES and the FGT and the 2MST have emerged in the CY, together with the increase in the inverse correlation with the 30s-CS test (r = -0.34 versus r = -0.57) that are not present in the CG. Studies have linked PF and the risk of falls, but even when they found positive results, they recurred to other assessments, so it seems to be more important emphasizing the preventive character of the exercise.

This probably happened because a measure of subjective assessment, first of all, should be combined with studies that use direct measures related to falls, with the objective to explore the real sensitivity of exercise effects under these scales. It would be important to check for the socially desirable answers; check if the initial values have been overestimated and finally, assess the relationship between the decreased FES with the improvement of the static and dynamic balance [50]. Improvements in such parameters were not found in our results (although a correlation between FES and the FGT, the test for static and dynamic balance, did appear), unlike other studies, which suggest that bodily practices like yoga or similar activity are more effective for the elderly population when compared to other exercise programs. The other HrPf tests results showed no improvements as no differences were found in the scores between the first assessment moment and 14 weeks after, at the end of the program. Regarding the IADL our results show a tendency ($p<.055$) for an increase in functional independency on these activities after the intervention program.

Although this institutionalized groups do not have the opportunity and real need to perform independent activities since they live in a care giver center where most of those activities are provided for them, other activities like mobility, endurance to walk and other physical activities can assist to avoid accidents in those environments. In fact, our results did show a correlation between FES and IADL, that was reinforced after the exercise intervention in the CYG. In our study both groups were classified as "severely dependent" (cut off > 20 points) at the beginning of the program and remained in that condition 14 weeks after. Studies with a similar methodological design and sample are scarce in the literature. Other studies used younger samples aged between 60-75 years old and that may justify the limited responses obtained with the chair based yoga/flexibility exercise program. A small and non-pathological increase of the sCOR levels in the CG was found in our study. A small rise in sCOR levels related to exercise practice was expected in the CY but not in the CG. Other factors may interact with sCOR levels such as psychosocial life stressful events with ageing [51].

It is possible that the chair-based exercise could have helped protect against such stressors. The lack of studies involving similar samples makes it difficult to create a solid evidence of the role of exercise as modulator of HPA axis in this population. At the same time, some studies involving analysis of the sAA reveal considerable variation in the activity of this enzyme across populations. The patterns of between-population differences have been linked to the number of AMY1 copies, which is seen as an adaptive response to the intake of dietary starch and It can also reflect a decrease in mucosal immunity since sAA is also used as a first barrier to bacterial colonization in the mouth [40]. In this study there was a substantial decline in sAA values in the CG but not in the CY where the values remained stable.

The similarities of the PF parameters between the CG and CY suggest that this type of exercise does not promote significant changes (at physiological and PF levels) to justify its use in older subjects with these specific characteristics. Importantly, this age group is characterized as having a 'very poor physical condition', comparing our baseline results with the cutoff values of the original study realized in older American population [52], and with other studies using Portuguese samples living in the community [53]. In addition, factors such as volume, intensity and frequency of exercise (exposure over time) or even another type of exercise practice could be used to promote significant changes in these variables. For example, more intense and challenging yoga exercises maybe more effective as shown in other studies [19]. In our study, the average intensity based on heart rate monitoring varied between 50%-57% of the theoretical HR_{max}. Such values are characterized as low-intensity exercise [54], even for very old participants. However, the chair-based method adopted to perform the Yoga exercises may have been a factor to the greater exercise adherence (average 69%) throughout the program compared to other studies.The age group of the participants may be seen as limiting factor that attenuated the usual progression of the YG exercise program. It is expected that activities like yoga exercises move forward and challenge flexibility in the sitting and lying positions [25], or stay longer in standing position stimulating to improve the strength, resistance and static/dynamic balance [19].

5.7 Conclusion

The results suggest that the chair-based yoga/flexibility program was able to maintain the levels of sCOR and sAA protecting against stress and infection but was not able to promote substantial increments in the other variables analyzed. However, comparison between groups after the exercise program showed that there were statistically significant differences (results not shown) found mainly in the PF variables, which may reflect the maintenance of the PF capacities in the CYG, corroborated by the increase seen in the IADL scores, as opposed to the CG that showed a trend towards a decline in the PF levels.

The advanced average age of the participants in our study has led us to choose the chair-based exercise method, which limited the progression expected of many parameters of PF. It can also be hypothesized that the effect of motivation for the tasks, caused by emotional instability or acute manifestations of chronic diseases is a striking feature of these populations, and seemed to have also influenced the predisposition to complete the some activities inherent to the study [46].

This study provides scientific evidence that, apart from the adaptation of the chair-based exercise program, other variables must be controlled so that the practice becomes more effective for this age-group population. Thus, we recommend that elderly health care centers incorporate these practices with the necessary adaptations from the traditional yoga, seen as a well-established practice with very positive benefits for elderly people. We suggest the implementation of more studies using samples with low HrPf and more advanced age groups. Given the inter-person variability of some of the biochemical markers used, especially the sAA, increasing the sample size is also recommended.

The progressive reduction of the time spent by the participants in the 'seated position in the chair' is also recommended. Such procedure would decrease the recovery interval to effort, increase intensity and add time to the exercise program. Thus, it would be expected that the participants perform more demanding routines from the physical point of view, which may raise the profile of the results and positively influence the subjective perception of functional autonomy related to activities of daily life and risk off falls.

5.8 References

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SECTION III

Cross-section design: relationships between physical frailty and global health domains

CHAPTER 06 (STUDY 4):

PHYSICAL FRAILTY AND HEALTH OUTCOMES OF FITNESS, SEX HORMONES, PSYCHOLOGICAL AND DISABILITY IN INSTITUTIONALIZED OLDER WOMEN: AN EXPLORATORY ASSOCIATION STUDY

Authors:

Guilherme Eustáquio Furtado

Miguel Patrício

Marisa Loureiro

Eef Hogervorst

Olga Theou

José Pedro Ferreira

Ana Maria Teixeira

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6.1 Abstract

Little is known about symptoms associated with frailty in institutionalized Portuguese older adults. The study aimed to investigate the association of frailty with diverse geriatric health characteristics and how the latter might contribute to the former. Cross-sectional data of 140 women aged over 75 years were analyzed. Data were collected between March and June, 2016. Fried's definition of physical frailty, psychological, sex hormones, disability and physical fitness outcomes were examined. Prevalence of frailty was 40%. Frail women had lower scores in cognitive and physical fitness, and high scores for depression and comorbidities. Significant correlations emerged between frailty and disability, fear of falling, aerobic resistance and cognition. Regression analyses and Receiver Operating Curve showed that only aerobic resistance (sensitivity [93-96%]; specificity [74-77%], p=0.001) and cognition (sensitivity [77-88%]; specificity [65-71%], p<0.001) remained in the equation to independently contribute to physical frailty. A trend towards lower systolic blood pressure in the frail group may reflect being less physically active and/or having more systemic comorbidity. Fried's model can be considered applicable. Using simple functional fitness and cognitive measures rather than using less reliable self-report assessments can better identify those with physical frailty The role of blood pressure in physical frailty status needs to be further explored.

Keywords: Frail-older adults, disability, physical fitness, sex steroid hormones, cognition.

6.2 Introduction

The growing numbers of older people in European Countries is one of the main reasons for increasing costs demands on public health systems, especially on medical services and long-term social services (Matlabi, Behtash, & Shafiei, 2016). In Portugal, the term “nursing homes” is used to define institutions that assist elderly people with (or not) chronic diseases and physical constraints, offering health care, social support, nutrition and leisure activities. It constitutes a social response developed in collective housing, temporary or permanent, for older people in situations of greater risk of loss of independence and/or autonomy (Almeida & Rodrigues, 2008). Although not all institutionalized older persons are classified as physically dependent, this state furthers functional decline and increases care demands (González-Vaca et al., 2014). It is therefore important to be able to identify/monitor frailty and its associated risk factors in this population.

Frailty is conceptualized as a state in which reserve function across multiple physiological systems decline, thereby predisposing them to poor functional health, institutionalization and death (Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013). Linda Fried and colleagues developed the phenotype of Physical Frailty (PF) construct whose primary characteristics are sarcopenia, negative energy intake and physical inactivity. The identification of five PF assessment criteria enables the characterization of older persons in three frail subgroups, namely as non-frail pre-frail and frail individuals (Fried et al., 2001). In the past 15 years, this construct has been shown to have good criterion validity to evaluate PF in different populations cohorts (Coelho, Paúl, Gobbens, & Fernandes, 2015). PF is an important predictor of serious adverse health incidents. The current evidence clearly shows the relationship between PF and chronic disease, disability, and psychosocial and biochemical markers, currently known as frail correlates (Morley, 2011). Frail older men have a higher risk of mortality than frail-older women (Theou, Brothers, Mitnitski, & Rockwood, 2014). However, findings in recent studies are unanimous in revealing a higher incidence of PF in older women when compared to older men (Chang & Lin, 2015).

Institutionalized older persons have more heterogeneous health conditions when compared with those living in the community (González-Vaca et al., 2014). It is essential to investigate different demographic and general health outcomes to understand the evolution of this phenotype. Importantly, robust findings support the idea that physiological systems and environmental factors are intrinsically interconnected with the PF condition. In Portugal, this is the first exploratory study that investigates the interconnections between Fried’s PF model and adverse biopsychological geriatric health outcomes.

Thus, the goals of this study were to characterize PF in people living in nursing homes, examine associations between PF and adverse general health outcomes and also, to explore the sensitivity, specificity, and prognostic performance of adverse geriatric health outcomes in identifying PF status in institutionalized women.

6.3 Methods

6.3.1 Study Design

The participants of this study consisted of a subset of participants from the study protocol previous published (Teixeira et. al., 2016). Cross-sectional data from the baseline assessments were used for the current paper. This is an exploratory case-control local population-based survey (Pearce, 2012), that collects information on PF incidence in older women living in nursing homes of social and health care support in Portugal (CHS). This pilot study was designed to provide information on the trends and results expected when using a representative probabilistic sample of this population in future studies. On the first stage of CHS selection, of a total of 206 collective accommodation located in the city of Coimbra, 57 institutions (27%) were classified as CHS. From these CHS, a total of five institutions that presented the following characteristics were selected: a) public or co-participated by local Social Security CHS; b) CHS where the elderly live in long-term accommodation, c) CHS that have the same daily routine, including health and social care practices.

6.3.2 Sample selection criteria

The participants were selected using a non-probably convenience sampling based on the geographical area of the Portuguese Center region of Coimbra city. The primary stage of assessment was information provided to the potential participants by the medical professionals from each CHS, combined with clinical primary outcomes information. The initial recruitment consisted of 305 (100%) institutionalized-dwelling potential participants. However, specific selection criteria were applied: women aged over 60 years and willing to assent to take part in the study spontaneously; drug therapy and clinical conditions controlled and updated; no presence of any type of health condition that could prevent testing of functional autonomy, such as severe cardiopathy, hypertension, uncontrolled asthmatic bronchitis, musculoskeletal conditions (i.e., osteoarthritis, recent fractures), mental disorders, and morbid obesity. Even before applying these criteria, 128 individuals (42%) were excluded due to several negative clinical conditions such as physical, cognitive, hearing or visual severe impairments. A total of 37 (12%) elders dropped out during the data collection phases. The final analyzed sample consisted of 140 (46%) older women.

6.3.3 Ethical aspects

The directors of the CHS, the participants and/or their legal representatives signed consent forms. This study was approved by the Faculty of Sport Science and Physical Education Ethical Committee (Reference code CE/FCDEF-UC/000202013) - the University of Coimbra, respected the Portuguese Resolution (Art. 4st; Law n. 12/2005, 1st series) and complied with research guidelines in humans of the Helsinki Declaration (Petrini, 2014).

6.3.4 Outcome measurements

All sample variables were measured by the same member of the research team. The quality of data was reported through scores of internal consistency reliability (ICR). As in previous studies, biosocial, anthropometric and clinical health variables that presented differences between frailty subgroups were considered as a co-variate in the correlation and regression models due to the potential confounding effect that these variables can exert on the results (de Vries et al., 2011). The general health indicators of mental health, psychological well-being, physical fitness, functional disability and sex steroid hormones, were analyzed as central outcomes. PF status was also analyzed as a central outcome.

6.3.5 Physical Frailty screening

The prevalence of PF was calculated, as well as the presence of each one of the five independent components of the PF criteria (Fried et al., 2001). Weight loss was assessed by self-reporting unintentional weight loss of four kilograms or more in the last six months. Exhaustion (self-reported) was evaluated by the negative concordance of questions number 7 and 20 from the Centre for Epidemiologic Studies in Depression (CES-D) scale (Gonçalves, Fagulha, Ferreira, & Reis, 2014). Weakness was analyzed using the handgrip strength test (HGT), adjusted for body mass index (BMI) and stratified by gender (ICR = 0.84). Slowness was measured using the 4.6 meters walking test (4.6-WT), whose results are expressed in seconds and adjusted for gender and height (ICR = 0.80). Low PA was assessed by the International Physical Activity Questionnaire short form (IPAQ). Participants classified with low levels of PA had a positive score for the PF (ICR = .78) (Santos et al., 2010). The positive evaluation of one or two criteria classified the participants as pre-frail, in three or more as frail and as non-frail, when the subject had none of the PF criteria.

6.3.6 Sociodemographic and anthropometric data

Chronological age was analyzed as a continuous variable. Marital status was classified into four categories. Level of education was classified according to the Portuguese educational system. Body mass was determined using a portable scale with a precision of 0.1 kilograms (ICR = 0.89) and stature was determined using a portable stadiometer with a precision of 0.1 centimetres (ICR = 0.87) for BMI calculation. Waist and hip circumferences were measured using a retractable glass fibber tape measure (ICR = 0.87, 0.94 and 0.76, respectively).

6.3.7 General health status

Comorbidity was assessed by using the Charlson Comorbidity Index (CCI) (Charlson, Szatrowski, Peterson, & Gold, 1994). Nutritional status was measured using the Mini Nutritional Assessment (MNA) (Guigoz, 2006). To register systolic (SBP) and diastolic blood pressure (DBP), the digital device OMRON model M1 Plus was used. Self-reported health status and medication use were assessed through questions number 6 and 18 of the MNA, respectively. Exercise behaviour was assessed by questions number 7 and 24 from the Attitudes to Ageing Questionnaire (AAQ) (Laidlaw, Power, & Schmidt, 2007).

6.3.8 Mental health and psychological well being

The Mini-Mental State Examination (MMSE) was used to assesses cognitive function (Folstein, Folstein, & McHugh, 1975). To assess health psychological status, CES-D depression scale (Gonçalves et al., 2014), Rosenberg Self-Esteem Scale (RSES) (Neto, 1996) and the Satisfaction with Life Scale (SWLS) were used (Barros, Félix; Neto, 2004).

6.3.9 Functional disability and physical fitness

The Portuguese version of the Katz Index of Independence in Activities of Daily Living (IADL) (Katz, Downs, Cash, & Grotz, 1970) and Tinetti Falls Efficacy Scale (FES) was used (Melo, 2009). Upper body muscle-strength was assessed with the '30 seconds arm-curl test' (30s-AC) (ICR = 0.89). Aerobic resistance was measured through the "2-minutes step test" (2m-ST) (ICR = 0.78) (Rikli & Jones, 2013).

6.3.10 Sex steroids hormone makers

Saliva samples to measure cortisol (CORT), Dehydroepiandrosterone (DHEA) and Testosterone (TEST) levels, were collected by passive drool always at the same time in the morning, to minimize circadian effects. The levels of sex steroids hormones were determined by competitive ELISA according to the kits manufacturer instructions (Salimetrics UK, 2017).

6.3.11 Statistical procedures

Normality assessment of continuous variables was performed resorting to Shapiro-Wilk tests. Continuous variables were described by their medians, 1st and 3st quartiles, absolute and relative frequencies. The comparison between the frailty sub-groups was done using ANOVA or Kruskal-Wallis. Total and partial Pearson or Spearman coefficients were computed to assess correlations controlling for predetermined co-variates that presented differences in the ANOVA. A linear regression using stepwise backward elimination was undertaken, considering the significant geriatric health outcomes which had been associated with PF status in correlations and regression analyses, adjusted for predetermined co-variates. To examine the contribution of each general health outcome in explaining PF, the univariate diagnostic value of each variable in the model was determined using ROC (receiver operating characteristics) analysis, comparing non-frail versus pre-frail and non-frail plus pre-frail versus frail subgroups. For each model, a 95% confidence interval (CI) from percentiles for the area under the curve (AUC) was determined. In all regression models the collinearity was checked using Variance Inflation Factors and the goodness of fit model was verified by Nagelkerke R square test. The level of significance adopted was 0.05. All computations were performed using IBM/SPSS Statistics 21 and R version 3.3.1 programs.

6.4 Results

In the total sample, median (1^{o} and 3^{o} quartiles) age was 83.0 (77; 88). In total 62.9% (n = 88) of the participants considered their health not to be good, 126 out of 140 participants (90%) reported that they did not participate in regular exercise programs and 87.3% of the total sample considered regular exercise ‘important or very important’ at any age. Of all participants, 56 (40%) were considered as frail, 53 as pre-frail (38%) and 31 were as classified as non-frail (22%). When frail sub-groups were compared, statistical differences were found for the level of education, comorbidities, mental health (CES-D and MMSE), functional disability (IADL, and FES) and physical fitness of 2-MST and 30s-AC (Table 6.1).

Table 6.1 Comparison by frailty syndrome index for adverse geriatric health outcomes (n = 140).

	Non-frail (n=31, 22%)	Pre-frail (n=53, 38%)	Frail (n=56, 40%)	*p* value
Sociodemographic data M(1;3)				
Chronological age (years)	83 (77; 88)	83 (76; 89)	83 (77; 87)	0.988
Level of education (degree)	4.00 (3.00; 6.00)	3.00 (3.00; 4.00)	3.00 (2.00; 4.00)	**0.034**
Anthropometric measurements M(1;3)				
Body mass index (kg/m^2)	27.24 (24.34; 30.08)	28.90 (24.45; 31.46)	30.03 (25.64; 32.16)	0.086
Waist circumference (cm)	93.00 (86.00; 100.50)	92.00 (83.00; 100.00)	92.00 (85.25; 97.25)	0.693
Hip circumference (cm)	99.50 (94.50; 104.60)	102.50 (97.00; 107.00)	102.53 (96.50; 109.00)	0.302
Waist-to-hip *ratio*	0.93 (0.88; 1.00)	0.90 (0.84; 0.97)	0.89 (0.83; 0.94)	0.078
General clinical health status M(1;3**)**				
Self-reported health status (n; %)				
Not as good	21 (67.7%)	30 (56.6%)	37 (66.1%)	
As good	2 (6.5%)	6 (11.3%)	9 (16.1%)	
Does not Know	0 (0%)	3 (5.7%)	1 (1.8%)	0.400
Better	8 (25.8%)	14 (26.4%)	9 (16.1%)	
Mini nutritional assessment M(1;3)	25 (24; 26.5)	25.5 (24; 26)	24 (22.75; 26)	0.074
Systolic blood pressure (mm/H)	137 (114; 153)	135 (119; 148)	129 (120; 139)	0.210
Diastolic blood pressure (mm/Hg)	65 (57; 77)	65 (61; 72)	66 (59; 74)	0.868
Charlson comorbidity index (score)	7 (6; 10)	6 (6; 8)	7.5 (7; 9)	**0.010**
Physical exercise behaviour (n, %)				
Little or nothing important	2 (6.5%)	6 (11.3%)	12 (21.4%)	
Important or very important	29 (93.5%)	47 (88.7%)	44 (78.6%)	0.118
Participation (n, %)				
I'm not involved	26 (83.9%)	47 (88.7%)	53 (94.6%)	
I'm involved	5 (16.1%)	6 (11.3%)	3 (5.4%)	0.254
Mental health status M(1;3)				
CES-D depression (score)	20 (13; 27)	18 (14; 27)	24 (21; 31)	**0.012**
Mini mental state exam (score)	25 (21; 27)	21 (17; 25)	17 (13; 22)	**< 0.001**
Psychological well-being M(1;3)				
Global self-esteem (score)	24 (19; 27)	23 (19; 25)	23 (21; 25)	0.453
Satisfaction with life (score)	23 (13; 27)	24 (21; 29)	22 (19; 27)	0.121
Functional disability M(1;3)				
Katz's instrumental ADL (score)	0 (0; 3)	1 (0; 1)	1.5 (1; 3)	**0.004**
Fear of falling scale (score)	33 (14; 40)	33 (13; 65)	41 (28.5; 59)	**0.023**
Physical fitness				
Two minutes step (aerobic) test (reps per time)	50 (42; 58)	40 (30; 45)	27.5 (16; 36.5)	**<0.001**
Thirty seconds arm curl test (reps per time)	13 (10; 15)	11 (9; 14)	9 (7.5; 10.8)	**<0.001**
Salivary sex steroids hormones M(1;3)				
Cortisol (µg/mL)	0.26 (0.16; 0.29)	0.21 (0.11; 0.27)	0.27 (0.16; 0.33)	0.115
Dehydroepiandrosterone (pg/mL)	26.97 (7.42; 33.16)	19.77 (5.05; 40.82)	31.2 (7.42; 45.98)	0.741
Testosterone (pg/mL)	59.01 (43.15; 100.74)	57.25 (39.29; 83.99)	64.15 (46.87; 82.3)	0.428

Notes: Abbreviations: ADL = activities of daily living; µg/mL = microgram per millimeter; pg/mL = picogram per millilitre**;** CES-D of depression scale; cm = centimeters; Kg/m^2 = kilograms square meter; mmHg = Millimetre of mercury; M (1;3) = Median of 1° and 3° quartlile.

Physical Frailty showed significant but small associations with CES-D, SBP and MNA; was moderately associated with IADL and FES; and strongly associated with the MMSE, 30s-AC and 2-MST. The results found indicate an indirect correlation of PF with CORT and 30s-AC (moderate association) and the expected associations within DHEA, CORT and TT also appeared. After partial correlations, associations remained stable (Table 6.2).

Table 6.2 Spearman and their equivalent partial correlations (p values in bold) between frailty syndrome total score and adverse geriatric health outcomes (n = 140)

	Uncontrolled		Controlling†	
General Health outcomes	r	p	r	p
Mini nutritional assessment	**-.222****	**.008**	**-.205****	**.016**
Systolic blood pressure (mm/H)	**-.232***	**.031**	**-.235***	**.005**
Diastolic blood pressure (mm/Hg)	-.045	.595	-.006	.946
Charlson comorbidity index (score)	.106	213	.056	.509
CES-D depression (score)	**.173***	**.041**	.104	.224
Mini mental state exam (score)	**-.452****	**.000**	**-.424****	**.000**
Global self-esteem (score)	.043	.616	.140	.101
Satisfaction with life (score)	-.079	.353	-.062	.469
Katz's instrumental ADL (score)	**.269****	**.001**	**.264****	**.000**
Fear of falling scale (score)	**.265****	**.002**	**.217****	**.010**
Two minutes step (aerobic) test	**-.585****	**.000**	**-.552***	**.000**
Thirty seconds arm curl test (	**-.403****	**.000**	**-.328****	**.000**
Cortisol (µg/mL)	.103	.226	.040	.644
Dehydroepiandrosterone (pg/mL)	.073	.226	097	.256
Testosterone (pg/mL)	.025	.773	.005	.953

Notes: ** *p*≤0.001; * *p*≤0.005; †partial correlation values are expressed in bold of each variable, controlling for level of education

On the basis of these outcomes, a stepwise linear regression model was built using all variables that had shown associations with PF total score, using stepwise backward elimination. In a second step, again using stepwise backward elimination, variables were entered which had shown differences between groups using ANOVA. Sex steroids hormones (DHEA, CORT and TT) were entered in a third step but were removed from analyses as they did not modify associations. In the first step model, the 2m-ST was left in the model (*B* = -.04, SE = .007, ß = -.43, p < 0.0001). Co-linearity was present for 30-sAC (tolerance = .83), but the 2m-ST offered better adjusted R squared (by itself adjusted R squared = .31, compared to 30s-AC, adjusted R square = .11). Lower SBP also predicted PF scores in the equation independently (*B* = -0.02, SE = .005, ß = -0.21, p = 0.002) in the first step. In the second step, the MMSE scores were entered (*B* = -0.09, SE = 0.02), ß = -.32, p < 0.0001).

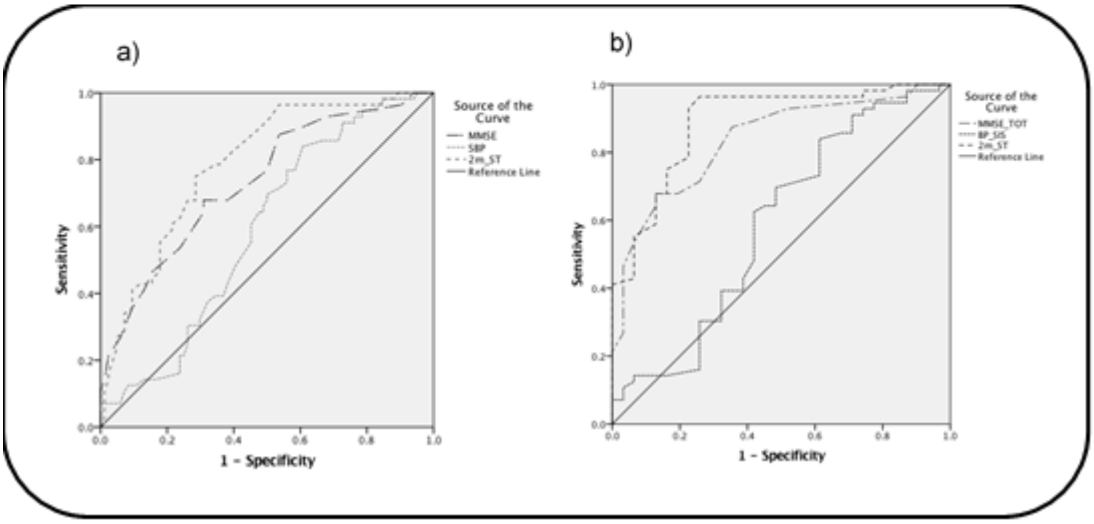

Figure 6.1 Receiver operating characteristic curve analysis for test performance: a) Frail versus non-frail group; b) Frail versus non-frail plus pre-frail group.

6.5 Discussion

The main findings of this study were that after regression analyses only aerobic resistance and cognition remained in the equation to independently predict PF. Our study showed that the prevalence of PF in these institutionalized women was 40%. This estimate is higher when compared to studies in community-dwelling people (34.9%) in Portugal (Duarte & Paúl, 2015). The prevalence in our study is lower than the FINAL (69.3%, n = 187), CUENCA (53.7% n = 281) and higher than the FRADEA (16% n = 993) Spanish studies (Abizanda et al., 2013; de la Rica-Escuín et al., 2014; Garrido, Serrano, Bartolomé, & Martínez-Vizcaíno, 2012). In our results, weakness and slowness were the two main components of PF with the highest incidence, wich were similar to findings reported in the FINAL study (de la Rica-Escuín et al., 2014).

All the subjects in the total sample and subgroups were classified as well-nourished. In contrast, a community Portuguese study with community dwellings samples, revealed a significant prevalence of malnutrition in PF (Sewo Sampaio et al., 2015). In our study, regular dietary control was performed by a nutritionist which seemed to exert a protective nutritional effect. However, the BMI scores classified the participants on average as obese, which associated with PF reveals a pattern known as sarcopenic obesity. We also found a trend for lower blood pressure (SBP) values in the frail sub-group. After 70 years, there are some comorbidities that can cause changes in vascular structure that when added to the polypharmacy use, can cause BP values to decrease substantially (Mermans et al., 2016). Some studies demonstrate that low scores of BP are associated with poor outcomes in frail people, however, BP as a marker of PF remains controversial (Muller, Smulders, De Leeuw, & Stehouwer, 2014).

Surprisingly, a large percentage of our sample mentioned the importance of regular exercise. The role of regular exercise in attenuation and reversal of PF is already well documented (de Labra, Guimaraes-Pinheiro, Maseda, Lorenzo, & Millán-Calenti, 2015). However, public policies to encourage regular participation in physical exercise programmes do not seem to extent to populations with special needs in Portugal. The relationship between PF, functional disability and physical fitness has already been observed in many other studies and some of these markers (i.e. ADL) were identified as PF-independent predictors (Chang & Lin, 2015). In the same direction, higher scores of comorbidity, depression and cognition impairment are also strongly associated with PF status. Unlike our results, previous studies have found associations between PF and free testosterone (Hyde et al., 2010) and lower levels of DHEA were significantly associated with increased odds of PF and mortality (Baylis et al., 2013). These differences could probably be explained by the larger samples used in both of those studies. Importantly, low cognitive function was also an important predictor of PF either as assessed by a total score or as group membership. While it could be argued that circular reasoning may confound the analyses for aerobic fitness variables, this is not the case for cognitive function. Earlier it was argued that cognitive decline as assessed by MMSE is an important part of PF (Lerner, Liben, & Mueller, 2015), which was confirmed in our analyses.

The main limitation of this study was the fact that the sample was not representative of all institutionalized Portuguese older populations and also, the predominance of institutionalized-dwelling female individuals in Portugal is a factual circumstance. The other limitation is the cross-sectional design, that does not permit assessment of the temporal and thus potentially causal relation of variables, as is the case of this study. Despite the study revealing interesting clues to future research, the relatively small sample size could have provided inadequate statistical power to detect some modest but meaningful associations as statistically significant. This study is the first cohort study using saliva samples. Salivary measures have emerged in biopsychological research because they are less invasive when compared to urine and blood collection. Our interest in the subsequent approach will be to verify the effects of a long-term exercise intervention as a co-adjuvant therapy on this population. In this sense, this study provided us with some clues to elaborate a non-pharmacological mediation approach, aimed to attenuate the age-related effects associated with the frail condition.

6.6 Conclusion

The phenotype of physical frailty status developed by Fried and colleagues can be considered applicable to institutionalized-dwelling Portuguese older women. Frailty was associated with a poor aerobic resistance fitness and cognitive function. We reported that two simple measures can provide an objective screening assessment for frailty in this population. The role of blood pressure in frailty needs to be further explored.

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CHAPTER 7 (STUDY 5):

PHYSICAL FITNESS AND FRAILTY SYNDROME IN INSTITUTIONALIZED OLDER WOMEN**

Authors:

Guilherme Furtado

Miguel Patrício

Marisa Loureiro

Ana Botelho Teixeira

José Pedro Ferreira

**Furtado G, Patrício M, Loureiro M, Teixeira AMAM, Ferreira JPJP. Physical Fitness and Frailty Syndrome in Institutionalized Older Women. Percept Mot Skills [Internet]. 2017 May 31 [cited 2017 Jun 12];124(4):3151251770991. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28560893; Impact factor: 0.703.

7.1 Abstract

Associations between frailty and physical-functional fitness (PFF) indicators in frail women over 65 years of age remain largely unexplored. This study analyzed the relationship between old physical frailty syndrome (PF) and PhFi indicators and assessed how the latter might predict the former. Participants were 119 elderly women (81.96 ±7.89 years) recruited from four social and healthcare centers. PhFi was assessed through muscle strength tests of upper and lower limbs, endurance, agility-dynamic balance, flexibility and body composition. The following PF indicators were assessed: weight loss, exhaustion, weakness, slowness and low physical activity level. Significant correlations were found between PF and endurance, agility-dynamic balance, upper and lower limbs muscle strength tests. Comparison analyses also revealed that, among PF groups, the frail subgroup performed significantly poorer on all PFF measures except body composition. Additionally, a Receiving Operating Characteristics curve analysis revealed good diagnostic accuracy for predicting PF by using the agility-dynamic balance test (AUC=.82, 95% CI [0.74, 0.90]; sensitivity and specificity were 70.4% and 84.8% for the cut-off = 16.22 seconds). Thus, the agility-dynamic balance test is a promising tool for screening institutionalized older people for risk of physical frailty.

Keywords: Physical Frailty, older women, physical fitness, agility-dynamic balance.

7.2 Introduction

Physical Frailty syndrome (PF) is a complex ageing expression determined by ontogenetic and phylogenetic factors (Fried et al., 2001). Chronic stress has been shown to have immuno-suppressive effects that accelerate aging and cause cumulative disorders in many physiological systems, resulting in a frail state (Clegg & Trust, 2011). In PF, physiological reserve and defense functions decline (Fried et al., 2001), compromising the individual's capacity to withstand chronic biological stress (Afilalo et al., 2014) and leading to institutionalization or hospitalization, often followed by a premature death (Lally & Crome, 2007). According to geriatric specialists, PF is a highly prevalent and important physical health impairment associated with five identifying criteria: weakness, low resistance to effort, slowness, low physical activity levels and unintentional weight loss (Abizanda et al., 2013; Rockwood, MacDonald, Sutton, Rockwood, & Baron, 2014).

Despite relationships between the decline in the physical functioning and PF, we cannot attribute to PF any central cause (Cho, Scarpace, & Alexander, 2004; Greene, Doheny, O'Halloran, & Anne Kenny, 2014; Kim et al., 2010). Progressive muscle damage related to the deleterious effects of senescence, seems to be at its pathophysiological core (Mohler, Fain, Wertheimer, Najafi, & Nikolich-Žugich, 2014). PF is associated with but not a direct result of aging (Romero-Ortuno, 2013). Currently, there are increasingly robust associations between PF and multiple comorbidities, that although less lethal, tend to accumulate during the aging process (Robinson et al., 2009). Physical disability seems to be a primary pathway to PF (Macklai, Spagnoli, Junod, & Santos-Eggimann, 2013). Notwithstanding the high correlation between low levels of physical-functional health in frail populations (Peterson et al., 2009), some studies have recently discussed the potential attenuation and prevention effect that exercise may have on PF, through stimulating positive improvement in physical-functional fitness (PhFi) indicators (Jeoung & Lee, 2015).

The American College of Sport Medicine (ACSM) describes PhFi as multidimensional, including cardiorespiratory fitness, flexibility, body composition, muscular strength and endurance (Garber et al., 2011). Despite the importance of all PhFi dimensions, the scientific consensus considers cardiorespiratory fitness and muscle strength/resistance as most important epidemiologically from childhood (de Chaves et al., 2016) to old age (Nelson et al., 2007). In this sense, maintaining satisfactory levels of PhFi through adherence to regular exercise, appears highly beneficial in attenuating and preventing cardiometabolic diseases (Murphy, McNeilly, & Murtagh, 2010), osteoarticular disorders (Peterson et al., 2009), sarcopenia and the frail condition (Mjm, van Uffelen, Riphagen, & van Mechelen, 2008; Park, Kwak, Harveson, Weavil, & Seo, 2015). Strong associations between health-related quality of life and PhFi in populations over 60 years old have been reported (Takata et al., 2010).

Some researchers reported that the decline on PhFi indicators associated with age is aggravated by a sedentary lifestyle (Kimura, Mizuta, Yamada, Okayama, & Nakamura, 2012). Women, aged over 60 years, have been found to be less physically active overall but more involved in household activities (Lee, 2008) than older men. On the other hand, the results of a recent and stronger epidemiologic study carried out in 11 countries revealed that women over 60 years of age in all these countries were more likely than men to have disabling, non-lethal conditions including physical disability (i.e., difficulties to perform general activities of daily life), osteoarticular diseases, depressive symptoms and hypertension (Crimmins, Kim, & Solé-Auró, 2011). Many of these diseases are robustly related to a sedentary behavior across life (Chastin, Fitzpatrick, Andrews, & DiCroce, 2014).

The study of associations between PF and some PhFi indicators has recently gained the interest of the scientific community in its search for simple and effective means of preventing PF. Most of these studies have focused on people over 65 years of age living in the community (Drubbel et al., 2014). However, recent research showed a higher prevalence of various comorbidities, PF, and mortality among people living in centers for social and health care support (Abizanda et al., 2014; Nóbrega, Maciel, de Almeida Holanda, Oliveira Guerra, & Araújo, 2014). This type of institution seems to exert a ‘protective effect’ for many people, preventing other adverse clinical events mostly through improved nutrition (Abizanda et al., 2014). However, since a decrease in physical-motor proficiency, loss of functional autonomy (related to mental health) and absence of family are also psychosocial characteristics of this population (Abizanda et al., 2013), these centers may also play a role in improved PhFi. Given the expected growth in the European adult population over 65 years of age and the fact that PF increases health costs and decreases health related physical activity, it is essential to better understand the relationship between PF and PhFi outcomes.

Therefore, a set of objective and accurate assessment criteria appropriate for use in institutionalized older people is essential to enable health staff to recognize PF cases at early periods and subsequently, provide timely and appropriate combined therapeutics. This study explored the relationship between PF status and PhFi indicators in institutionalized dwelling older women and also explored the sensitivity, specificity, cut-off points and predictive performance of specific senior PhFi tests for identifying frailty status. We hypothesized that PF participants would be at higher risk of PhFi decline, when compared to individuals identified as pre-frail or not frail (robust), and we looked for independent associations between PF and PhFi tests to better predict frailty.

7.3 Methods

This study was a prospective, cross-sectional, local, older population-based survey in which we collected information about PF incidence in older people living in centers for social and health care support (CHS). The sample consisted of a subset of participants within the PRO-HMESCI study protocol (Teixeira et al., 2016). Our initial sample consisted of 203 older participants aged over 60 years minus 84 participants who failed to meet exclusion criteria or dropped out as follows: physical impairment associated with musculoskeletal disorders and joint or muscle pain in the performance of some specific movements or tests (n=34), closed diagnosis of early-stage of dementia or mental disorder (n=09); severe impairment of hearing or visual functions that made it impossible to perform all tests (n=07); need of palliative health care or special nutritional support, with medical indications not to participate in the study (n=04); participants who dropped-out when applying the tests (n=10); and male participants excluded for methodological reasons (n=20).

Participant inclusion criteria used were: women aged over 60 years and willing to assent to take part in the study spontaneously who were under control and updated with prescribed medications. The final number of participants was 119 older women. Needed statistical power was computed by considering the agility-dynamic balance test values in studies comparing frail and pre-frail groups, using a Mann–Whitney U test, with a significance level of 0.01. The computations were performed on G*power 3.1.9.2, and the power was determined to be 0.99 (Faul, Erdfelder, Buchner, & Lang, 2009) with a sample of 119 and an effect size of 1.12.

7.3.1 Ethical Procedures

CHS directors and elders who expressed interest in participating in the study signed an informed consent form, in which the privacy and anonymous identity of the data collected were guaranteed and any needed access to participants' medical records were given. The study protocol was approved by the Faculty of Sport Sciences and Physical Education Ethical Committee - University of Coimbra [reference code: CE/FCDEF-UC/000202013], in respect of Portuguese Resolution [Art.º 4st; Law n. 12/2005, 1st series] on ethics in research (Braga, 2013) and complied with the guidelines for research with human beings of the Helsinki Declaration (Petrini, 2014).

7.3.2 Outcome Measures

Data collection of sociodemographic and medical history status, frailty syndrome, physical fitness and anthropometric indicators was organized by the principal investigator and were performed by independent specialists (properly trained) of the research team. To minimize differences in data collection procedures, the same evaluator carried out data collection for all participants.

7.3.3 Sociodemographic Status.

Information on chronological age (continuous variable); marital state (assessed as a four categories variable: single, married, widowed and divorced) and level of education (assessed as a continuous variable) was collected for each participant. The level of education was classified according to the Portuguese educational system and analyzed as a continuous variable (Fernandes, 2007).

7.3.4 Anthropometric Measures

The standardized procedures described by Lohan and colleagues (Chumlea, Baumgartner, 1989) were followed for the collection of anthropometric data, including body mass weight determined using a portable scale (Seca®, model 770, Germany) with a precision of 0.1 kilograms, stature determined using a portable stadiometer (Seca Body meter®, model 208, Germany) with a precision of 0.1 centimeters, and body mass index (BMI), calculated according the formula [$BMI = weight/height^2$].

7.3.5 Comorbidities

The Charlson Comorbidity Index (CCI) was used in this study, is a method of predicting mortality by classifying or weighting comorbid conditions. The CCI has been widely utilized by health researchers to measure burden of disease and has a weighted index based on 19 comorbid conditions. Its score can be combined/adjusted with age and gender to form a single index (continuous variable). One point for each additional 10 years is added to the initial score, that has been shown to predict one-year and 10-year mortality (Charlson, Szatrowski, Peterson, & Gold, 1994). Medical records provided by the medical and health professional team were used to verify the accuracy of information provided by study participants for use within the CCI.

7.3.6 Medication-use assessment.

Daily medications used by the participants was assessed through question number six of the Mini Nutritional Assessment (Guigoz, 2006), that asks the participant if she takes more than 3 or less prescription drugs per day. Additionally, the number of medications-used was checked systematically through the institutional medical record of each participant, identifying and reporting polypharmacy (takes more than 3 prescription drugs per day) according to the Portuguese Classification System of Human Medicine (Santos & Almeida, 2010).

7.3.7 Cognitive Status Assessment.

The Mini Mental State Exam (MMSE) used in this study assesses five areas of cognition: orientation, immediate recall, attention and calculation, delayed recall, and language (Folstein, Folstein, & McHugh, 1975). The maximum MMSE score is 30 points, and a score below 24 points is considered abnormal and used for dementia and mild cognitive impairment (MCI) screening (Melo & Barbosa, 2015). The MMSE was used to classify participants by cognitive profile as a category variable, according to the following cut off values: severe cognitive impairment, 1 to 9 points; moderate cognitive impairment, 10 to 18; MCI, 19 to 24 points and normal cognitive status, 25 to 30 points (Mungas, 1991). Additionally, the MMSE can be analyzed as a continuous variable. Its purpose in this study was to help determine whether a low cognition profile might have affected physical fitness trainability as has been shown by prior research (Uemura et al., 2013).

7.3.8 Physical Frailty Syndrome Screening.

Assessment of Physical frailty was evaluated according to the following Fried's five criteria of the frailty phenotype index (Fried et al., 2001):

i) Weight loss assessed by self-report of unintentional weight loss of four kilograms or more in the last six months; ii) Poor endurance and energy (self-reported exhaustion) evaluated by negative concordance of two questions, number seven and twenty, of the questionnaire developed by the Center of Epidemiologic Studies for Depression, called the CES-D scale (Gonçalves, Fagulha, Ferreira, & Reis, 2014); iii) Weakness, analyzed using the handgrip strength test (HGT). This test uses a hand-held dynamometer (Lafayette Dynamometer, model 78010, United States) and strength is measured in kilograms. The subject holds the dynamometer in the hand to be tested, with the elbow by the side of the body. When ready the subject squeezes the dynamometer with maximum isometric effort, which is maintained for 5 seconds. The best result of the two trials was used for scoring purposes (Syddall, Cooper, Martin, Briggs, & Aihie Sayer, 2003). Participants who were unable to perform the HGT and those in the lowest 20% (adjusted for BMI and stratified by gender) were categorized as positive for the weakness criterion; iv) Slowness, as measured by the '15 feet walking test', consisting in an individual walk without assistance (4,6 meters) where the time taken to complete it is measured and expressed in seconds, adjusted for gender and height. The best time of the two trials was used for final scoring (Newman, Haggerty, Kritchevsky, Nevitt, & Simonsick, 2003); v) low physical activity level, assessed by the International Physical Activity Questionnaire (IPAQ) short form such that participants classified as having 'low levels of PA' and 'very low sedentary' on this instrument scored negatively in the PF criteria (Guessous et al., 2014; Pitanga, Pitanga, Beck, Gabriel, & Moreira, 2012). The prevalence of FS combined score was calculated, as well as the presence of each of the five items (0 to 5 points). According to the Fried Protocol, the negative evaluation in one or two criteria classifies the participants as pre-frail, in three or more as frail and as non-frail or robust, when the subject has no void in any of the five criteria of PF (Fried et al., 2001).

7.3.9 Assessment of Physical Fitness Indicators.

The following Senior Fitness Test battery developed by Rikli and Jones (2013) was used to measure PhFi: i) The lower body strength is determined with the '30 second's chair-and-stand test' (30s-CS), measuring the number of total full chair-stands that can be completed in 30 seconds with the arms folded across the chest; ii) The upper body strength was assessed with the '30 seconds arm-curl test' (30s-AC) that measures the total number of bicep curls that can be completed in 30 seconds, seated in a chair and holding a hand weight of 5 lbs (2.27 kg) for women. iii) For lower-body flexibility we used the 'chair sit-and-reach test' (CSR), from a sitting position at front of chair, with leg extended and hands reaching toward the toes, the number of inches (centimeters, + or -) between extended fingers and tip of toe are measured; iv) The upper-body flexibility (shoulder girdle) was measured using the 'back Stretch' test, that assesses the distance (centimeters, + or -) of approach between the middle fingers when one hand reaching over the shoulder and one up the middle of the back; v) Agility-dynamic balance (ADB) was assessed using the eight-foot-up and go test, that assesses the time in seconds required for the participant to get up from a chair (seated position), walk as quickly as possible around either side of a cone placed 2,44 meters away from the chair, turn and sit back down in the seated position; vi) Aerobic resistance was measured through the "2-minutes step test" (2m-ST), that consisted of the number of full steps the subject completed in two minutes performing a stationary gait, with one hand resting on the wall and raising each knee to a midway point between the kneecap and iliac crest. Score is the number of times the right knee reaches the required height. (Rikli,& Jones, 2013).

For all the PhFi tests the best score of the two trials performed was used for final scoring purposes. When upper and lower members were tested in both sides (i.e. left and right) the best scoring side was the one considered for scoring purposes.

7.4 Statistical Analysis

The assumption of normality was checked by resorting to Shapiro Wilk tests and by visual inspection of normality plots. When normally distributed, quantitative variables were described by their means and standard deviations. When not normally distributed, medians and the first and third quartiles were used instead. Nominal variables were described with absolute and relative frequencies.

A comparison of quantitative variables between PF categories (no frail, pre-frail and frail) was performed using one-way ANOVA test or Kruskal-Wallis test, as applicable. Associations between nominal variables were assessed using the chi-squares test and Monte Carlo simulations were performed when appropriate. Partial correlations between the PF combined score and PhFi indicators were computed, together with partial correlations controlling for the cognitive status, comorbidities and both factors at the same time. The variables expressing PhFi results were analyzed regarding their predictive value to distinguish between frail and pre-frail subgroups by performing a Receiver Operating Characteristics (ROC) curve analyses. A multivariate logistic regression was subsequently undertaken, considering all of the aforementioned PhFi test performance variables as predictors of PF. IBM SPSS Statistics 21.0 and in 'R 3.3.1' software were used for all computations. The level of significance adopted was P= 0.05.

7.5 Results

Data from 119 participants were analyzed, and Table 7.1 presents descriptive characteristics of the participants for all variables. Analysis of the sociodemographic variables indicated that our participants were older women (81.96 ± 7.89), mostly without husbands (94.1%) and with low academic achievement levels according to the Portuguese education classification system (3^{rd} grade). When the 'no frail,' 'pre-frail' and 'frail' subgroups were compared, there were no statistical differences between these groups for chronological age, weight and marital state. Statistical differences were found for height ($p < 0.05$).

Concerning clinical status, the average scores of the total sample classified the sample as a whole as showing a cognitive status of MCI (MMSE, 20 points), a high incidence of multi-comorbidity and a high risk of mortality (CCI, 7 points) and a high incidence of polypharmacy. Differences between groups were found for MMSE scores that were lower (p<0.001) and CCI scores that were higher (p = 0.026) in the frail group. There was also a clear tendency for increased polypharmacy in the frail subgroup. Regarding PF assessment, 19 participants were classified as nonfrail (16%), 46 subjects as pre-frail (38,7%) and 54 as frail (45.4%).

Table 7.1 Characterization of the total sample study population[a] and comparison by frailty phenotype index for sociodemographic, clinical status, frailty and physical fitness indicators.

	Total sample (n=119, 100%)	**Nonfrail (n=19, 16%)**	**Pre-frail (n=46, 38.7%)**	**Frail (n=54, 45.4%)**	**p**
Bio-sociodemographic					
Chronological age (years, A±SD)	81,96 ±7,89	81.68 ±6.72	81.80 ± 8.65	82.19 ± 7.72	0.959
Weight (kilograms, A±SD)	65.45±12.58	66.22 ± 11.33	65.08 ±11.54	65.49 ± 13.98	0.946
Height (meters, M1;3)	1.51 (1.47 ; 1.56)	1.56 (1.49 ; 1.62)	1.51 (1.47 ; 1.55)	1.50 (1.46 ; 1.52)	0.008
Marital state (n,%)					
Single	31 (26.1)	6 (31.6)	12 (26.1)	13 (24.1)	
Married	7 (5.9)	4 (21.0)	1 (2.2)	2 (3.7)	0.073
Widowed or divorced	81 (68.0)	9 (47.4)	33 (71.7)	39 (72.2)	
Level of education (degree; M1;3)	3 (3 ; 4)	4 (3 ; 6)	3 (3 ; 4)	3 (2 ; 4)	0.063
Clinical status					
Mini mental state exam (score, M1;3)	20 (15 ; 25)	25 (21 ; 27)	21 (17 ; 25)	17 (13 ; 22)	< 0.001
Charlson comorbidity index (score, M1;3)	7 (6 ; 9)	8 (6 ; 10)	7 (6 ; 8)	8 (7 ; 9)	0.026
Medication use, per day (n, %)					
I use more than three	108 (91.5%)	17 (89.5%)	43 (95.6%)	48 (88.9%)	0.465
I use three or less	10 (8.5%)	2 (10.5%)	2 (4.4%)	6 (11.1%)	
Frailty Syndrome (n, %)					
Weakness (N:P)	85 (71,4): 34(28.6)	0 (0) : 19 (100)	36 (78.3) : 10 (21.7)	49 (90.7) : 5 (9.3)	< 0.001
Slowness (N:P)	62 (52.1): 57(47.9)	0 (0) : 19 (100)	14 (30.4) : 32 (69.6)	48 (88.9) : 6 (11.1)	< 0.001
Poor energy (N:P)	49 (41.2): 70 (58.8)	0 (0) : 19 (100)	10 (21.7) : 36 (78.3)	39 (72.2) : 15 (27.8)	< 0.001
Weight loss (N:P)	19 (16): 100 (84)	0 (0) : 19 (100)	3 (6.5) : 43 (93.5)	16 (29.6) : 38 (70.4)	0.001
Low physical activity level (N:P)	55 (46.2): 64 (53.8)	0 (0) : 19 (100)	13 (28.3) : 33 (71.7)	42 (77.8) : 12 (22.2)	< 0.001
Physical Fitness (M1;3)					
Back stretch test (centimetres)	43.00 (34 ; 56)	53.00 (39.00 ; 70.50)	44.00 (37.50 ; 60.50)	40.25 (31.00 ; 51.00)	0.022
Agility-dynamic balance (seconds)	13.00 (10 ; 20.56)	9.75 (7.12 ; 10.58)	11.15 (9.20 ; 14.90)	20.14 (14.30 ; 25.97)	< 0.001
Chair sit and reach (centimetres)	36.00 (25.50 ; 42.50)	35.00 (23.00 ; 43.50)	38.75 (34.50 ; 43.50)	32.25 (22.50 ; 38.50)	0.002
30 seconds chair-and-stand test (reps)	8.00 (6.00 ; 11.00)	11.00 (10.00 ; 12.00)	9.00 (7.00 ; 11.00)	6.00 (5.00 ; 8.00)	< 0.001
30 seconds arm curl test (reps)	10.60 (8.00 ; 12.00)	13.00 (11.00 ; 15.00)	11.00 (9.00 ; 14.00)	9.00 (7.00 ; 11.00)	< 0.001
2-minutes step test (reps)	37.00 (20.00 ; 44.00)	52.00 (44.00 ; 60.00)	39.50 (30.00 ; 45.00)	27.00 (16.00 ; 35.40)	< 0.001
Body mass index (A±SD)	28.49±5.05	26.95± 3.78	28.22± 4.60	29.27± 5.69	0.205

[a]Data presented as (A±SD): average ± standard deviation; (M1;3): median; 1st quartile; 3rd quartile or as (n, %): number (percentage) of participants, where applicable; N = negative: P: positive.

Analysing scores from the senior PhFi tests battery and comparing the frailty sub-groups, the frail group exhibited lower performance results on all tests. A comparison between the three groups showed statistically significant differences attained for all tests battery variables except for body mass index, whose results indicated higher values in the direction of the frail group. In addition to the descriptive scores described in Table 7.1, a graphical representation also showed PF-differences in PhFi scores. In Figure 7.1 of radar plot, to ensure comparability and an easier visualization, the medians were computed for each of the three PF sub-groups and then divided by the maximum of the three medians. It is worth mentioning that, for each PF component represented in the plot, higher results mean better performances. The frail group can be seen to have lower scores for all PhFi variables except for body composition.

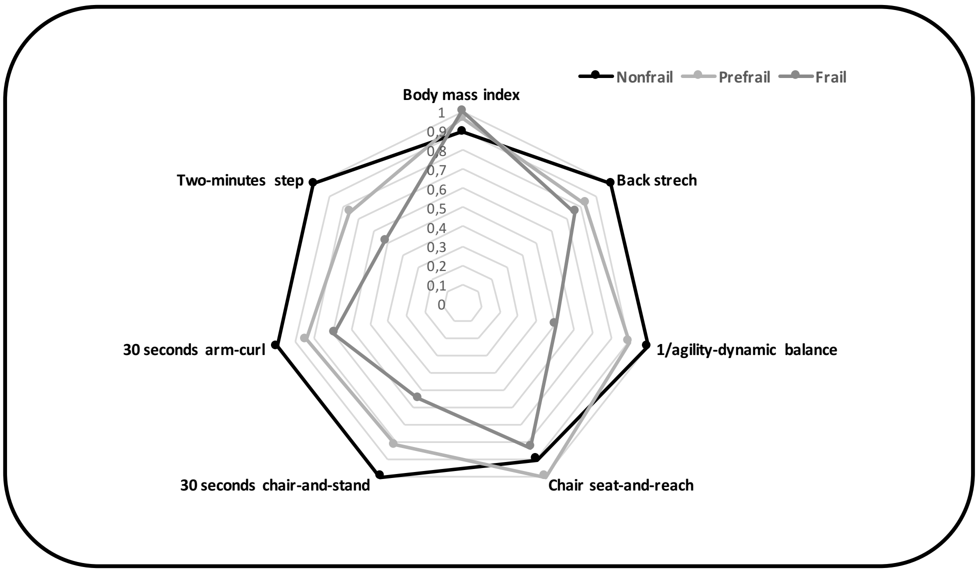

Figure 7.1 Radar plot of the variables of the physical fitness tests comparison by physical frailty subgroups (n= 119).

Correlations between the combined score of PF and PhFi indicators can be seen in Table 7.2. Additional partial correlation, controlling for cognitive state, comorbidity and both variables were also included. Direct and strong correlations emerged from associations between PF combined score and ADB test (*r* = 0.662; p < 0.001). An inverse and strong association emerged in 2m-ST variables (*r* = - 0.617; p < 0.001). Inverse and moderate association appears in 30s-CS (*r* = - 0.555; p < 0.001) and 30s-AC (*r* = - 0.456; p < 0.001) tests; inverse and small associations values appear in BST and 30s-CS tests (*r* = - 0. 255 and *r* = - 0.289; p < 0.001, respectively).

No statistical correlation between BMI and FS combined score was found. When the effects of cognitive profile, comorbidity and interaction between both variables were removed, correlation scores decreased but did not change the magnitude of the correlations.

Table 7.2 Spearman total and partial correlations (controlling for cognitive, comorbidity and both) between combined score of FS and indicators of physical fitness tests (n =119).

Control Variables		BST	ADB	CSR	30-SCS	30s-AC	2m	BMI
None	r	- 0.255	0.662	- 0.289	- 0.555	- 0.456	- 0.617	0.119
	p	0.005	< 0.001	0.001	< 0.001	< 0.001	< 0.001	0.198
MMSE	r	- 0.212	0.617	-0.292	-0.509	- 0.411	- 0.556	0.157
	p	0.021	< 0.001	0.001	< 0.001	< 0.001	< 0.001	0.090
CCI	r	- 0.231	0.653	- 0.279	- 0.542	- 0.446	- 0.616	0.096
	p	0.012	< 0.001	0.002	< 0.001	< 0.001	< 0.001	0.303
MMSE and CCI	r	- 0.181	0.604	- 0.280	- 0.489	- 0.398	- 0.552	0.131
	p	0.051	< 0.001	0.002	< 0.001	< 0.001	< 0.001	0.159

Subsequently, ROC analyses were performed to assess how PhFi indicators may be used to predict PF status (see Table 7.3). The highest AUC value was attained for the ADB test, the 95% confidence interval being [0.739, 0.901]. The corresponding cut-off value, maximizing Youden's Index, was seen to be 16.22 (seconds), the sensitivity 70.4% and the specificity 84.8%.

Table 7.3 Predictive performance of physical fitness tests for frailty syndrome (n =119).

Variables	Cut-off	Sensitivity	Specificity	AUC	AUC 95% CI
Back stretch	≤33.75	37.0%	89.1%	0.631	[0.522, 0.740]
Agility-dynamic balance	≥16.22	70.4%	84.8%	0.820	[0.739, 0.901]
Chair sit and stand	≤35.75	68.5%	73.9%	0.712	[0.609, 0.815]
30 seconds chair stand	≤6.50	51.9%	89.1%	0.754	[0.661, 0.847]
30 seconds arm curl	≤11.50	92.6%	47.8%	0.728	[0.626, 0.829]
Two minutes step	≤36.50	77.8%	65.2%	0.738	[0.640, 0.836]
Body mass index	≥29.89	53.7%	63.0%	0.550	[0.436, 0.664]

Test performance indicators were used as predictors for PF in a logistic regression analysis aimed at distinguishing between pre-frail and frail sub-groups. Non-frail participants were thus excluded from this analysis. Out of the seven variables assessing test performance, only ADB test (β = 0.198; SE=0.052; p = 0.0000; OR = 1.218; OR 95% CI [1.110; 1.349]) and 30s-AC (β = -0.213; SE=0.086; p = 0.013; OR = 0.808; OR 95% CI [0.683; 0.956]) were found to be statistically significant predictors. These two predictor variables were linearly related to the logit of the dependent variable using the Box-Tidwell procedure. A multivariate outlier was identified using standardized residual and kept in the analysis. The model was seen to be statistically significant ($\chi^2[2] = 45.181$, $p < 0.001$) and to explain 48.6% (Nagelkerke R^2) of the variance in the outcome variable. It achieved a sensitivity and specificity of 70.4% and 84.8%, respectively, with AUC 0.848 with the corresponding 95% confidence interval being [0.773, 0.922]. Figure 7.2 shows only those significant variables in multivariate logistic regression analysis.

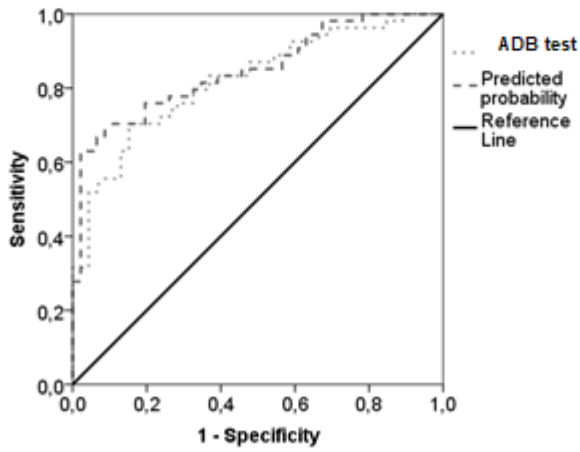

Figure 7.2 Results of Receiver operating characteristic curve analysis for test performance used physical fitness indicators (n = 119).

7.6 Discussion

The goals of this study were to explore associations between PF and PhFi indicators and to analyze predictive performance of PhFi tests among women living in centers for social and health care support in the district of Coimbra, Portugal. To our knowledge, this study is the first scientific examination of the predictive performance of PhFi indicators for evaluating PF in a Portuguese population over 65 years old.

Frailty has similar prevalence (45.4% frail subgroup) when compared to other European countries that have studied samples living in social and health care support (Abizanda et al., 2013). According to other international studies, there is a clear trend towards an increasing prevalence of PF in samples of institutionalized individuals. Portuguese women over 65 years of age have distinct sociodemographic characteristics, when compared to South American (Yassuda et al., 2012), North American (Kiely, Cupples, & Lipsitz, 2009) and Asian populations (Han, Lee, & Kim, 2014). In agreement with other studies of participants with similar sample characteristics (González-Vaca et al., 2014), our bio-sociodemographic data revealed a trend toward lower levels of education in the pre-frail and frail subgroups.

Unlike other studies in which frail subjects were underweight (Donini et al., 2013), we found no statistically differences between groups in body weight and BMI. This fact may be explained by the nutritional support these individuals received from the care center in which they were living, consistent with a cross-sectional study conducted in Spain (González-Vaca et al., 2014). According to several researchers, in recent years, malnutrition is a frequent problem among people living in institutionalized context (Cereda, Valzolgher, & Pedrolli, 2008; De Luis et al., 2011; Donini et al., 2013). Our data highlight the importance of adequate nutritional balance, one of the variables at the core of the FS status. Especially for this study, it is important to note that body weight probably did not affect the assessment of PhFi.

In terms of clinical history, cognitive impairment and incidence of comorbidities are the most explored dimensions in studies combining PF-correlates (Brigola et al., 2015; Chang & Lin, 2015). Despite ICC scores, present data does not indicate an increase in the number of diseases in the direction of the frail subgroup. The prevalence of a high comorbidity index in our study sample was present in all the PF subgroups. The results of cognitive function assessed by the MMSE showed statistical differences between PF subgroups. The pattern of increased MCI occurrence among the pre-frail and the frail people in this study was comparable to previous studies (Abizanda et al., 2013; Han et al., 2014). However, studies with similar samples with participants living in community-dwelling context have higher values in MMSE scores when compared to studies with institutionalized samples (Robertson, Savva, Coen, & Kenny, 2014). Regarding differences in PhFi indicators between FS subgroups, frail people exhibited smaller scores in the lower and upper body strength, lower and upper body flexibility, agility, dynamic balance and aerobic resistance capacities compared to the non-frail and pre-frail sub-groups.

An improvement on PhFi performance, through regular physical exercise practice, reportedly enhanced physiological parameters related to physical health, exerting therapeutic treatment effect for prevention and mitigation of specific outcomes of physical impairment and can also contribute to increasing physical activity and quality of life (Patel, Newstead, & Ferrer, 2012), even in people aged over 65 years old (Vrantsidis et al., 2014).

The scientific literature recognizes the importance of maintaining an active lifestyle across life, to mitigate adverse and harmful negative effects on physical health. However, muscle strength and cardiorespiratory fitness are consensually the most encouraged PhFi components to be predominantly trained, because of the direct relationship between the human vital capacity and physiological reserve (Charansonney, 2011). A closer look at the FS sub-groups, specifically the frail subjects, revealed that weakness (muscular strength), slowness (walking speed) and low physical activity levels were the three FS components on which a larger number of participants scored negatively. The results of partial correlation between PF combined score and PhFi indicators (seeTable 7.2) showed satisfactory correlations between these dimensions, even when controlling for the effects of comorbidities, cognition profile or both. Some studies indicate that these clinical conditions exert influence on PhFi variables, though this was not demonstrated in the present study. Generally, our results are consistent with other studies that explored associations among similar variables and dimensions (Chang et al., 2014; Jeoung & Lee, 2015).

A second central focus of the present study was an analysis of the potential performance of PhFi tests for predicting the FS condition. We identified the 30s-AC and ADB test as two potential predictors of PF. The longer the ADB test took to be completed and the lower the number of repetitions in 30s-AC, the greater the risk of being frail. Notably, the ADB test was the best predictor. According to recent studies, this test seems to be an appropriate, independent and predictive tool to detect frail subjects (Chang et al., 2014). Note that for the same sensitivity as the best univariate predictor (ADB test), the logistic regression model allows for a slightly higher specificity (89.1%, whereas it was 84.8%).

In analytical terms, for this population or another with similar characteristics, taking longer than 16.22 seconds to complete this test predicts the existence of a frail condition. Accurately, the risk of frail condition (not pre-frail) increases about 2.12% per second spent in the ADB test (see Table 7.3). Similar results were previously found in a similar study using an analogous test (the time-up-and-go test) for predicting frail condition in community-dwelling subjects (Greene et al., 2014; Savva et al., 2013).

However, in their sample, unlike the present study, the authors excluded individuals with MCI. As mentioned, the comparison of the ADB test values between frail and pre-frail sub-groups is of particular importance, since statistically significant differences were found between the ADB test values of the two groups, ($U=446$, $p<0.01$). The satisfactory execution of this test requires awareness, concentration on the information received (attention) and fast decision-making (reaction time) when the participant receives the signal to 'raise from the chair' and walk as quickly as possible (Barry, Galvin, Keogh, Horgan, & Fahey, 2014);

Additionally, rising from a chair unassisted by upper limbs requires lower limbs muscle strength, and walking fast and turning around a cone placed at 2.44 meters requires quickness, agility, dynamic balance and body support (Cebolla, Rodacki, & Bento, 2015). Thus, this test requires the integration of physical capacities, highly dependent on a satisfactory neurocognitive functioning. Perhaps this is the reason why the cut-off values for predicting risk of PF status in the present study were higher than previous studies in which the predictive cut off value was ≥ 8.12 seconds (Chang et al., 2014) as our sample contained individuals whose MMSE test values were in the range of mild cognitive impairment.

The central findings of the present study support the power of the agility-dynamic balance test for predicting PF in institutionalized populations aged over 65 years, where application of Fried's criteria is not feasible. This study's limitations include a sample that was only representative of institutionalized women since randomly selected institutions in a 'universe' of many others was the most feasible, fast and economical method of data collection and the number of male participants motivated to participate was very low. However, comparing these data to similar results from previous research, we conclude that the agility-dynamic balance test is gaining clinical utility because of its accuracy in detecting physical frailty. It has potential for use as a reference measure in future exercise intervention studies.

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CHAPTER 8 (STUDY 6):

THE RELATIONSHIP BETWEEN FUNCTIONAL DISABILITY OUTCOMES AND INDEPENDENTS COMPONENTS OF PHYSICAL FRAILTY IN INSTITUTIONALIZED OLDER WOMEN

Authors:

Guilherme Eustáquio Furtado

Miguel Patrício

Marisa Loureiro

Eef Hogervorst

Ana Maria Teixeira

José Pedro Ferreira

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8.1 Abstract

Introduction: The associations between functional disability (especially related to the activities of life activities) and frailty have already been explored. However, the contribution of each component of physical frailty and their contribution to understanding the early physical decline of older individuals are poorly explored. **Objectives**: To determine the relationships between physical frailty and functional disability and to identify the independent components of frailty that most influence on disability in institutionalized-dwelling older women. **Methods:** A cross-sectional study of 119 (81,96±7,89) institutionalized older women aged 75 and over. Functional disability was assessed through Agility-dynamic and Static balance tests, Activities of daily life and Falls risk screen outcomes. Physical frailty components were assessed by Fried Protocol that encompasses Low levels of physical activity, Self-reported exhaustion, Weakness (low handgrip strength), Slowness (low gait speed) and non-intentional weight loss. **Results:** A comparative analysis showed that the frail subgroup displayed the weakest results for all functional disability outcomes ($p < 0.05$). Despite the statistically significant associations between frailty total score and all disability outcomes, the linear regressions analysis showed that in the two models tested, Low physical activity levels and Slowness were the frailty independent components most associated to disabilities. **Conclusion:** More studies with larger samples across different cohorts of institutionalized-dwelling populations will help to better understand the independent relationship of each physical frailty component to the different adverse-disability outcomes may help to provide a more real prognostic value and assist to design a co-adjuvant treatment to attenuate and reverse physical frailty.

Key-words: Frail older adults, women, disability evaluation, activities of daily living, motor skills.

8.2 Introduction

The Frailty Syndrome is a state in which reserve function across multiple physiologic domains decline, compromising the individuals' capacity to withstand stress, thereby predisposing them to poor general health, functional decline, institutionalization and death [1,2]. Linda Fried and colleagues [3] developed a construct known as the Physical Frailty (PF) and identified five components: weakness, low resistance to effort, slowness, low physical activity levels and weight loss and operationalized a criteria for characterizing a person as frail, pre-frail and no frail [3].

Recently, findings suggested that PF is strongly linked to different functional disability (FD) outcomes comprising an independent component of PF, increased caregiver burden, and greater financial costs for public health [4–6]. Currently, FD is understood as a multidimensional construct that integrates the analysis of compensation strategies to maintain a satisfactory physical health to perform daily life activities autonomously [7]. The assessment of FD can be quantified by direct (simple and low cost functional fitness and motor tasks tests) or indirect measures (through questionnaires evaluating specific daily life tasks), both clinically validated [8,9]. Positive changes in FD are primary determinants of quality of life in advanced age. Perception of a positive physical condition, for example, (i.e. not be afraid to face possible physical barriers that condition the fear of falling) might reflect a personal sense of predicted support from others despite being PF.

Currently, there is poor information about the contribution of each PF independent component to physical-functional decline [10]. Epidemiological studies reported that poor scores on the handgrip strength test were associated with high risk of mortality [11], dementia and mild cognitive impairment [12]. Low levels of physical activity were consistently associated with mortality [13] and cognitive decline [14]. Poor walking speed proficiency and low physiological reserve [15]. However, it remains to be explored how each independent component of PF can contribute to explain functional disability in frail older adults. Geriatric researchers have started to explore the independent association of each PF components with some FD outcomes [6], However, the relationship of PF independent components and different FD outcomes, as well as their contribution to understand the decline frail institutionalized-dwelling individuals, are poorly explored.

Thus, the aim of this study was to analyse the relationship between the PF and functional disability outcomes, as well as to verify the frailty subgroups-differences on FD outcomes in institutionalized-dwelling people aged 75 years or more.

8.3 Methods

This was a cross-sectional data collection study design of institutionalized-dwelling Portuguese older adults aged 75 and over. The sample consists of a subset of the participants of the previous published study protocol. Initially, 5 centres of health care and social support (CHS) were approached and four institutions were randomly selected to participate in the study. The directors of the CHS, the participants and their legal representatives signed consent forms. This study was approved by the Faculty of Sport Science and Physical Education Ethical Committee (Reference code CE/FCDEF-UC/000202013) - the University of Coimbra, respected the Portuguese Resolution (Art. 4st; Law n. 12/2005, 1st series) and complied with research guidelines in humans of the Helsinki Declaration[18].

8.3.1 Sample selection criteria

Participant inclusion and exclusion criteria were validated through a face-to-face interview. The inclusion conditions for the participants were: to take part in the research spontaneously and to have controlled and updated medicine treatment. The presence of severe chronic health illness that could prevent performance of the physical tests of functional disability outcomes, such as severe cardiomyopathy, hypertension, uncontrolled asthmatic bronchitis and any musculoskeletal, mental, hearing or vision disorders, including morbid obesity or the use of drugs that could cause attention impairment, were adopted as exclusion criteria of participants. The first eligible sample consisted of 183 institutionalized-dwelling participants. In total, 64 women participants were excluded due to a poor clinical health condition (high physical and cognitive impairment). A total of 119 older women were finally included in the study. Needed statistical power was computed by considering the Lawton index values in studies comparing differences between frail and pre-frail groups, using a Mann–Whitney U test, with a significance level of $p = 0.01$. The computations were performed on G*power 3.1.9.2, and the power was determined to be 0.97 with a sample of 119 and an effect size of 1.12 [16].

8.3.2 Measurement

Data collection was executed by the principal investigator and a properly trained research team constituted of a nurse, physiotherapist and physical educator. To minimize differences, the same evaluators performed data collection. Sociodemographic, anthropometric and health status indicators that presented statistical differences on frailty subgroups comparison were analyzed as a covariate. The quality data of physical tests was examined and internal consistency reliability (ICR) for each test was reported.

8.3.3 Frailty screen

The positive evaluation in one or two PF components classified the participants as pre-frail, three or more as frail and as non-frail when the subject had none of the five frailty independent components, forming a categorical classification [3]. The incidence of PF based on the five components was calculated by generating a continuous score (0 to 5 points). The following Fried of PF protocol was applied:

i) unintentional weight loss was assessed by self-reporting loss of four kilograms or more in the last six months, validated by medical records over one year;

ii) exhaustion (self-reported weariness) was evaluated by negative concordance of questions number 7 and 20 from the Centre of Epidemiologic Studies in Depression (CES-D) scale [19];

iii) weakness was analyzed using the handgrip strength test (HGT). This test uses a hand-held dynamometer (Lafayette Dynamometer, model 78010, United States) and strength is measured in kilograms. The subject holds the dynamometer in the hand to be tested, with the elbow by the side of the body. When ready, the subject squeezes the dynamometer with maximum isometric effort, which is maintained for 5 seconds. The best result of the two trials was used for scoring purposes [20]. Participants who were unable to perform the HGT and those in the lowest 20% (adjusted for BMI and stratified by gender) scored positive, based on cut off values of Fried's study population; iv) slowness was measured using the 4.6 meters walking test (4.6-WT), which results are expressed in seconds and adjusted for gender and height. Based on cut off values of Fried's study population, the best time of the two trials was used for final scoring [15];

v) low PA levels were assessed by the International Physical Activity Questionnaire (IPAQ) short version [21]. The IPAQ short form asks about three specific types of activity undertaken in the three domains introduced above and time being sedentary. The specific types of activity that were assessed are walking, moderate-intensity activities and vigorous intensity activities; frequency (measured in days per week) and duration (time per day) are collected separately for each specific type of activity. The total volume and the number of day/sessions were included in the IPAQ analysis. There are four levels of PA suggested for classification: inactive, minimally active, medium active and a highly active. Participants classified as inactive and minimally active had a positive score for the frailty status [22].

8.3.4 Functional disability outcomes

The assessment of FD was organized in a test battery following the approach proposed in a previous study [7]:

i) The Katz Index of Independence (ADL) and The Lawton Index Instrumental (IADL) were used for assessing autonomy in daily life tasks. ADL scale ranks adequacy of performance in six functions (dressing, transferring, toileting, continence, feeding and bathing). Individuals are scored for each function as an independent (1 point) or dependent (0 points), for the six functions. A score of 6 indicates full function, 4 indicates moderate impairment, and 2 or less indicates severe functional impairment [8,23].

ii) The Lawton Instrumental Activities of Daily Living (IADL) was used for identifying deterioration or improvement over time in 8 socio-biological functions. A summary score ranges from low function (8 points) dependent, to independent for high functions, 32 points [24].

iii) Fear of falling was measured using the Tinetti Falls Efficacy Scale (FES), where individuals are asked to rate, on a 4-point Likert scale, their concerns about the possibility of falling when performing 16 activities. Scores range from 10 to 100 points, with a lower score indicating a high self-efficacy and little fear of falling [25].

iv) The eight foot-up-and go test was used to assess agility-dynamic balance (ADB). The ADB test measures the total time in seconds needed for the participant to get up from the chair, walk the distance of 2.44 meters as quickly as possible around either side of a cone, and to sit back down in the chair (ICR = 0.80). A total time of more than 9 seconds indicates a “risk zone”. [26].

v) The Semi-Tandem Stance Balance test (TSB) was used to evaluate static balance, and consists of the participant maintaining the standing position with open eyes and one foot in front of the opposite foot for a maximum of 30 seconds. The time of 10 seconds or less indicating very poor static balance (ICR = 0.77).

8.3.5 Sociodemographic screening

Information on chronological age was assessed through the date of birth and analyzed as a continuous variable. Marital status was categorized in single, married, widowed or divorced and level of education (assessed as a continuous variable) was collected for each participant. Level of Education was classified according to the Portuguese educational system.

8.3.6 Anthropometric measures

The standardized procedures described by Lohan and colleagues (Chumlea, Baumgartner, 1989) were followed for the collection of anthropometric data, including body mass weight determined using a portable scale (Seca®, model 770, Germany) with a precision of 0.1 kilograms; stature using a portable stadiometer (Seca Body meter®, model 208, Germany) with a precision of 0.1 centimeters and BMI, calculated according to the standard formula (BMI = weight/height^2).

8.3.7 Clinical-mental health status

Comorbidity was assessed using the Charlson Comorbidity Index (CCI) that measures the burden of disease and has a weighted index based on 19 comorbid conditions. The score ranging from 0 (low) to 10 points (high), can be combined with age and gender to form a single index [30]. Those individuals that presented a comorbidity index above 10 points were excluded from the study. The Mini-Mental State Examination (MMSE) was used to assesses five areas of cognition. The maximum score is 30 points and a score below 24 points is usually considered indicative of dementia screening [31,32]. Depression state was assessed using the scale developed by CES-D [19]. The 20-items, totalling an overall score of 0 to 60 points, in which the highest scores correlate with the frequency of depressive symptoms [33].

8.3.8 Statistical analysis

The Shapiro-Wilk test was used to assess the normality of continuous variables. Normally distributed continuous data were described by their averages and standard deviations, whilst non-normally distributed continuous data were described by median and first and third quartiles. As for categorical variables, absolute and relative frequencies were used. Independent samples ANOVA tests and Kruskal-Wallis tests were performed to compare continuous variables between groups and Chi-square tests to assess the association between categorical variables. Spearman's rank correlations and corresponding partial Spearman correlations were used to test the associations between FD outcomes PF total score. The relationships between the ADL and each of PF components was evaluated using logistic regressions. The relationships between PF and all other FD outcomes were analyzed using linear regressions. The unadjusted model simply included one dependent variable and one independent variable. In model 1, stature, comorbidities, depressive state and cognitive state were included as covariates. The outcomes of disability were assumed as dependent variables and the PF components were independent in the regression analysis [34] ($p=0.05$). All computations were performed on IBM/SPSS Statistics 21 and R version 3.3.1.

8.4 Results

Characteristics of the population are shown in Table 8.1. Mean age of the total sample was 81,96±7,89, 68% of the participants were divorced or widowed and the median level of education was third grade. Analysing differences in frailty subgroups, no significant changes were found in sociodemographic and anthropometric variables, except for stature. The mean of stature data showed that the frailest individuals had a statistically significant shorter stature ($p = 0.008$). None of the other sociodemographic and anthropometric parameters showed significant differences between frail subgroups. Frail individuals presented a lower score on the cognitive test ($p < 0.001$), a worse depressed mood ($p = 0.026$), and a higher comorbidity index ($p < 0.001$) when compared to the other subgroups.

Table 8.1 Characterization of the total study sample and comparison by physical frailty subgroups for biosocial and global health outcomes.

	Total sample (n=119, 100%)	**Nonfrail (n=19, 16%)**	**Pre-frail (n=46, 38.7%)**	**Frail (n=54, 45.4%)**	**p value**
Sociodemographic					
Chronological age (years, A±SD)	81,96 (±7,89)	81.68 (±6.72)	81.80 (± 8.65)	82.19 (± 7.72)	0.959
Level of education (degree; M1;3)	3 (3 ; 4)	4 (3 ; 6)	3 (3 ; 4)	3 (2 ; 4)	0.063
Marital state (n,%)					
Single	31 (26.1)	6 (31.6)	12 (26.1)	13 (24.1)	
Married	7 (5.9)	4 (21.0)	1 (2.2)	2 (3.7)	0.073
Widowed or divorced	81 (68.0)	9 (47.4)	33 (71.7)	39 (72.2)	
Anthropometric data					
Weight (kilograms, A±SD)	65.45(±12.58)	66.22 (± 11.33)	65.08 (±11.54)	65.49 (± 13.98)	0.946
Stature (meters, M1;3)	1.51 (1.47; 1.56)	1.56 (1.49; 1.62)	1.51 (1.47; 1.55)	1.50 (1.46; 1.52)	**0.008**
Body mass index (A±SD)	28.49 (± 5.05)	26.95 (± 3.78)	28.22 (± 4.60)	29.27 (± 5.69)	0.205
Clinical-mental health state					
Mini mental state (0-30 pts, M1;3)	20 (15; 25)	25 (21 ; 27)	21 (17 ; 25)	17 (13; 22)	**< 0.001**
Comorbidity index (0-10 pts, M1;3)	7 (6; 9)	8 (6 ; 10)	7 (6 ; 8)	8 (7; 9)	**0.026**
CES-D depression scale (0-60 pts, A±SD)	21.92 (± 8.00)	19.42 (± 7.99)	19.46 (± 8.09)	24.89 (± 6.98)	**0.001**

A=Average (mean), SD = standard deviation, M1; 3 = Median (25^{th} Percentile; 75^{th} Percentile); pts = points

The results of FD outcomes showed that statistical significant differences were found for all variables indicating that the frail subgroup presented more dependence (Katz index of ADL = p < 0.001 and Lawton index of IADL p = 0.002), higher fear of falling (p = 0.002) and less static (p = 0.039) and dynamic balance (p < 0.001) scores when compared to pre-frail and non-frail subgroups.

Table 8.2 Characterization of total sample and comparison of physical frailty subgroups for functional disability outcomes.

	Total sample (n = 119, 100%)	Nonfrail (n = 19, 16%)	Pre-frail (n = 46, 38.7%)	Frail (n = 54, 45.4%)	p value
Katz index of ADL (0-6 pts, n,%, disability)	43 (36.1)	13 (68.4)	20 (43.5)	10 (18.5)	**< 0.001**
Katz index of ADL (0-6 pts, n,% no disability)	76 (63.9)	6 (31.6)	26 (56.5)	44 (81.5)	
Lawton index of IADL index (9-32 pts A±SD)	20.11 (± 5.70)	17.37 (± 7.24)	18.70 (± 5.27)	22.28 (± 4.65)	**0.002**
Falls efficacy scale (10-100 pts M1;3)	40.00 (18.00; 61.00)	33.00 (14.00; 40.00)	34.50 (13; 70)	41.00 (26.00; 59.00)	**0.048**
Static balance test (per time,M1;3)	1.30 (0.05; 4.11)	2.52 (0.71 ; 11.00)	1.56 (0.17 ; 4.15)	1.09 (0.01; 3.38)	**0.039**
Agility-dynamic balance test (per time,M1;3)	13.00 (10.00; 20.56)	9.75 (7.12; 10.58)	11.15 (9.20 ; 14.90)	20.14 (14.30; 25.97)	**< 0.001**

A=Average (mean), SD=standard deviation, M1; 3= Median (25th Percentile; 75th Percentile); pts = points

As an additional analysis The Spearman's rank and partial correlations, controlling for covariates that presented were performed. Statistical differences in the group-treatment comparison was found. A moderate to strong correlation between PF total score and all FD outcomes was found (p<0.005). When looking at the partial correlations, only that between the Lawton index of IADL and FES scale disappears. On the basis of this first phase of statistical treatment, the multivariate regression analyses were performed and the results are presented in Table 8.3 showed above. Two models of independent relationships were generated between each disability and frailty independent components. The unadjusted results showed that Weakness was significantly associated with Katz of ADL and DBT tests, Slowness was associated to all FD outcomes, Exhaustion was associated to all FD components (except the STB test) and Low PA levels also associated with all FD outcomes, except with the FES scale. However, all these associations were trivial (r < 0.10).

After adding the adjusted covariates, Weakness presented a significant trivial correlation with the Katz of IADL index (β = - 0.047; OR = 0.954; IC95% [0.898, 1.016] ;p <0.001) and ADB test ($r^{2} =$ 0.18; β = -0.325; p = 0.007). The PF component of Slowness also showed a small correlations with Katz of ADL index (β = 0.28; OR = 1.316; IC95% [1.076, 1.609]; p <0.001) and moderate association with ADB test ($r^{2} =$ 0.53; β = 1.982; p <0.001) and a trivial correlation with TSB test ($r^{2} =$ 0.05; β = -0.444;; p = 0.034). Self-reported Exhaustion maintain independent and small significant association with Lawton of IADL index ($r^{2} =$ 0.53; β = 1.982; p <0.001) and a significant but small association with the ADB test ($r^{2} =$ 0.21; β = -6.642; p = 0.001) was also seen. Weight loss presented a small association with Katz of IADL index (β = - 1.707; OR = 0.181; IC95% [0.044, 0.749] ;p < 0.001) and a trivial association with the TSB test ($r^{2} =$ 0.05; β = -4.379;; p = 0.016).

Finally, Low PA levels had the smallest association with the Katz index (β = - 0.245; OR = 0.783; IC95% [0.509, 1.204] ;p <0.001), a moderate association with the Lawton index of IADL ($r^{2} =$ 0.30; β = -1.182; p = 0.010) and a small association with the ADB test ($r^{2} =$ 0.25; β = -3.528; p = 0.010). Lastly, residual and analytical analyses did not show violations of the assumptions underlying regression analysis and indicated a satisfactory fit of the model.

Table 8.3 Association between each physical frailty and functional disability components (n = 119).

Functional Disability outcomes	Katz's index of ADL				Lawton's index of IADL			Falls efficacy scale			Agility-dynamic balance test			Static Balance test		
Physical Frailty components	β coefficient	OR	95% CI for OR	omnibus test p-value	R^2	β coefficient	p value	R^2	β coefficient	p value	R^2	β coefficient	p value	R^2	β coefficient	p value
Low hand grip test (Weakness)																
Unadjusted	-0.056	0.946	[0.898, 0.996]	**0.028**	0.016	-0.096	0.166	<0.001	0.069	0.825	0.095	-0.400	**0.001**	0.006	0.070	0.415
Adjusted*	-0.047	0.954	[0.896, 1.016]	**<0.001**	0.236	-0.043	0.507	0.091	0.035	0.912	0.178	-0.325	**0.007**	0.008	0.049	0.600
Low 15-feet walking test (Slowness)																
Unadjusted	0.288	1.334	[1.134, 1.570]	**<0.001**	0.112	0.523	**<0.001**	0.059	1.695	**0.008**	0.533	1.978	**<0.001**	0.059	-0.471	**0.008**
Adjusted*	0.275	1.316	[1.076, 1.609]	**<0.001**	0.252	0.244	0.098	0.108	0.201	0.516	0.531	1.982	**<0.001**	0.046	-0.444	**0.034**
Self-reported weariness (Exhaustion)																
Unadjusted	-1.405	0.245	[0.106, 0.568]	**0.001**	0.101	-3.631	**<0.001**	0.021	-7.353	0.120	0.141	-7.474	**<0.001**	<0.001	0.209	0.874
Adjusted*	-1.487	0.226	[0.078, 0.659]	**<0.001**	0.293	-1.551	0.133	0.891	0.289	0.349	0.210	-6.442	**0.001**	0.007	-0.559	0.704
Unintentional reported (Weight loss)																
Unadjusted	-0.706	0.493	[0.167, 1.458]	0.184	0.025	-2.354	0.086	<0.001	0.762	0.902	<0.001	0.135	0.955	0.021	-2.712	0.113
Adjusted*	-1.707	0.181	[0.044, 0.749]	**<0.001**	0.238	-1.134	0.379	0.095	0.279	0.363	0.122	-0.684	0.776	0.057	-4.379	**0.016**
IPAQ - short version (Low PA levels)																
Unadjusted	-0.460	0.632	[0.434, 0.919]	**0.013**	0.107	-1.754	**<0.001**	<0.001	0.043	0.985	0.176	-3.909	**<0.001**	0.031	1.173	**0.047**
Adjusted*	-0.245	0.783	[0.509,1.204]	**<0.001**	0.277	-1.182	**0.010**	0.094	0.270	0.382	0.253	-3.528	**<0.001**	0.029	1.053	0.110

Notes: *Adjusted for age, education level, morbidity index, body mass index and cognitive status (model 1). For each logistic regression and each of the FS components, the corresponding β coefficient, odds-ratio (OR), 95% confidence intervals for the OR and the p-value of the omnibus tests of model coefficients were computed. For each linear regression and each of the frailty components variables, the coefficient of determination of the model (R^2), the β coefficient, the corresponding p-value and the p-value for the ANOVA test were computed; IPAQ = International Physical Activity Questionnaire

8.5 Discussion

The aim of the present study was to investigate the relationship between PF and FD outcomes in institutionalized women over 75 years old. We also examined the disability-differences between the three frail sub-groups. The main findings of this study were that the regression analyses showed that low levels of physical activity and slowness were the PF component most associated with FD outcomes even after adjusting models. On the other hand, the Katz index of ADL and the ADB test were de FD outcomes most associated with physical frailty independent components in both regressions models.

After Linda Fried described the PF Phenotype [3], several studies examined the prevalence of physical frailty in institutionalized samples [35]. Studies realized in Spain (Abizanda et al., 2014; de la Rica-Escuín et al., 2014), North America [38] and Brazil [39] corroborate the findings in the present study. First, the prevalence of PF was similar (45.4%) and second, frail individuals had the worst FD scores when compared to the other PF subgroups. The other finding of this study that drew attention was the short stature found in the frail subgroup when compared to the other frailty sub-groups. According to previous evidence, stunted growth as a developmental delay is a risk factor for later life functional impairments [40,41]. Height could be related to osteopenia/osteoporosis leading to loss of height. This fact was independent of age and needs to be further explored. Previous researchers have also found that a high comorbidity index, lower cognition and depressive status also appear to strongly associate with physical frailty (Abizanda et al., 2014; de la Rica-Escuín et al., 2014).

Similar to the present study, low PA levels were found to be a PF independent component that had a relationship with Katz of ADL and Lawton of IADL indexes [42–44]. The probable mechanisms that for this association were proposed in a previous study by Theou and colleagues [45]. The construct of daily life activities includes underlying socio-biological functions that are highly dependent on a satisfactory level of physical activity (PA). The biological mechanisms remain weakly comprehended, however, the main effects of low PA on functionality could be mediated by reduced muscle strength, and also possibly by a down-regulated inflammation and sex steroids hormone expression [46]. Gait speed is the most used motor skill test in studies related to physical performance in older frail populations [47].

Low capacity of walking speed has been found to be an independent component of physical frailty status linked with FD outcomes in numerous previous findings [48,49]. On the other hand, the Katz of ADL Index was the FD outcome most closely interrelated with all independent components of frailty and may explain the physical deficit on the functional status that occurs in an advanced frailty stage. For this reason, some researchers recognize it as an independent maker of frailty status [50].

Additionally, the results showed that, not the static balance, but the dynamic balance motor skill test, showed the best relationship with all the independent components of frailty status. This test has shown satisfactory associations with PF independent components in previous studies [51,52]. In addition, recent research has demonstrated that the ADB test proved to be a good predictor of PF, for instance, when the full application or interpretation of Fried's criteria is impracticable [51,53,54]. A critical analysis of the ADB test can help understand the satisfactory associations with PF found in this study since this test requires the integration of different physical capacities such as timed reaction, upper body strength and agility [55,56].

The limitations of this study is its cross-sectional design and the associations may be bidirectional and the study sample was small number of people in frailty subgroups, due to excessive and unexpected number of dropouts. However, the results of the present study showed a similar trend to the other studies with larger samples. Exploring these associations in institutionalized-dwelling individuals has a particular interest since their risk for age-physical decline was approximately four times higher when compared to community-dwelling individuals.

8.6 Conclusion

Our findings showed that low levels of physical activity and slowness are the independent components of physical frailty most associated with functional disability outcomes. These relationships have a specific interest in institutionalized samples and are in agreement with findings of previous studies. More epidemiological studies are needed across different sample cohorts of institutionalized-dwelling populations, to determine the real prognostic value of frailty independent components and to help design a co-adjuvant treatment to prevent frailty based on active lifestyle police interventions, aiming to increase levels of physical activity and also, encourage changes in sedentary behaviours in this type of population.

8.7 References

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CHAPTER 9 (STUDY 7):

THE RELATIONSHIP AMONG PSYCHOLOGICAL WELL-BEING AND PHYSICAL FRAILTY IN INSTITUTIONALIZED OLDER WOMEN REVEALS A PSYCHOLOGIC FRAIL STATUS.

Authors:

Guilherme Eustáquio Furtado

Miguel Patrício

Marisa Loureiro

Eef Hogervorst

Stephan Bandelow

Margarida Figueiredo-Braga

Ana Botelho Teixeira

José Pedro Ferreira

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9.1 Abstract

Background: The term 'Psychological Frailty' has appeared as a new frailty phenotype and implies a parallel to the Physical Frailty phenotype, suggesting perhaps a relationship between physical and psychological factors in frailty. **Purpose:** Very little is known about the associations between psychological status or mental health-related outcomes and the physical Frailty Syndrome in institutionalized populations. The main goal of this study was to analyse the relationship between physical frailty and psychological status in institutionalized older women. **Methods:** Cross-sectional data were collected. Participants were 118 older women aged 65 years old or more, recruited from four nursing homes, who were asked to complete a sociodemographic and a general health assessment survey. Psychological status was assessed using cognitive status, self-perceptions (self-efficacy and self-esteem), mood states (stress, depression) and emotional well-being (happiness and satisfaction with life) investigated using psychometric rating scales. Physical Frailty was assessed using the Fried of frailty Phenotype, that includes Weakness, Self-reported Exhaustion, Low Physical Activity levels and Unintentional Weight Loss assessments. **Results:** Frail older women had a poor score in all psychological well-being outcomes, except for global self-esteem and satisfaction with life. A hierarchical regression model analysis showed that cognitive status, attitudes to aging and a subjective feeling of happiness had a significant relationship with PF in both unadjusted and adjusted models (explaining 34% and 40% of variance, respectively). **Conclusions:** Psychological factors are strongly associated with PF. Implementing active lifestyle interventions to improve positive psychological outcomes in geriatric assessments could assist in the older institutionalized patient's physical and mental health care.

Key-word: Frail Older adults, women, psychology, emotional well-being and mental health.

9.2 Introduction

Frail populations are at increased risk for adverse negative health consequences (Middleton, Mitnitski, Fallah, Kirkland, & Rockwood, 2008). Disability, morbidity, institutionalization, and hospitalization are likely outcomes of this clinical time-progressive form of unsuccessful ageing (Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013). In the frail person, the order of adverse events occurs earlier and faster, significantly affecting their quality of life (Gobbens, Luijkx, & van Assen, 2013; Kanwar et al., 2013). Consensual statements on the core feature of the physical frailty (PF) syndrome, recognises it as an ageing-phenotype that increases vulnerability to stressors, due to impairments in multiple inter-related systems that lead to a decline in homeostatic reserve and resiliency. The concept of PF developed by Fried and colleagues (Fried et al., 2001), understood as a robust construct, has five components (Weakness, Low levels of Physical, Activity, Weight Loss, Exhaustion and Slowness) and is assumed to be very helpful for health professionals and researchers to comprehend the heterogeneity of health trajectories linked to frailty (Morley et al., 2013).

However, in spite of the considerable progress to date in the development of both the phenotypic and index models, the observational identification of frailty recognises other health dimensions that could further explain this phenomena (Kelaiditi et al., 2013). The coined concept of PF has been reported to mediate risk of several types of neuropsychological impairments (Buchman & Bennett, 2013). The concept of 'cognitive frailty' proposes a parallel to physical frailty, a loss of resilience and adaptability in the dominion of brain function and denotes a linkage to physical functions (Canevelli, Cesari, & van Kan, 2015). Numerous studies on expanded PF have implicated cognition as a possible factor influencing geriatric health outcomes (Panza et al., 2015). As with the concept of cognitive frailty, the term of 'Psychological frailty' (PsyF) appears as a new frailty phenotype, and implies a parallel to PF in the brain activities dimension, suggesting a relationship between the two (Fitten, 2015).

Frailty has been characterized by factors connected with multiple negative Psychological well-being (PwB) facets that manifest during the aging process already studied previously, but the difference is that the PF condition seems to worsen some psychological aspects (Freitag & Schmidt, 2016). In addition to cognitive status, studies aimed to analyse the multifaceted interactions between PwB outcomes and frailty, revealed that motivation (i.e. self-efficacy, attitudes), negative and positive mood state (i.e. depression, stress, emotional well being) were identified as core dimensions of PsyF (Dent & Hoogendijk, 2014; Freitag & Schmidt, 2016; Gale, Cooper, Deary, & Aihie Sayer, 2014; McAuley et al., 2006).

Each person has a unique genotype and a set of lifetime involvements that will fare in terms of global-health and risk of illness (McEwen, 2015). Thus, distinct mood states are the most important contributors to emotional adjustment and reflect in good perception of physical health (Thoits, 2011). Psychosocial stress, for example, is associated with the onset and progression of many and costly comorbidities, including chronic pain conditions linked to functional disabilities (Muscatell et al., 2015). Positive self-esteem is seen as a protective factor that contributes to a high positive physical self-perception in frail subjects (McAuley et al., 2005). High self-efficacy appears to be associated with good levels of motor skills in frail people (Chou, Hwang, & Wu, 2012). Adverse negative conditions of physical health can influence older people's subjective perception of positive feelings, mostly when they determine a reduction in their levels of PwB and their individual perception of their general health (Cho, Martin, Margrett, Macdonald, & Poon, 2011; Wu et al., 2013).

In spite of the critical contribution of PwB outcomes to explain PF, not many studies used PwB to describe how frail populations evaluate their levels of well-being, self-perceptions and mood states and how these are related to PF. Previous research looking at these associations was done in the community and hospital-based populations (Dent & Hoogendijk, 2014). Other recent findings show that some domains of subjective well-being impaired by a frailty identity crisis may play an central role in describing self-reported health status in older populations (Andrew, Fisk, & Rockwood, 2012a). However, very little is known about this relationship in specific populations, e.g. those living in nursing homes. The context of nursing homes provides a crucial location for the study of these connections, due to the patients' heterogenic condition in terms of physical status, comorbidities and psychological adjustment.

Thus, the main goal of this study was to analyse the association of physical frailty-with psychological well-being domains as well as to explore the relationship between frailty and PwB in institutionalized older women.

9.3 Methods

Data collection of all outcomes measures were organized by the principal investigator and were performed by independent specialists (properly trained) from the research team. The same evaluators for each study domain performed the data collection in all study participants using a face-to-face approach. Individual attention was provided to participants with interpretation doubts, questions were read to clarify the meaning assuring that no emphasis was put on the phrase in order to avoid directing the answer.

9.4 Design and procedures

This study a was cross-sectional study using a survey on frailty incidence in old people living in nursing homes. The sample consisted of a subset of participants within a previously published study protocol (Furtado, Patrício, Loureiro, Teixeira, & Ferreira, 2017). In the first stage, 10 CSHS were selected as eligible to participate in the study in the city of Coimbra, Portugal. After the visits to the homes to communicate the purpose of the study and to verify the eligibility selection criteria, four institutions were selected to participate in this study.

9.4.1 Participants and eligibility criteria

In a first phase all female participants aged over 75 years, willing to participate in the study and with their prescribed medications controlled were admitted to the study. The specific exclusion criteria were: i) the presence of any type of health condition that could prevent testing of autonomy, such as severe cardiomyopathy, uncontrolled cardiorespiratory illness and any musculoskeletal conditions that might prevent performance (i.e. recent fractures); ii) mental disorder, uncorrected hearing and vision impairments, morbid obesity; iii) no control and/or not up to date with drug therapy or the use of medications that could cause attention impairments. The first eligible participants included in the study were 183 institutionalized-dwelling old adults aged over 75 years. After applying the sample selection criteria, 64 participants were excluded or dropped out due to: i) physical impairment associated with musculoskeletal disorders and joint or muscle pain (n=34), ii) closed diagnosis of early-stage of dementia or mental disorder (n=09), iii) severe uncorrected impairment of hearing or visual functions that made it impossible to perform all tests (n=07), iv) need of palliative health care or special nutritional support, with medical indications not to participate in the study (n=04), v) participants who dropped-out when applying the tests (n=10), vi) inconsistent data (n =1). The final number of participants consisted of 118 older women.

9.4.2 Ethical Procedures

The NH directors and those who decided to participate in the study signed an informed consent form, in which the privacy and anonymous identity of the data collected were guaranteed and any needed access to participants' medical records was given. This study was approved by the Faculty of Sport Science and Physical Education Ethical Committee (Reference code CE/FCDEF-UC/000202013) - the University of Coimbra, respected the Portuguese Resolution (Art. 4st; Law n. 12/2005, 1st series) and complied with research guidelines in humans of the Helsinki Declaration (Petrini, 2014).

9.4.3 Outcomes measures

PF (and its components) was the primary outcome and the domains of PwB were secondary outcomes. Sociodemographic, general health status and anthropometric measures that presented statistical differences in frail sub-groups comparison were treated as possible confounders (and were entered as co-variates in analyses).

9.4.4 Physical Frailty screening

The prevalence of each of five items was calculated to generate the PF total score (continuous). A negative evaluation in one or two criteria classified the participants as pre-frail, in three or more as frail and as non-frail when the subject had a void in any of the five criteria, forming a categorical classification.

The following Fried's PF protocol was used (Fried et al., 2001): i) Weight loss was assessed by self-report of unintentional weight loss of four kilograms or more in the last six months, which was validated by medical records over one year; ii) Poor endurance and energy (self-reported exhaustion) was evaluated by negative concordance of two questions, number seven and twenty, of the questionnaire developed by the Center of Epidemiologic Studies for Depression, the CES-D scale; iii) Weakness was analysed using the handgrip strength test (HGT). This test uses a hand-held dynamometer (Lafayette Dynamometer, model 78010, United States) and strength is measured in kilograms. The subject holds the dynamometer in the hand to be tested, with the elbow by the side of the body. When ready the subject squeezes the dynamometer with maximum isometric effort, which is maintained for five seconds. The best result of two trials was used for scoring purposes (Syddall, Cooper, Martin, Briggs, & Aihie Sayer, 2003). Participants who were unable to perform the HGT and those in the lowest 20% (adjusted for BMI and stratified by gender) were categorized as positive for the weakness criterion; iv) Slowness was measured by the '15 feet walking test', consisting in an individual walk without assistance (4,6 meters) where the time taken to complete it, is measured and expressed in seconds, adjusted for gender and height. The best time of the two trials was used for final scoring; v) Low physical activity level was assessed by the International Physical Activity Questionnaire short form. Participants classified as inactive and minimally active had a positive score for the frailty status score.

9.4.5 Psychological well-being assessement

The psychological tests described below were chosen because they had been validated in the Portuguese population and characterize the main psychological domains described in the concept of PsyF as defined previously (Fitten, 2015):

i) Cognitive status: The Mini-Mental State Examination (MMSE) was used to assess cognitive state. The MMSE assesses five areas of cognitive function: orientation, immediate recall, attention and calculation, delayed recall, and language. The maximum MMSE score is 30 points, and a score below 24 points is considered abnormal and used for dementia and cognitive impairment screening (Macuco et al., 2012).

ii) Mood states: Depression was assessed using the CES-D scale reflecting major facets of this state. The 20-items are given on a four-point Likert scale, with scores between 0 and 60 in which the highest scores correlate with more depressive symptoms for the last week (Gonçalves, Fagulha, Ferreira, & Reis, 2014). The Perceived Stress Scale (PSS) assesses the perception of stressful experiences. Seven out of the 14-items is considered negative and seven as positive. Final scores can vary from 14 to 70 points, a higher score indicating greater feelings of stress (Taylor, 2015)

iii) Self-perception: The Rosenberg Self-esteem Scale (RSES) analyses global self-worth. The sum of all 10-item scores gives results between 10 and 40 points, where higher values represent higher levels of self-esteem (McKay, Boduszek, & Harvey, 2014). The General Self-Efficacy Scale (GSES) was used to assess optimistic self-beliefs related to efficacy to cope with a variety of difficult demands in life. Responses sum up to a composite score with a range from 10 to 40 points, where higher values represent higher levels of GSES (McAuley et al., 2005). The Attitudes to Aging Questionnaire (AAQ) was used to assess attitudes toward the ageing process as a personal experience from the perspective of older people. The AAQ contains 24 items and total scores range from 8 to 40 points. The higher the score the more positive the attitude towards one's own ageing process (Low, Molzahn, & Donald Schopflocher, 2013);

iv) Emotional well-being: The Satisfaction With Life Scale (SWLS) measures global cognitive judgments of satisfaction with one's life. The 5-item scale results in scores between one to 35 points, with higher values representing higher levels of life's satisfaction (McKay et al., 2014). The Happiness Face Scale (HFS) consisted of a graphical scheme where for each face is assigned one letter, in which the letter A (seven points) is considered the maximum and the letter G, the minimum (one point). The participant has to identify with one of the faces, depending on his/her state of happiness (Andrews & Withey, 1976).

9.4.6 Sociodemographic variables

Information on chronological age (continuous variable); marital state (assessed as four categories variable: single, married, widowed and divorced) and level of education were collected for each participant. The level of education was classified in years and analysed as a continuous variable.

9.4.7 Anthropometric measurements

Standardized procedures were followed for the collection of anthropometric data and included: i) weight or body mass as determined using a portable scale (Seca®, model 770, Germany) with a precision of 0.1 kilograms; ii) stature determined using a portable stadiometer (Seca Body meter®, model 208, Germany) with a precision of 0.1 centimeters. Body mass index (BMI) was calculated according to the formula [BMI = weight/height^2] (Chumlea & Baumgartner, 1989).

9.4.8 Clinical health status

Comorbidity was assessed using the Charlson Comorbidity Index (CCI) that measures the burden of disease to form a single index and is used as a continuous variable. One point for each additional 10 years is added to the initial score, that has been shown to predict one-year and 10-year mortality. A recent studied carried out a successful update of the index to 12 comorbidities (Quan et al., 2011). Medical records provided by a medical and health professional´s team were used to verify the accuracy of information provided by study participants within the CCI. The number of medications used was checked systematically through each participant institutional medical record, reporting polypharmacy according to the Portuguese Classification System of Human Medicine.

9.4.9 Statistical analysis

The assumption of normality was checked using Shapiro Wilk tests and by visual inspection of normality plots. Continuous data were described by their medians, 25th and 75th percentiles, whereas categorical data were described by absolute and relative frequencies. The comparison of quantitative variables between the frail sub-groups was performed using ANOVA or Kruskal-Wallis, depending on whether the variables were found to be normally distributed which, in turn, was ascertained employing Shapiro Wilk tests. The association between the groups and qualitative variables was assessed using Chi-square tests. Partial correlations between the PF and PwB were computed, together with partial correlations controlling for the assumed co-variates (cognitive status, comorbidities, marital status and height). The magnitude of the associations was classified following recommendations: trivial ($r < 0.1$); small (r from 0.1 to 0.3); moderate (r from 0.3 to 0.5); strong (r from 0.5 to 0.7) and robust (r from 0.7 to 0.9) (Batterham & Hopkins, 2006). In addition, the relationships between PF and PwB were analysed using a hierarchical stepwise regression model. In these, cognitive status was introduced as a first block. Secondly, depression state was entered together with cognitive status.

Lastly, all other psychological outcomes were entered to explain the maximal variance of the regression model. In addition, the unadjusted bivariate model 1 simply included the dependent variable (PF total score) and independent variable (PwB outcomes). Model 2 was further adjusted for variables of height, marital status and comorbidity. IBM SPSS Statistics 22.0 and in R 3.3.1 software were used for all computations. The level of significance adopted was $P = 0.05$.

9.5 Results

Table 9.1 presents the descriptive characteristics of the participants ($n = 118$) for all variables. Concerning the PF assessment, 19 participants were classified as non-frail (16%), 45 subjects as pre-frail (38%) and 54 as frail (46%). Analysis of the sociodemographic variables indicated that participants were older women with a median age of 83.0 (76.0; 88.0) years, mostly without husbands (94%) and with very low median (3^{rd} grade) academic achievement levels. When the frail sub-groups were compared, there were statistical differences between these sub-groups in marital status ($p = 0.028$) and anthropometric height ($p = 0.008$), but not weight.

With regards to the general health status, the mean scores of the total sample reflected a high incidence of comorbidity and a high risk of mortality with a median of 7 (6; 9) points on the CCI, as well as a high incidence of polypharmacy. There was also a clear trend for increased polypharmacy in the frail subgroup. Statistical differences between groups were found for CCI scores, that were higher ($p = 0.013$) in the frail group.

Table 9.1 Characterization of the total sample study population[a] and comparison by physical frailty subgroups syndrome for sociodemographic, anthropometric and general health status outcomes.

Variable	**Total sample (n=118, 100%)**	**Nonfrail (n=19, 16%)**	**Pre-frail (n=45, 38%)**	**Frail (n=54, 46%)**	**p value**
Sociodemographic (M1;3)					
Chronological age (years)	83.0 (76.0; 88.0)	82.0 (77.0; 88.0)	83.0 (76.0; 89.0)	83.0 (76.0; 87.0)	0.954
Level of education (degree)	3.0 (3.0; 4.0)	4.0 (3.0; 6.0)	3.0 (3.0; 4.0)	3.0 (2.0; 4.0)	0.060
Marital state (n,%)					
Single	30 (25.4)	6 (31.6)	11 (24.4)	13 (24.1)	**0.028**
Married	7 (5.9)	4 (21.1)	1 (2.2)	2 (3.7)	
Widowed or divorced	81 (68.6)	9 (47.4)	33 (73.3)	39 (72.2)	
Anthropometric (M1;3)					
Weight (kilograms)	66.1 (57.2; 71.4)	65.7 (58.6; 77.9)	65.7 (56.8; 71.4)	66.5 (53.1; 70.5)	0.951
Height (meters)	1.5 (1.5; 1.6)	1.6 (1.5; 1.6)	1.5 (1.5; 1.6)	1.5 (1.5; 1.5)	**0.008**
Body mass index (M1;3)	29.0 (24.6; 31.5)	27.0 (24.6; 30.1)	29.2 (24.4; 31.6)	30.2 (25.3; 32.3)	0.207
General Heath state					
Comorbidity (index, M1;3)	7.0 (6.0; 9.0)	8.0 (6.0; 10.0)	7.0 (6.0; 8.0)	8.0 (7.0; 9.0)	**0.013**
Medication use, per day (n, %)					
I use more than three	108 (91.5)	17 (89.5)	43 (95.6%)	48 (88.9)	0.434
I use three or less	10 (8.5)	2 (10.5)	2 (4.4)	6 (11.1)	

Notes: = M1; 3: The first and third quartile.

Figure 9.1 shows the characteristics of the total study sample and descriptive according to whether they were frail, pre-frail or frail. Examining scores from the PwB outcomes, the results showed statistically significant differences in the frail group, expect for self-esteem as assessed by RSES (p = 0.928) and SWLS (p = 0.171). This group also had high scores for negative mood states using the CES-D depression scale (p = 0.001) and the PSS stress scales (p = 0.003), as well as low scores for cognitive status using the MMSE (p < 0.001), self-perception using the GSES (p = 0.017), attitudes to ageing as assessed with the AAQ (p = 0.005) and subjective well-being using the HFS (p =0.037). Independent of directions of the scale's quotation, the statistically significant results indicated worse values for the frail subgroup.

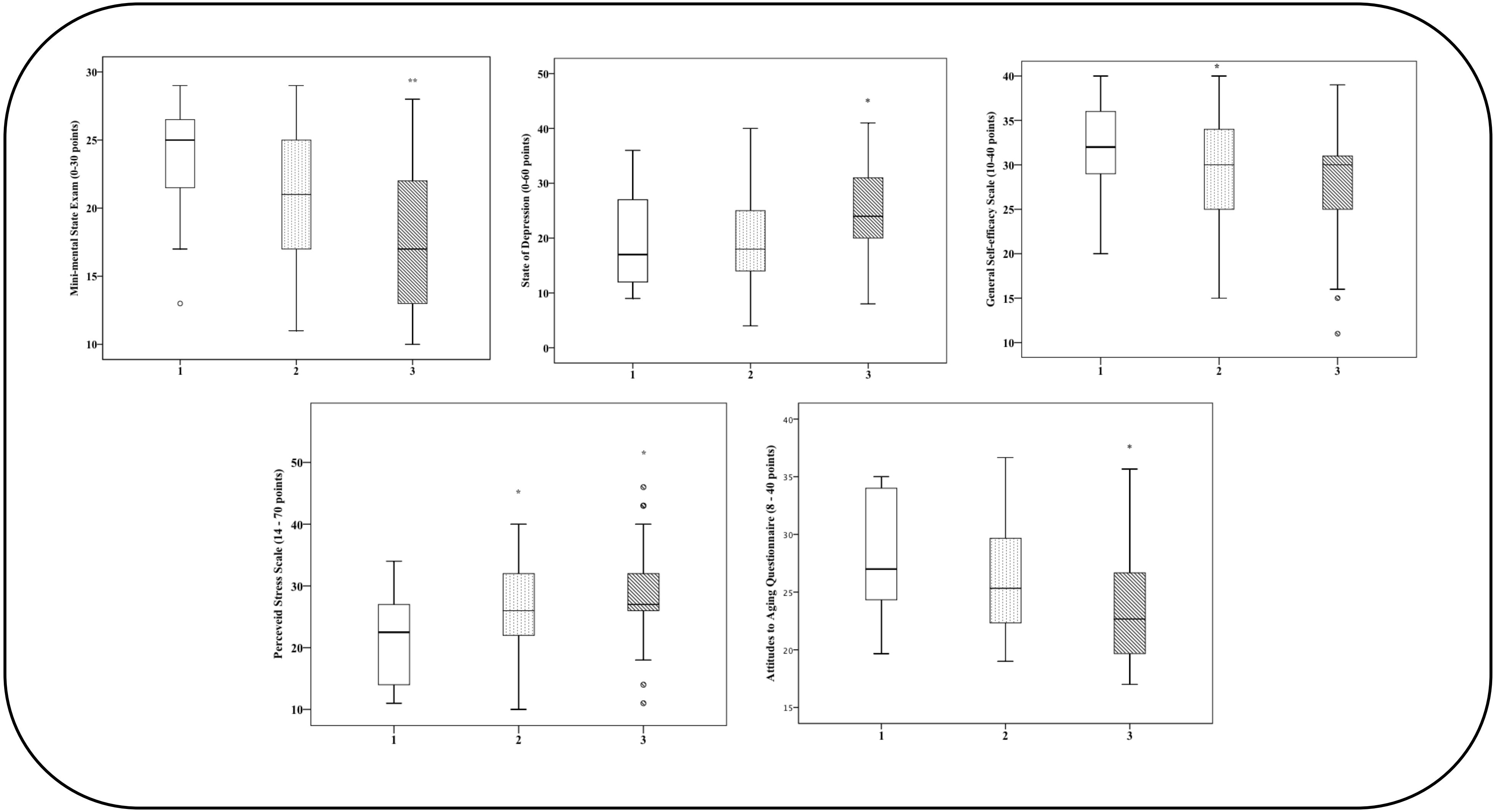

Figure 9.1 Box plots of the psychological well being outcomes only for each significant variable when comparing physical frailty sub-groups; X axis = psychological variables and Y axis = frail subgroups (1 = frail, 2 = Pre-frail and 3 = Frail). Statistical treatment was performed using Kruskal-Wallis tests, following Dunn's post-hoc test. The significance level was set at * p < 0.05; ** p < 0.01.

Table 9.2 shows the Spearman's rank and partial correlations, controlling for potential confounders. A significant correlation emerged between PF and all PwB, outcomes except with satisfaction with life as assessed by the self-esteem as assessed by the RSES. After applying statistical adjustment, correlations were moderately attenuated or increased, but some some important associations persisted. In the correlations between the psychological variables it was verified that all values were lower than r = 0.70, indicating that the assumption of non-multicollinearity among factors (taking into account the introduction of these variables in the regression model) was not violated.

Table 9.2 Spearman and their equivalent partial correlations between physical frailty total score and psychological well-being outcomes (n = 118).

Variables	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
1. Physical Frailty Total score								
2. Mini-mental State Examination	-0.401** **(<0.001)** -0.438 **(0.008)**							
3. CES-D of depression Scale	**0.317** **(<0.001)** **0.248** **(0.008)**	-0.152 (0.101) **-.201** **(0.047)**						
4. Perceived stress Scale	**0.294** **(0.001)** **0.238** **(0.011)**	-0.162 (0.081) -0.187 (0.065)	**0.416** **(<0.001)** **0.375** **(<0.001)**					
5. Global self-esteem Scale	0.085 (0.361) 0.036 (0.704)	-0.085 (0.363) -0.114 (0.164)	0.093 (0.315) 0.060 (0.525)	**0.398** **(<0.001)** **0.375** **(<0.001)**				
6. General self-efficacy Scale	**-0.274** **(0.003)** -0.161 (0.091)	**-0.322** **(0.000)** **-0.252** **(0.012)**	**-0.278** **(0.003)** **-0.258** **(0.006)**	**-0.453** **(<0.001)** **-0.439** **(<0.001)**	**-0.251** **(0.007)** **-0.256** **(0.007)**			
7. Attitudes to ageing Questionnaire	**-0.332** **(<0.001)** **-0.221** **(0.019)**	**0.205*** **(0.026)** **0.285** **(0.004)**	**-0.321** **(<0.001)** **-0.271** **(0.004)**	**-0.385** **(<0.001)** **-0.337** **(<0.001)**	**-0.315** **(0.001)** **-0.269** **(0.004)**	**0.302** **(0.001)** **0.254** **(0.008)**		
8. Satisfaction with life Scale	**-0.204** **(0.027)** **-0.212** **(0.024)**	-0.008 (0.934) **-0.266** **(0.008)**	**-0.315** **(0.001)** **-0.330** **(<0.001)**	**-0.307** **(0.001)** **-0.294** **(0.002)**	**-0.238** **(0.010)** **-0.212** **(0.024)**	**0.223** **(0.017)** **0.221** **(0.020)**	**0.381** **(<0.001)** **0.379** **(<0.001)**	
9. Subjective Face Happiness Scale	-0.182 (0.053) **-0.240** **(0.011)**	-0.034 (0.715) **-0.249** **(0.014)**	**-0.237** **(0.011)** **-0.280** **(0.003)**	-0.024 (0.804) -0.045 (0.643)	**0.266** **(0.004)** **0.243** **(0.010)**	0.027 (0.775) 0.055 (0.576)	-0.180 (0.058) -0.144 (0.137)	0.072 (0.450) 0.113 (0.243)

Notes: †partial correlation values are expressed in underline of each variable, controlling for marital status, height and comorbidity; MMSE = Mini-mental State Examination; CES-D = Depression Scale; RSES = Rosenberg Self-Esteem Scale; SHS = Subjective Happiness Scale; GSES = General Self Efficacy Scale; AAQ = Attitudes to Ageing Questionnaire; EWB = Emotional Well Being Scale.

Supported by the evidence presented in correlational analyses, multiple linear regression analyses were used to explore relationships between PF (as the dependent variable) and PwB outcomes (as independent variable). RSES and EWB were not introduced in this analysis as these were not correlated with PF. A hierarchical stepwise model was used, considering the theoretical assumption that cognitive profile and depression state presented a closed relationship with frailty (Buchman & Bennett, 2013; Lohman, Dumenci, & Mezuk, 2016). The results in Table 9.3 showed that, as expected, the cognitive profile of MMSE explained 22% of the variance by itself (model 1). Both unadjusted [F(6.100) = 11.613; p <0.001; R^2 = 0.340)] and adjusted [F(9.97) = 6.789; p <0.001; R^2 = 0.401)] regression analysis (block 3) models were statistical significant. In model 3, cognitive status using the MMSE, the Happiness Face Scale score, and the score of the Attitudes to Aging Questionnaire showed a significant relationship with PF in both unadjusted and adjusted models (explaining 34% and 40% of variance, respectively). Stress, negative mood of depression and self-efficacy did not significantly contribute to the model. The results indicated that decreased cognition, self-efficacy and happiness was accompanied by an increased likelihood for being frail. In regression model 3, associations were moderately attenuated by further adjustment for other potential confounding factors but persisted.

Table 9.3 - The association of PF with psychological well-being and physical frailty indicators (n = 118).

Regression Models	Unadjusted			Adjusted		
	R^2	B coefficient	p value	R^2	B coefficient	p value
Model (block) 1						
Mini-mental State Examination	.22	-.467	**.000**	.29	-.452	**.000**
Model (block) 2						
Mini-mental State Exam	.30	-.440	**.000**	.32	-.420	**.000**
CESD depression scale		.169	.052		.169	.163
Model (block) 3						
Mini-mental State Examination		-.378	**.000**		-.369	**.000**
CESD depression scale		.011	.909		.028	.771
Perceived Stress Scale	.34	.143	.157	.40	.112	.264
General Self-Efficacy Scale		-.024	.809		-.024	.798
Happiness Face Scale		-.188	**.032**		-.198	**.022**
Attitudes To Ageing Questionnaire		-.212	**.034**		-.209	**.038**

9.5 Discussion

The purpose of the present study was to analyse the relationship between PF and PwB. Firstly, we verified the PF-differences in PwB indicators and results indicated that frail individuals had a poor satisfaction with life, poor attitudes to ageing, poor general self efficacy, and a increased level of depression and perceived stress. Based on the relationship of depressive and mood states and cognitive status symptoms, additional PwB variables were investigated to explain incremental variance in PF scores.

Besides the expected effect of the cognitive profile, results showed that not depressive mood states, but a negative attitude to ageing and low feelings of happiness proved to independently contribute to the variance in PF status. To our knowledge, this is the first scientific evidence for the association of psychological health outcomes with PF scores in a Portuguese female institutionalised population over 75 years old.

9.5.1 Comparison by frailty subgroups

In agreement with other studies using samples with similar attributes, PF had similar prevalence (46%) when compared with other European countries with studied samples living in nursing homes (González-Vaca et al., 2014). The general health was poor and comorbidities presented with high scores in frail subgroups, showing that a possible overlap between morbidity and frailty exists (Wong et al., 2010). Interestingly, the sociodemographic of height (but not weight) and marital status (more widowed or divorced) presented with worse results in the frail subgroup. Height could be related to osteopenia/osteoporosis leading to loss of height. This was independent of age, and needs to be further explored. Marital status has also been shown in several longitudinal studies to be a powerful predictor of a number of chronic diseases (Lunenfeld & Stratton, 2013), and seems to follow the same trend towards the PF condition.

Analysis of PWB outcomes showed that higher scores were found with an increased incident of frailty. As in the Canadian Aging Study (N= 5.703), which results revealed that frailty was associated with low levels of well-being. The authors confirmed that PWB impaired by a frailty identity crisis may play an important role in defining subjective health in older adults (Andrew, Fisk, & Rockwood, 2012b). A more recent longitudinal study carried-out in similar population was found that a higher feeling of psychological well being was associated with a sense of control, self-realization and autonomy and may exert a protective effect against PF (Gale et al., 2014). Despite the differences in the different protocols for the evaluation of frailty, these studies were unanimous in confirming the robust link between frailty status and low general psychological well-being.

9.5.2 Relationships among PF and PWB outcomes

Several PWB outcomes were found to be directly associated with the PF total score. A recent study showed a clear interconnection between PF status and a set of PWB outcomes highlighting self-efficacy, anxiety, depression and resilience (Freitag & Schmidt, 2016). But, unlike our results, in this study depression emerged as an important psychological domain that explained the variance in PF scores.

In the regression analysis of the present study, a satisfactory relationship explained the PWB variance of PF, and the co-variates had only a slight attenuating effects on these relationships. It may be that cognitive status explained the association of depression, self efficacy and stress with frailty in our sample. Similar to Campbell and Bucher's findings at 20 years ago, this study found that the MMSE independently predicted frailty syndrome (Lerner, Liben, & Mueller, 2015). Cognitive frailty is already a widely accepted concept, as is the temporal similarity between the onset of cognitive decline and subsequent deficit in physical function (Kelaiditi et al., 2013).

Other factors associated with PF, such as perceived stress and self-efficacy did not contribute to the regression models in this sample. However, these outcomes play an important role in the establishment of the indirect relationships with frailty. The interconnections between stress and physical health remain the most widely studied under a biological approach (Corazza et al., 2013). However, it is possible that several psychosocial events exist activating emotional stressors with ageing. Also the ability to cognitively adjust to these events and reduce stress and improve self efficacy to deal with stressors could mediate the relationships found. Attitudes to aging, subjective feelings of happiness and their association with PF appeared as surprising findings. Attitudes towards ageing played an important role in the regression model.

A robust cross-sectional survey that collected data in 20 countries and was carried out by WHO quality of life research group showed that attitudes to ageing mediated the relationship between health satisfaction and physical, psychological, social and environmental quality of life (Low et al., 2013). These associations represent solid evidence, since the AAQ is a multidimensional construct, which includes three sub-dimensions: psychosocial loss, reflecting an high perception of negative feelings; and psychological growth, related to the increase of positive feelings regarding the life events; and physical change, emphasizing on items primarily associated to health and to the experience of ageing itself, therefore resulting in a subjective individualised psychological viewpoint affecting physical health (Laidlaw, Power, & Schmidt, 2007).

In this study, happiness displayed an additional factor to explain PF in this population. Positive psychology in recent years has advocated for the assessment of happiness rather than only assessing negative mood and its associations with general health status (Jones, Rapport, Hanks, Lichtenberg, & Telmet, 2003). Our data suggest that positive mood may have a more satisfactory contribution to PF rather than a negative mood which may have been explained by other factors present in the model. Interestingly, satisfaction with life and self esteem were not associated with frailty.

Experimental studies including those which can improve mood such as regular exercise will show whether our findings may reflect causality. If this is the case it may be that through exercise or other activities that improve mood and perceived coping styles (reducing stress and possibly a related increase in self-efficacy and self-esteem), improved attitudes to ageing (and possibly the related life satisfaction) will also improve and mediate improvement in PF symptoms. A take-home significance of this study is that increasing evidence supports the protective features of maintenance of a stronger sense of psychological well-being, which may help to reduce risk for physical frailty and support a reasonable end-life-course. Doctor Carol Ryff, who has high expertise of psychological well-being domains makes clear the importance of introducing new concepts to help understanding the links between the aging process and psychological well-being, highlighting attitudes and resilience (Ryff, 2014). They are important psychological skills for the development of capacity to maintain or regain well-being in the face of adversity.

9.6 Conclusions

Frailty was related to poor scores of psychological well-being outcomes outcomes in institutionalized older women. In addition, cognitive status, attitude toward aging and individual feelings of subjective happiness were revealed as independent predictors of frailty. Despite a construct of satisfactory evidence, this study had some limitations. Firstly, these lie within the sample characteristics, which included more fit individuals than frail people and could have caused biased results. Furthermore, this study has a cross-sectional design and the associations may be bidirectional and causal reasoning is difficult here as those with PF, because of their limitations may be more likely to feel less in control, more stressed and have a more negative attitude and lower feelings of happiness in life. However, the results of the present study showed a similar trend to the other studies with larger samples. Implementing active lifestyle interventions that take into consideration positive feelings outcomes in geriatric assessments will assist in patients physical and mental health care planning. Future research needs to investigate the mechanisms underlying this finding, perhaps exploring some biopsychological mechanisms.

9.7 References

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CHAPTER 10 (STUDY 8):

EXPLORING THE POTENTIAL OF SALIVARY AND BLOOD IMMUNE PROFILE MAKERS TO EXPLAIN PHYSICAL FRAILTY IN INSTITUTIONALIZED OLDER WOMEN.

Authors:

Guilherme Eustáquio Furtado

Luciele Minuzzi

Matheus Uba Chupel

Miguel Patrício

Marisa Loureiro

Eef Hogervorst

Stephan Bandelow

José Pedro Ferreira

Ana Maria Teixeira

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10.1 Abstract

Background: Early identification of older populations at increased risk for the physical frailty syndrome using biological approaches is potentially important for screening accuracy. **Goals:** To assess how different blood and salivary biomarkers may be applied to accurately explain frailty status and study the relationship between immune markers and independent components of physical frailty in institutionalized older women**. Methods:** A group of 139 institutionalized-dwelling women, aged 75 years and older, were assessed for sociodemographic, anthropometric and general health variables. The five Fried's physical frailty components (weakness, exhaustion, slowness, weight loss and low levels of physical activity) were also assessed. The quantification of different biochemical makers, including pro and anti-inflammatory cytokines, sex steroid hormones, anti-microbial proteins and blood cells count was performed in plasma and salivary samples. **Results:** The present study indicates that salivary α-amylase was the biomarker that better explained the frail condition and the one biomarker that best associated with the independent components of physical frailty. Inflammatory markers and blood counts also presented a link to the Physical Frailty components with Mean Corpuscular Hemoglobin, IL-10, IL-1ß, TNF-α- and cortisol levels associating with Exhaustion. **Conclusion:** These results are in accordance with previous studies observed for similar populations and have uncovered a new salivary marker (α-amylase) that may be used as a screening tool. Future research needs to investigate the causal-effect association between immune makers and physical frailty and further explore other markers of the multiple systems involved in the immune response, including those found in saliva samples, as this could be an easier non-invasive method for screening for frailty.

Key-words: Frail older adults, immune system, sex steroid hormones, cytokines, alpha-amylase

10.2 Introduction

The overall biochemical markers of organ systems are intrinsically inter-related and are best studied in the development of frailty (Gale, Baylis, Cooper, & Sayer, 2013; Walston, 2002). Especially in advanced age, clinical health status is characterised by a set of long-term musculoskeletal, immune and neurocognitive morbidities, that impact on people's physical-functioning. Clinical health outcomes are more than just the absence of disease, and includes all physiological structures related to the aging process. Studies revealed that lower clinical health is associated with an imbalance in several biochemical makers (BM) involved in the immune system, especially in frail individuals (Leng, Xue, Tian, Walston, & Fried, 2007).

The frailty syndrome is a challenging aging expression determined by phylogeny and ontogeny factors (Morley et al., 2013). Nowadays, frailty is conceptualized as a state in which reserve function across multiple physiologic systems declines, compromising the individuals' capacity to withstand biological stress, thereby predisposing them to poor health, functional decline, institutionalization and death (Mitnitski et al., 2015; Rockwood & Bergman, 2012). Using a classical approach, Linda Fried and colleagues (2001) established the Physical Frailty (PF) concept and identified five components which were Weakness, Slowness, Exhaustion, Weight loss and Low levels of Physical Activity (PA) to characterize it. According to this protocol it is possible to categorise the older population in frail, pre-frail and non-frail subgroups, according to the negative scores obtained on the individual factors (Fried et al., 2001). However, accumulating evidence from observational studies supports a progressive relationship between frailty, immune and neuroendocrine systems (Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013).

Numerous studies have shown that a decrease in the immune response is closely associated with a number of aspects of frailty, including sarcopenia and osteopenia (Aw, Silva, & Palmer, 2007). The molecular mechanisms involved in this relationship are quite complex, which occasionally hinders a reasonable conclusion about which biomarkers may have a greater power in explaining the early development of the frailty phenotype (Yao, Li, & Leng, 2011). However, some specialists suggest that the major reason for the difficulty in understanding the phenomenon is the diversity of mechanisms involved in the immune system, which include molecules, such as catecholamines, sex steroid hormones, anti and pro-inflammatory interleukins, and several cellular subsets that impact on in immune function. The cross-talk between these biochemical markers pathways are usually linear, although sometimes the lines of action through a chemokine signalling are diffuse, and do not follow the expected predictability of the linear pathway (Soysal et al., 2016a).

Numerous researchers have sought or assessed clinical or physiologically relevant biomarkers for their relationship with PF and poor clinical status, or assessed how putative predictors of PF may serve as additional screening tools (Schoufour, Echteld, Boonstra, Groothuismink, & Evenhuis, 2016). The Newcastle 85+ Study assessed whether a 40 Biochemical makers (BM) based frailty index allowed examination of their collective effect in predicting mortality compared with individual biomarkers (Mitnitski et al., 2015). The results showed that the combined BM of Frailty-index was more powerful for mortality prediction than any individual biomarker. In another study, serum sirtuins (NAD dependent deacetylases with anti-ageing properties) were described as promising non-invasive biomarkers for PF status (Kumar et al., 2014). Associations between PF in older institutionalized men and inflammatory makers, in particular Interleukin-6 (IL-6), Tumour Necrosis Factor-Alpha (TNF-α) and high sensitivity C-reactive Protein (CRP) serum levels have also been reported (Hubbard, O'Mahony, Savva, Calver, & Woodhouse, 2009).

Analysing multisystem risk factors of frailty in cross-sectional data of 1685 older adults aged 55 and older in the Singapore Longitudinal Ageing Studies, the researchers found that white blood cell counts, haemoglobin, albumin, lymphocytes and total cholesterol were highly associated with pre-frail and frail subgroups (Ng, Feng, Nyunt, Larbi, & Yap, 2014). The most recent study that focused on the female population found that high concentrations of the inflammatory marker CRP were more strongly predictive of incident frailty in women than in men (Gale et al., 2013). Many of the studies in the scientific literature came from community-dwelling elderly people, and the extrapolation of these results to a sample of institutionalized older people can be imprecise. Older adults living in institutionalized care are a dissimilar population with regards to many geriatric clinical health outcomes. Many questions remain unresolved for this population, as for example, whether and how BM of the different physiological systems have a close relationship with PF status. To our knowledge, the use of salivary biomarkers associated with mucosal immunity and their association with PF has not been reported in the literature.

In this study, we propose to assess how biomarkers (cytokines, sex steroid hormones, anti-microbial proteins and blood count analysis) of different systems may be applied to explain PF status and to test the strength of their relationship with independent components of PF in institutionalized older women. It was hypothesized that the frail sub-group would have a lower immune profile than those who are pre-frail and non-frail, and that salivary biomarkers could also reveal useful associations with frailty in this population.

10.3 Material and Methods

This exploratory study evolving institutionalized-dwelling individuals was based on **a** survey aimed to verify PF incidence in people living in centres for social and health care support (CHS). The sample consisted of a subset of the participants who took part in the previous published study protocol (Teixeira et al., 2016). Cross-sectional data from the baseline assessments were used for the current paper.

10.3.1 Eligibility criteria

Included participants were female, aged 75 years and over, who were willing to take part in the study and who were under medical supervision with updated prescribed drugs. The specific criteria for participant's exclusion were: the presence of any type of health condition that could prevent testing of autonomy, such as severe cardiomyopathy, uncontrolled cardiorespiratory illness and any musculoskeletal conditions that might prevent testing (i.e. recent fractures); having a mental disorder, hearing and vision impairment, morbid obesity; having no controlled and updated drug therapy or the use of medications that could cause attentional impairments.

10.3.2 Sample selection

A total of five institutions of CHS where the older person lives in long-term care and has the same daily routine, including health and social care were selected. The primary stage of participants' assessment was information provided on the potential participants by the medical professionals from each CHS, combined with clinical primary outcomes information. A convenience sampling assignment was used. The initial recruitment consisted of 305 (100%) institutionalized-dwelling potential participants. Before the initial screen, 128 individuals (42%) were excluded because of several negative clinical health conditions, such as severe physical, cognitive, hearing or visual impairment and other specifics impairments. A total of 37 (12%) older people dropped out during the data collection phases. The final analysed sample consisted of 139 (46%) older women.

10.3.3 Ethical statement

All the CHS directors and potential participants who expressed interest in participating in the study signed an informed consent form, in which the privacy and anonymous identity of the data collected were guaranteed and any needed access to participants' medical records were given. This study was approved by the Faculty of Sport Science and Physical Education

Ethical Committee (Reference code CE/FCDEF-UC/000202013) - the University of Coimbra, respected the Portuguese Resolution (Art. 4st; Law n. 12/2005, 1st series) and complied with research guidelines in humans of the Helsinki Declaration (Petrini, 2014).

10.3.4 Outcomes measures

Data collection of all variables was organized by the principal investigator and was performed by independent specialists (properly trained) of the research team. The same evaluators for each study domain performed the data collection in all study participants. The biosocial and general health indicators which had shown statistical differences between frail sub-groups in the comparison analysis were treated as covariates in the subsequent correlational statistical analyses.

10.3.5 Physical Frailty screening

Assessment of PF was evaluated according to Fried's PF protocol (Fried et al., 2001). Weight loss was assessed by self-report of unintentional weight loss of four kilograms or more in the last six months, validated by medical records. Poor endurance and energy (self-reported exhaustion) was evaluated by negative concordance of two questions (number 7 and 20) of the Center of Epidemiologic Studies for Depression questionnaire (CES-D), which in the original study had shown a significant association with a direct measurement of maximum rate of oxygen consumption (VO^2_{max}). Weakness was analyzed using the handgrip strength test (HGT). Participants who were unable to perform the HGT and those in the lowest 20% (adjusted for BMI and stratified by gender) were categorized as positive, based on cut off values. Slowness, as measured by the '15 feet (4,6 meters) walking test', adjusted for gender and height. Based on cut off values of Fried's study population, the best time of the two trials was used for final scoring. Low PA levels were assessed by the International PA Questionnaire short form, such that participants classified as having inactive and minimally active on this instrument scored positively. The PF total score was calculated according to the presence of each of the five items (0 to 5 points), classifying the participants as pre-frail (with 1 or 2 points), as frail (with 3 or more points) and as non-frail when the subject had none of the five frailty independent components, establishing a categorical classification.

10.3.6 Biochemical markers analysis

All saliva and blood collections for the biomarkers analysis occurred in the morning (between 10:00h – 12:00h). Saliva samples were collected by passive drool, that consisted in the participant allowing saliva to collect on the floor of the mouth, then to lean forward and dribble into a polypropylene tube for 3 minutes. Prior to the saliva collection, subjects were asked to rinse their mouth with water to remove food residues 20 min before sample collection. Saliva samples volumes were measured, aliquoted and stored at −20°C until further analysis.

Salivary concentrations of testosterone (TT), cortisol (COR), dehydroepiandrosterone (DHEA), lysozyme (Lys), and immunoglobulin-A (Ig-A) were analyzed by competitive ELISA [Salimetrics®, UK]. Salivary alpha-amylase (α-amylase) was analyzed using a kinetic assay [Salimetrics®, UK]. Additionally, salivary concentrations of interleukin-1 beta (IL-1β) and IL-6 were also analyzed by standard ELISA [Salimetrics®, UK]. Blood samples were collected by venepuncture by a registered nurse, and were allocated into kEDTA and serum tubes. Determination of blood counts was done immediately after blood collection, using an automated haematology analyzer [Coulter AcT Diff, Beckman Coulter, USA]. The remaining blood was separated by centrifugation and the plasma and serum samples kept frozen at -80°C until further use. The plasma levels of TNF-α, interferon gamma (IFN-γ) and interleukin-10 (IL-10) and were analyzed by ELISA [Invitrogen®, CA]. Serum CRP was determined using the Horiba Medical Pentra C200 [Kyoto, Japan].

10.3.7 Biosocial status

Sociodemographic information on chronological age (continuous variable) and level of education (assessed as a continuous variable) was collected for each participant. The level of education was classified according to the Portuguese educational system and analyzed as a continuous variable (Fernandes, 2007). Anthropometric measures included body mass, determined using a portable scale (Seca®, model 770, Germany) with a precision of 0.1 kilograms; stature, determined using a portable stadiometer (Seca Body meter®, model 208, Germany) with a precision of 0.1 centimeters, and body mass index (BMI), was calculated according the standard formula [BMI = weight/height^2]. The standardized procedures described by Lohan and colleagues were followed for the collection of anthropometric data (Chumlea, Baumgartner, 1989).

10.3.8 General health status screen

Nutritional status was measured using the Mini Nutritional Assessment (MNA). It consists of 18 questions. The maximum score is 30 points (pts), and classifies subjects as well-nourished (24 to 30 pts), at risk of malnutrition (17 to 23.5 pts) or as malnourished when scoring 17 points and lower (Guigoz, 2006). The *Charlson Comorbidity Index* (CCI) measures burden of disease and has a weighted index based on 19 comorbid conditions (Charlson, Szatrowski, Peterson, & Gold, 1994). *Daily medications used* (MU) by the participants were assessed through question number six of the MNA, that asks the participant if he/she takes more than 3 or less prescription drugs per day. The *Mini Mental State Examination* (MMSE) was used to assess cognitive profile. MMSE assesses five areas of cognition (Folstein, Folstein, & McHugh, 1975). The scores range from 0 to 30 points, and a score below 24 pts is considered abnormal and used for dementia screening.

10.3.9 Statistical analysis

The assumption of normality was checked by using Shapiro Wilk tests and visual inspection of plots. Continuous data are described by their medians, 25^{th} and 75^{th} percentiles, whereas qualitative data are described by absolute and relative frequencies. The comparison of continuous variables between the frail sub-groups was performed using ANOVA or Kruskal-Wallis, aimed to test biosocial and global health outcomes to control for selection bias. The association between PF sub-groups and category variables was assessed using Chi-square tests (Monte Carlo simulations were used when applicable). Correlations were computed to check de assumption of collinearity, together with partial correlations controlling for predetermined co-variates. To examination the contribute of each BM to explain frailty, the univariate diagnostic value of each BM was determined using ROC (receiver operating characteristics) analysis, comparing non-frail versus (vs) pre-frail and non-frail vs frail subgroups. For each model, a 95% confidence interval (CI) from percentiles for the area under the curve (AUC) was determined. The relationship between independent PF components of Slowness, Weakness and low levels of PA and some BM were made using linear regression. The PF of Exhaustion and Weight loss and their association with BM was assessed through logistic regression. The unadjusted model simply included one dependent variable and one independent variable. Model 1 presented unadjusted analysis results and model 2 included educational level, comorbidities, and cognitive state as co-variates. The outcomes of BM were assumed as dependent variables and the all BM were independent in the regression analysis. IBM SPSS Statistics 21.0 and in R 3.3.1 software were used for all computations. The level of significance adopted was P = 0.05.

10.4 Results

Table 10.1 presents biosocial characteristics of the complete sample and results from the frail subgroups analysis of the participants. Of all participants, 55 (39.6%) were considered as frail, 53 as pre-frail (38,1%) and 31 were classified as non-frail (22.3%). When frail sub-groups were compared for biosocial and global health status (co-variates), statistical differences were found for the level of education (p = 0.030), stature (p < 0.001), comorbidities (p = 0.006), depression (p = 0.009) and cognitive status (p < 0.001).

Table 10.1 Characterization of the total sample and comparison by physical frailty categories for biosocial and general health status.

	Total sample (n = 139, 100%)	**Nonfrail** (n= 31; 22.3%)	**Pre-frail** (n= 53; 38.1%)	**Frail** (n= 55;39.6%)	p value
Biosocial status (M1;3)					
Chronological age (years)	83 (77; 88)	82,5 (77; 88)	83 (76; 89)	83 (78; 87)	0.945
Level of education (degree)	3 (3; 4)	4 (3; 6)	3 (3; 4)	3 (2; 4)	**0.030**
Body mass index (M1;3)	28.74 (25.02, 31.16)	27.24 (24.49, 29.6)	28.9 (24.45, 31.46)	30.09 (26.13, 32.16)	0.070
General health status (M1;3)					
Mini-nutritional assessment (0-30 points)	24 (20, 26)	24 (21, 25.25)	24 (2, 26)	24 (22, 26)	0.918
Comorbidity index (0-10 points)	7 (6, 9)	7 (6, 10)	6 (6, 8)	8 (7, 9)	**0.006**
Polypharmacy use, per day (unit)	3 (2, 4)	3 (2, 4)	2 (2, 4)	4 (2, 4)	0.142
Mini Mental State Exam (0-30 points)	21 (16, 25)	25 (21.5, 27)	21 (17, 25)	17 (13.5, 22)	**0.000**

Notes: M (1;3) = Median vale of the first and third quartile.

The biochemical markers characteristics of the complete sample and results by frail subgroups analysis of the participants were presented in Table 10.2. Statistical differences were found for the levels of salivary IL-6 (p < 0.001), IL-1β (p = 0.011), COR (p < 0.001) and α-amylase (p = 0.020) as well as plasma cytokine of IL-10 (p = 0.049) and TNF-α (p = 0.035). In the differential blood counts, differences in mean corpuscular haemoglobin (MCH) (p = 0.013) were also found.

Table 10.2 Characterization of total sample and comparison by physical frailty subgroups for biochemical makers.

Biochemical makers	Total sample (n = 139, 100%)	Nonfrail (n= 31; 22.3%)	Pre-frail (n= 53; 38.1%)	Frail (n= 55; 39.6%)	P value
Salivary Interleukin-6 (pg/mL)	16.75	34.18	18.46	13.07	**0.000**
	(9.22, 25.7)	(16.75, 40.66)	(8.09, 25.2)	(8.04, 19.95)	
Salivary Interleukin-1 beta (pg/mL)	117.5	239.24	115.84	73.01	**0.011**
	(20.35, 208.95)	(61.9, 486.95)	(16.55, 203.89)	(8.36, 203.89)	
Plasma Interleukin-10 (pg/mL)	9.46	15.61 (3.88, 19.73)	6.13	20.53	**0.049**
	(3.01, 27.3)		(1.8, 19.73)	(3.75, 27.52)	
Interferon-gamma (pg/mL)	5.55	4.17	3.39	7.57	0.503
	(1.19, 11.4)	(1.19, 8.03)	(1.19, 11.4)	(1.19, 11.4)	
Tumour Necrosis Factor (pg/mL)	94.31	102.15	47.51	131.09	**0.035**
	(25.09, 145.35)	(31.86, 159.2)	(23.58, 133.14)	(25.09, 186.88)	
C-Reactive Protein (pg/mL)	3.93	4.73	2.48	3.93	0.126
	(0.7, 5.66)	(1.9, 6.41)	(0.65, 4.7)	(1.3, 5)	
Salivary Cortisol (µg/mL)	0.24	0.26	0.21	0.27	**0.055**
	(0.15, 0.29)	(0.16, 0.29)	(0.11, 0.27)	(0.16, 0.32)	
Salivary Testosterone (pg/mL)	59.01	59.01	57.25	65.29	0.365
	(41.45, 85.25)	(44.71, 93.53)	(39.29, 83.99)	(49.95, 82.3)	
Salivary Dehydroepiandrosterone (pg/mL)	26.97	26.97	19.77	32.16	0.701
	(6.25, 41.23)	(7.42, 33.16)	(5.05, 40.82)	(7.42, 45.98)	
Salivary Lysozyme (µg/mL)	2.1	2.1	1.37	3.02	0.386
	(0.44, 4.65)	(2, 3.05)	(0.18, 4.65)	(0.5, 4.65)	
Salivary Immunoglobulin-A (µg/mL)	231.44	258.23	199.25	234.81	0.173
	(105.73, 258.23)	(171.56, 258.23)	(105.74, 247.73)	(94.25, 351.58)	
Salivary alpha-amylase (U/mL)	45.59	84.95	41.49	25.91	**0.020**
	(2.95, 102.66)	(25.01, 197.81)	(2.71, 98.73)	(0.82, 61.13)	
Brain Derived Neurotrophic Factor (ng/mL)	4.92	5.45	5.17	4.85	0.964
	(2.89, 7.97)	(2.7, 8.21)	(2.88, 8.27)	(3.09, 6.89)	
Leucocyte (*10-3/uL)	6.81	7.3	6.5	7.1	0.428
	(5.9, 8.4)	(5.65, 8.9)	(5.5, 8.1)	(6.4, 7.85)	
Lymphocyte (*10-3/uL)	1.93	2.2	1.9	1.9	0.393
	(1.6, 2.3)	(1.55, 2.7)	(1.6, 2.2)	(1.6, 2.3)	
Monocyte (*10-3/uL)	0.34	0.3	0.34	0.34 (0.3, 0.4)	0.870
	(0.3, 0.4)	(0.3, 0.45)	(0.2, 0.4)		
Granulocyte (*10-3/uL)	64.7	65.4	64.5	64.7	0.812
	(58.15, 71.6)	(56.65, 71.6)	(58.9, 70.8)	(60.25, 71.9)	
Erythrocyte (*10-6/uL)	4.39 (4.12, 4.7)	4.43	4.39	4.39	0.987
		(3.96, 4.7)	(4.22, 4.66)	(4.12, 4.71)	
Haemoglobin (g/dL)	12.3	12.2	12.5	12.02	0.189
	(11.55, 13.1)	(11.35, 13.6)	(11.7, 13.3)	(11.3, 12.8)	
Mean Corpuscular Haemoglobin (pg)	27.8	28.3	28	31.4	**0.013**
	(26.75, 29.2)	(27.1, 29.3)	(27, 29.4)	(26.2, 32.4)	
Mean Cell Volume (fL)	88.2	89.2	88.5	87.67	0.185
	(85.9, 91.55)	(86.35, 93)	(86.5, 91.5)	(84.85, 89.4)	
Percentage of red cell distribution width	13.31	13.2	13.4	13.31	0.955
	(12.8, 14.1)	(12.7, 14.15)	(12.8, 14.3)	(12.8, 14.05)	
Platelets (*10-3/uL)	218.43	204.52	220	224	0.156
	(175, 258)	(158.5, 230)	(186, 261)	(184.5, 258.5)	
Mean Platelet Volume (fL)	8.6	8.6	8.66	8.6	0.641
	(8, 9.2)	(8.05, 9.05)	(7.8, 9.7)	(8.2, 9)	

Notes: = M1; 3: Median value of the first and third quartile in the bracket.

Subsequently, the first model of logistic regression analysis (using stepwise backward elimination) following a receiver operating characteristics curve analysis was performed to test the contribution of each BM to explain the frail condition, comparing non-frail versus (vs) pre-frail and non-frail vs frail. For both comparisons, the previously selected co-variates were entered. In the non-frail vs frail analysis, co-linearity was present for IL-1β and TNF-α (tolerance = .85) and was removed from the statistic model. The results show that when comparing non-frail vs frail groups, only salivary α-amylase contributed to the frail condition in the equation independently (ß = -.006, OR = .994, 95%CI [998;1000], p = .022). A satisfactory area under curve (AUC) reference value was attained for α-amylase (AUC = 0.613, AUC 95%CI = [0.518; 0.707]), with a sensitivity of 64.6% and a specificity of 75.4%.The corresponding cut-off value, maximizing Youden's index, was seen to be 63.7 U/mL. The analysis of non-frail vs pre-frail subgroups was not found to have statistical significant results.

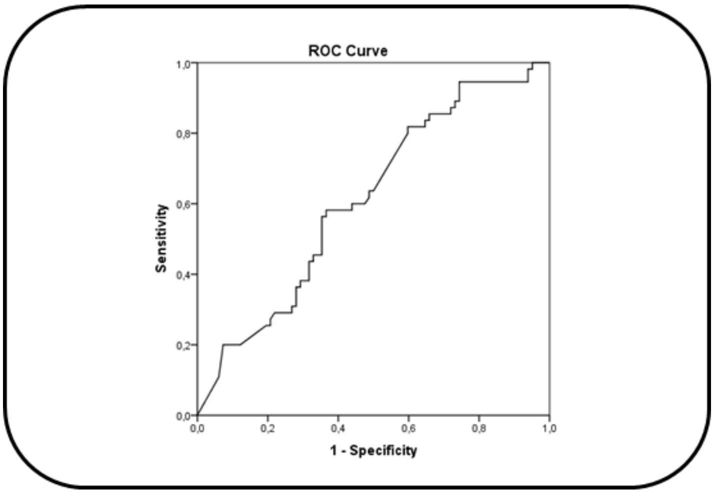

Figure 10.1 Receiver operating characteristic curve analysis for biochemical maker of salivary α-amylase, (n =140).

In the second regression analysis we opted for exploring the relationship between each independent PF component and the same biochemical makers were used as in the previous regressions analysis. The results of Table 10.3 show that in the unadjusted and adjusted (CCI, MMSE and Education levels) models, salivary IL-6, IL-1β and α-amylase makers were associated with the frailty component of Weakness. Plasma IL-10, TNF-α, MCH and salivary α-a, COR and IL-1- ß showed an association with Self-reported Exhaustion, although α-a presented a statistical significant relationship only after adjusting the model (ß-. = 003, OR = 998, 95%CI = [.997; 1003], p = .048). Only salivary α-amylase presented a statistical significant association with the independent physical frailty component of Low Levels of physical activity, considering both adjusted (r^2 = .044, ß-. = 002, p = .008) and unadjusted (r^2 = .033, ß-. = 003, p = .009) regression models.

Table 10.3 Association between each physical frailty independent component and available biochemical makers (n = 139).

Physical Frailty components	**Weakness (Low Hand grip strength)**			**Slowness (Low Gait speed)**			**Exhaustion (Self-reported weariness)**				**Weight loss (Unintentional reported)**				**Low PA levels (IPAQ-short version)**		
Biochemical markers	R^2	β coefficient	p value	R^2	β coefficient	p value	β coefficient	OR	95% CI for OR	p value omnibus test	β coefficient	OR	95% CI for OR	p value omnibus test	R^2	β coefficient	p value
IL-6 (pg/mL)																	
Unadjusted	.020	.054	**.044**	-.007	-.005	.710	-.007	.993	[.979; 1007]	.321	-.003	.997	[.979; .1007]	.707	.015	.006	.090
Adjusted*	.026	.057	**.050**	.016	-.004	.744	-.009	.991	[.997; 1006]	.140	-.003	.997	[.980; .1015]	.438	.000	.006	.096
IL-1β (pg/mL)																	
Unadjusted	.048	.005	**.008**	-.002	-.001	.386	-.001	.999	[.998; 1000]	.126	.000	1000	[.998; 1003]	.585	.000	.003	.237
Adjusted*	.076	.005	**.007**	-.003	-.001	.389	-.001	.999	[.997; 1010]	**.023**	.000	1000	[.999; 1001]	.401	-.011	.000	.242
IL-10 (pg/mL)																	
Unadjusted	-.002	-.012	.401	-.004	.004	.523	-.042	959	[.935; .983]	**.001**	-.002	.998	[.991; 1005]	.552	-.006	-.001	.680
Adjusted*	.032	-.012	.395	.005	.004	.554	-.040	961	[.937; .984]	**.000**	-.002	.998	[.991; 1007]	.466	-.018	-.001	.695
α-amylase (U/mL)																	
Unadjusted	.089	.019	**.009**	.004	-.003	.218	-.001	.996	[.996;1001]	.256	.000	1000	[.996; 1003]	.798	.044	.002	**.008**
Adjusted*	.104	.019	**.000**	.007	-.003	.229	-.003	.998	[.997; 1003]	**.048**	.000	999	[.996; 1003]	.488	.033	.003	**.009**
MCH(A) (pg/mL)																	
Unadjusted	-.006	.145	.655	.001	.147	.300	.255	1.290	[1.061; 1559]	**.011**	.048	1049	[846; 1301]	.658	.010	.066	.125
Adjusted*	.007	.183	.572	.014	.180	.206	.238	1.268	[1.037; 1551]	**.009**	.056	1057	[847; 1321]	.490	-.002	.063	.148
COR (μg/mL)																	
Unadjusted	-.004	-.936	.529	-.003	.526	.421	.311	1.365	[1.361; 1367]	.467	.593	1089	[1000; 1099]	.495	.007	-.200	.311
Adjusted*	.142	-.580	.506	.154	.265	.328	.373	1452	[1.449; 1458]	**.026**	.220	1773	[1769; 1785]	.512	.146	-.211	.256
TNF-α (pg/mL)																	
Unadjusted	-.001	.004	.327	-.001	-.002	.369	-.008	.992	[.990; 1.001]	**.000**	-.002	.998	[.991; 1011]	**.035**	-.002	.389	.389
Adjusted*	.144	.580	.484	.156	-.277	.169	-.007	.993	[.991; 1004]	**.000**	-.003	.997	[.994; 1008]	0.75	.120	.212	.212

Notes: *Adjusted for education level, morbidity index and mini-mental state exam. For each logistic regression and each of the FS components, the corresponding β coefficient, odds-ratio (OR), 95% confidence intervals for the OR and the p-value of the omnibus tests of model coefficients were computed. For each linear regression and each of the frailty components variables, the coefficient of determination of the model (R^2), the β coefficient, the corresponding p-value and the p-value for the ANOVA test were computed; PA = Physical activity; Salivary Interleukin-6 = IL-6, Salivary Interleukin-1 beta = IL-1β, Plasma Interleukin-10 = IL-10, Tumour Necrosis Factor = TNF-α, Salivary α-amylase = AA, Mean Corpuscular Haemoglobin = MCH; IPAQ-SV = International Physical Activity questionnaire – short version.

10.5 Discussion

Analysing the associations between the immune markers and frailty status in institutionalized older women, the results indicated that of all biomarkers that presented statistical differences in the frailty subgroups comparison, only salivary α-amylase contributed to explain frailty status in this study sample. Exploring the relationship between PF independent components and salivary IL-6, IL-1β, COR, α-amylase, plasma TNF-α, the results showed that mucosal immune makers (α-amylase and cortisol), pro-inflammatory (IL-6, IL-1β and TNF-α) and anti-inflammatory (IL-10) cytokines showed a statistical significant relationship with the independent PF components of Weakness and/or Exhaustion. The human immune system is a host defence system involving many biological structures within an organism that defends against several types of pathogens or other substances from the environment, neutralizing viruses, bacteria and fungi through mechanisms such as phagocytosis (Licastro et al., 2005). All BM involved in this study have protective functions directly or indirectly in different immune sub-systems, but its efficacy decreases with advanced ageing. Recent studies suggest that there are abnormal increased immunosenescence processes in frail individuals, namely in the pro-inflammatory cytokines levels, such IL-6 and IL-1β (Soysal et al., 2016b).

High levels of IL-6 and IL-1β in older people were associated with neurodegenerative, cardiometabolic, and musculoskeletal disorders (Licastro et al., 2005). However, our study showed unexpected lower values of IL-6 in the frail subgroup, contradicting the results of some recent findings (Leng et al., 2007). The likely explanation for these results is presented by Maggio and colleagues, that elucidate the causal role of lower levels of IL-6 (and other cytokines such as IL-1β, IL-12 and IL-23) in very old frail people (as was the case in our study sample), with an intrinsic relationship with possible decreases in the immune response, involving the Pattern Recognition Receptors-PRR (Maggio, Guralnik, Longo, & Ferrucci, 2006). The action of PRR intramolecular mechanism associating with the immune response is the pathway that can explain the lowering of these cytokines levels. PRR recognize varied pathogen by their molecular patterns, leading to the secretion of inflammatory cytokines, chemokines and upregulation of co-stimulatory molecules (Compté et al., 2013). In very old frail individuals, this response does not occur in the same proportion, and poor nutrition and low muscle mass were closely associated with low activation of this mechanism (Compté et al., 2013; Leng et al., 2007).

In the present study, IL-6 and IL-1β were associated with Weakness (low hand grip strength), corroborating the findings previously described by Compté and colleagues (Compté et al., 2013).It is important to mention that some recent studies suggested that IL-6 also exerts important signalling in the inflammatory process, not requiring its suppression, but rather an expression which may be beneficial for the activation of some anti-inflammatory mechanisms (Maggio et al., 2006) or a direct response to elevate TNF-α levels (Walston, 2012; Welsh et. al, 201), as it seems to be the case in our study.On the other hand, IL-10 exerts a potent anti-inflammatory activity regulating the immune system response (Bruunsgaard & Pedersen, 2000). Decreases in IL-10 have been linked to the aging process and found in obese individuals (Bruunsgaard & Pedersen, 2000). A number of studies showed different IL-10 levels on different frail sub-groups. Curiously IL-10 knock out mice have been used as frail-induced animal models (Dagdeviren et al., 2017; von Zglinicki et al., 2016). Relationship between IL-10 and Exhaustion emerged in our study that could be explained by the direct relationship between IL-10 and low cardiorespiratory function shown in previous findings (Su, Hao, Liu, & Dong, 2017). Elevations in IL-10 are expected as a counter regulatory mechanism to arrest and limit further inflammation in chronic inflamed tissues. Furthermore elevation of IL-10, with or without elevation in IL-6, is associated with an increased risk of cardiovascular disease (Welsh et al., 2011). TNF-α levels were higher in the pre-frail and frail individuals which could have elicited higher levels of IL-10 in the frail subgroup. However, the limited number of studies that associated frailty and IL-10 do not permit an accurate inference (von Zglinicki et al., 2016). While IL-10 was inversely associated with Exhaustion, TNF-α, levels were positively associated with Exhaustion.

According to a recent literature review, increases in the levels of this pro-inflammatory cytokine are associated with the chronic fatigue syndrome, which in turn has a pathophysiological core common to the frail condition: bone and muscle weakness (Morey, Boggero, Scott, & Segerstrom, 2016). In our study sample the second highest incidence of comorbidity were bone degenerative diseases (Louati & Berenbaum, 2015). PF and anaemia in the older individuals appear to share a common biological disorder, especially immune - endocrine dysregulations linked to frailty (Leng et al., 2009). In this study, a slightly but significant increase in MCH levels in the frail subgroup may give clues to understand an established association between blood count cells, sarcopenia and frailty (Silva et al., 2014). The MCH represents the average mass of haemoglobin per red blood cell (RBC) which main function is to carry oxygen to the body tissues via the blood current through the circulatory system (Snyder & Sheafor, 1999). As self-reported Exhaustion is understood as a PF component of fatigue, the associations found in the present study makes sense, corroborating some findings with similar population from the FIBRA study (Silva et al., 2014).

Notwithstanding the above findings, the primary findings of this study revealed that α-amylase was the only marker that could explain the frail condition. Interestingly, α-amylase presented a statistical and direct relationship with Exhaustion, low levels of PA and Weakness (low grip strength), which explains why α-amylase was the marker that showed the best fit in the ROC analysis. Research on saliva samples in older populations has grown in the last years for two apparent reasons, easy and non-invasive data collection and the existence of moderate and strong correlations with their similar blood markers (Schumacher, Kirschbaum, Fydrich, & Ströhle, 2013). Although α-amylase was included in our statistical model considering its important contribute to mucosal immunity (acting as a first barrier of host immune defence), in the last years, α-amylase has also been studied in a behavioural perspective, due to its identification as a modulator of the autonomic nervous system activity in both biological and psychological stress (Allgrove, Gomes, Hough, & Gleeson, 2008). The small concentration found in our study sample is possibly explained by the high prevalence of low levels of PA (40% of total sample), since recent findings suggested that maintaining an active life style in older individuals (i.e. moderate exercise) can help preserve a reasonable response of the ANS, contributing to a stronger first immune barrier (Walsh et al., 2011).

In contrast to the α-amylase results, the salivary cortisol (COR) response had higher levels in the frail individuals group. While COR is a useful maker as a measure of hypothalamic-pituitary-adrenocortical activity (HPA) and psychobiological stress, the expression of α-amylase occurs in the parotid gland (in response to adrenergic activity) and the sympathetic adrenomedullary system (SAM). This difference may be the first step in understanding the antagonist results in the frail sub-group. Previous studies have shown that the responses of the HPA and the SAM systems may differ depending on the type of stressor (i.e. psychosocial stress, chronic disease, exercise) (Maruyama et al., 2012; Schumacher et al., 2013). As was the case of this study, evidence suggests that higher levels of salivary COR may be due to the vulnerability of clinical status in older women (high ICC values were observed in this sample), corroborated with similar findings from previous studies (Varadhan et al., 2008).

Furthermore, experts recognize that high psychological state of depression and anxiety (other important characteristic of this sample) have been empirically linked to dysregulation and inhibition of some immune responses (Morey et al., 2016). This marker also presents an association with the independent PF component of Exhaustion after adjusted model statistics, suggesting associations between global health status, low cardiorespiratory fitness and high levels of biological stress.

Despite of the results obtained, this study has some limitations. First, the number of participants was relatively small, considering the individual variability in some of the biochemical makers studied. Future studies with institutionalized samples should include larger samples, especially if involving markers that act in different pathways of the immune system. Second, the cross-sectional data does not permit a causal-effect association. The high number of biomarkers examined was very positive. However, we recognize that when examining the results, the reader must take into account that we introduced in the statistical model different biological materials, although the correlation between the salivary and blood samples of the markers used in the present study were proven. The introduction of saliva made the study interesting from the methodological point of view. Although the regression models used levels of comorbidity (and cognitive profile) in the adjustment of statistical models, future analysis should also try to examine relationships between immune markers and a group-type of medication used.

10.6 Conclusions

In conclusion, the present study indicates that salivary α-amylase was the better biomarker in the model to explain the frail condition and was the one that was most strongly associated with the independent physical frailty components. The inflammatory and blood cell makers studied also revealed interesting links to the the five independent components of physical frailty and and all the associations made sense from a biological point of view with Weakness and Exhaustion being the frailty components most associated with the immune profile.

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SECTION IV

Intervention design: modulation of exercise on general health indicators

CHAPTER 11 (STUDY 9):

MUSCLE-STRENGTH AND MULTIMODAL CHAIR-BASED EXERCISE PROGRAMMES INCREASE DHEA AND TESTOSTERONE LEVELS, DECREASE FRAILTY STATUS AND FUNCTIONAL DISABILITY IN OLDER WOMEN

Authors:

Guilherme Eustáquio Furtado

Humberto Moreira Carvalho

Miguel Patrício

Marisa Loureiro

Matheus Uba Chupel

Juan Colado

Eef Hogervorst

Stephan Bandelow

Ana Maria Teixeira

José Pedro Ferreira

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11.1 Abstract

Many people experience ageing-related losses in different physical functioning domains, resulting in a physical frail status. The aim of this study was to analyse the effects of two different 24-weeks class chair-based exercise protocols on frailty, disability and salivary steroids hormones in frail older women. A sample of older women was divided into three groups: the control non-exercising group (CG_{ne}, n = 17), muscle-strength (CSE, n=18) and multimodal (CME, n =24) exercise groups. Supervised exercise programs consisted of 50 minutes' chair-based group classes, carried out 3 times a week. CME participants performed a progressive resistance exercise-circuit using walking and body height resistance exercises. The muscle-strength resistance exercises with elastic-bands followed a bi-set protocol. The controls did not change their usual lifestyle. **Results:** Frailty, disability and hormone outcomes were analyzed before and after the intervention. Both exercise groups diminished the frailty status, showing significant time (p = 0.003) and time *versus* treatment interactions (p=0.000). A small increase in CME between baseline and 12-weeks for Testosterone concentrations (*p*=0.009) were observed. D-hydroepiandrosterone increase after 24 weeks (*p*=0.01) in CME. Both exercises programs decreased negative scores in several domains of disability, especially fear of falling that showed a significant effect of time (*p*=0.01), and time *versus* intervention (*p*=0.03). **Conclusion:** Both chair-exercise programs were effective in stimulating positive changes in physical health and simultaneously, satisfactory responses in sex steroids hormones. The control group did show a negative trend towards increased frailty status and decreased levels of anabolic hormones. These results support the importance of an active lifestyle in very old frail women.

Key-words: Muscle-strength, Multimodal, physical exercise, Frail-Older adults, Sex steroids hormones, Functional disability

11.2 Introduction

Nowadays, the recently coined concept of physical Frailty (PF) is understood to be a decreased resistance to stressors and an increased risk for adverse health outcomes as well as to modulate the risk of several types of physical, mental and hormonal disorders (Bernabei et al., 2014). A sedentary lifestyle also proves to be a powerful condition linked to the frail condition. Progressive neuromuscular changes in old people, such as the decrease in type II fibres and increase in type I contributing to a reduction of physical activity levels, added numbers of falls and modulated negative changes in the endocrine system (Chen et al., 2007). Compared to men, women experience more intense alterations in their endocrine function with ageing, especially in menopause (Copeland, Chu, & Tremblay, 2004).

Recent findings provided some evidence that changes in sex steroids hormones such as Cortisol (CORT), Testosterone (TT) and D-hydroepiandrosterone (DHEA) may be involved in the vulnerability observed in frail older women (Holanda et al., 2012).However, some studies suggest that regular exercise can stimulate hormones expression in older adults (Walsh & Oliver, 2016). While high levels of stress can determine physical impairment, moderate stress with a mild increase in CORT levels may have a positive effect on coping and physical fitness performance (Mura et al., 2014). TT is an essential hormone for women, with physiological actions mediated via estradiol throughout the body (Davis & Wahlin-Jacobsen, 2015). Low TT levels have been associated with a higher risk of anemia, poor performance on cognitive tests and sarcopenia (Mitchell et al., 2012). DHEA is a hormone that shows a reduction (10% to 20%) from peak levels reached in early adulthood to old age and is implicated in the disturbance of the musculoskeletal system, neurotransmitters receptors, immune system functions and androgenic activity (Labrie, 2010). Values of TT to CORT ratio correlated significantly with individual increases obtained in one repetition maximal strength test in older women after 24-weeks exercise participation (Häkkinen et al., 2002). However, the literature describes that involvement of salivary hormones is not clear in their response to regular exercise in this specific population, despite advanced research in exercise related to hormone response (Walsh & Oliver, 2016).

Resistance elastic-bands appear to be an equitable alternative to traditional strength training devices, with reduced risk of injury and adjust the exercise intensity based on the rate of perceived exertion (Colado & Triplett, 2008). This method has demonstrated the efficacy in improving muscle strength, a better anti-inflammatory balance and an increase in cognitive status in older people (Chupel et al., 2017). At the same time, improvements in maximal oxygen uptake after multimodal exercise programs in frail individuals were reported in several studies, as well as gains in gait speed, dynamic balance, reaction time and the time spent in the stand position. (Theou et al., 2011).

However, the effect of strength or multimodal chair-exercises on the modulation of different physical functioning domains (hormonal, behavioural and disability) still needs to be explored. Therefore, the aim of this study was to analyse the effects of two different class groups of chair multimodal and muscle-strengthening exercises with elastic bands on indicators of frailty status, functional disability and sex steroids hormones in institutionalized pre-frail and frail women. Based on previous findings, we hypothesized that both 28-weeks of exercises programs would be able to decrease disability, reverse frailty status and simultaneously increase the levels of sex steroids hormones.

11.3 Methods

Participants or their legal tutors signed an informed consent term. This study was approved by the Ethics and Human Subjects Review Board of the University of Coimbra, respecting the guidelines for human research of the Helsinki declaration.

11.3.1 Participants' selection

Participants were institutionalized-dwelling women living in centres of health and social support (CHS) in the city of Coimbra, Portugal, aged 75 years and above, with drug therapy updated and clinically stable. Not completing the dynamic balance test in 30 seconds, an involvement in other exercise programs, use of medications that significantly impaired attention, individuals classified with morbid obesity, medical diagnosed cardiometabolic, respiratory and musculoskeletal dysfunctions, the presence of severe mental, hearing and vision impairment or involvement in hormone therapy were the main exclusion criteria.

11.3.2 Sample size and allocation

Sample size estimation was performed by comparison of frail outcomes based on previous studies (de Labra, Guimaraes-Pinheiro, Maseda, Lorenzo, & Millán-Calenti, 2015). Assuming a minimum power of .80 as realistically expected, the sample size was 19 participants per group. Further supposing a dropout rate of 30% (Picorelli, Pereira, Pereira, Felício, & Sherrington, 2014), the sample was increased to 28 per group, allocated into three groups. The final sample analyzed consisted of 59 participants: non-exercising control group (CG_{ne}, n = 17), chair elastic-band muscle strength (CSE, n=18) and chair multimodal exercises (CME, n =24) programmes. The allocation to treatment followed the Consolidated Standards of Reporting Trials (CONSORT).

11.3.3 Assessments

The data collection was done in the morning period (09:00 to 11:30 am). The quality of data assessment was made and reported for each physical markers through internal consistency reliability scores (ICR). The Cronbach's alpha (C-α) or Cohen's kappa coefficient (*k*) were reported for rate scales.

11.3.4 Physical Frailty

The Fried of PF protocol was used (Fried et al., 2001). Shrinking was assessed by self-report of unintentional weight loss of four kilograms or more in the last six months; Self-reported exhaustion was evaluated by concordance of two questions (7 and 20) of the CES-D depression scale; Weakness, was analyzed using the handgrip strength test, adjusted for gender and body mass index (ICR = .88); Slowness, was measured by the 4.6 meters walking test, adjusted for gender and height (ICR = .80); levels of PA were assessed by the International Questionnaire short form (ICR = .78). The prevalence of PF was calculated to generate a PF total score.

11.3.5 Sex steroids hormones

Saliva samples to measure CORT, DHEA and TT levels, were collected by passive drool always at the same time in the morning (between 10:00h to 11:30h) to minimize circadian effects. Individuals salivated without any orofacial movement into high-quality polypropylene vials to avoid problems with analytic retention or the introduction of contaminants that could interfere with the immunoassays. The tubes containing the saliva samples were then frozen (-20ºC), until the day of the analysis, when they were defrosted and centrifuged in order to obtain a clear sample. The levels of hormones were determined by competitive enzyme-linked immunosorbent assay (ELISA), according to the manufacturer instructions [Salimetrics, United Kingdom]. The following values for CORT (<0.007 ug/dL, r = .91), TT (1 pg/mL, r = .96) and DHEA (5 pg/mL, r =.86) were reported by the manufacturer, in terms of sensitivity and their respective correlation with serum samples.

11.3.6 Functional disability

The Katz Index of Independent daily life activities (ADL, α = .81) were used to rank adequacy of performance in the biosocial functions and a summary classifying people as dependent or independent (Wallace & Shelkey, 2007). Fear of falling was measured through the Falls Efficacy Scale (FES, α = .88) (Melo, 2009). Static balance was assessed through the Tandem Stance Balance test (TSB, ICR = .76), consisting of the participant maintaining the standing position with eyes opened and one foot in front of the opposite foot for 30 seconds (Cho, Scarpace, & Alexander, 2004).

11.3.7 Clinical health status

The Mini Nutritional Assessment (MNA, *k* = .74) was used to evaluate nutritional status, classified as predetermined state of malnutrition (< 17 points), malnutrition risk (17 to 23.5 points) and adequate nutritional status of > 23.5 points (Loureiro, 2008). The Charlson Comorbidity Index (CCI, ICR = .94) was used to classify comorbid conditions based on the register of each individual (Charlson, Szatrowski, Peterson, & Gold, 1994). Medication use (MU) was assessed through medical record over one year for each participant. To reduce potential confounding effects, all the participants were encouraged to maintain unchanged diets, drugs treatment, and routines across the 24-weeks of the intervention.

11.3.8 Biosocial and anthropometric

Information about chronological age was collected. Body mass was determined using a portable scale (Seca®, model 770, Germany) with a precision of 0.1 kilograms (ICR = .89). Stature was determined using a portable stadiometer (Seca Body meter®, model 208, Germany) with a precision of 0.1 centimetres (ICR = .87). Body mass index (BMI) was calculated according the formula [BMI = weight/height^2]. The standardized procedures were followed (Lohman, Roche, & Martorell, 1988).

11.3.9 Intervention programmes

The chair-based exercise programmes were conducted by exercise specialists. The guidelines for integrated exercise periodization to non-active older adults were respected. For safe reasons, in both exercises programs intensity was indirectly calculated using the Karvonen's formula to predict target heart rate (HR), with HR_{max} being calculated using a specific formula for older populations [HR_{max}= 207 beats per minute (bpm) - 0.7 x chronological age].

The participants of the exercise programs were monitored using heart rate monitors Polar, RCX5® model (Guderian, Johnson, & Mathiowetz, 2013). The interventions were offered for 24-weeks, totalling 74 exercise sessions, with two-three sessions per week on nonconsecutive days (separated by 48 hours). The percentage of exercise frequency was calculated individually through the total sum of class participation entries recorded in a checklist. A total of 74 (100%) sessions were offered and the values of engagement in different moments were reported as a percentage. Based on previous reports, an adherence to the exercise program up to 65% was established as a minimum for each participant to be included in the final data analysis. The CG_{ne} did not participate in any physical exercise intervention but was encouraged to maintain their normal routine, which included a monthly agenda of artistic and cultural activities.

11.3.10 Chair multimodal exercises (CME)

The CME program was performed with a determined number of exercises (7-9), repetitions (8-16), sets (2-4), the rhythm of execution (1:2) and active rest in the sit position between sets (20-30) seconds and passive rest between circuits (60-120 seconds). Each session was conducted using a functional circuit training protocol. During the first 12 weeks, the body weight exercises executed in the set and reach position were used. In the last 12 weeks, the increase of exercise intensity was induced by the inclusion of more difficult and complex exercises and challenge sequences, increasing walking time and placed obstacles during the walking route (cones, floor markers, arcs) to work handedness, changes in direction, balance and coordination. A low to moderate intensity effort around 50-75% of HR_{max} values was attained. Additionally, intensity was measured through the modified BORG PES, that consists of an arbitrary scale ranging from 0 to 10 points with reference to the quality of effort: (0) nothing at all; (1) very weak; (2) weak; (3) moderate; (4) somewhat strong; (5-6) strong; (7-9) very strong; (10) very, very strong (almost maximal). Each exercise session was divided into three parts: 5 minutes of warm-up exercises for general body mobilization (PSE = 1-3, HR_{max} = 50-55%); 35 minutes of body weight exercises aimed to improve walking proficiency in a sitting and standing position (PSE 3-5, HR_{max} = 56-85%) and finally 5 minutes of cool down (PSE 1-2, HR_{max} = 45-50%).

11.3.11 Chair muscle-strength exercises (CSE)

To create progressive CSE training, exercises were performed with a determined number of exercises (8-10), sets (2-3); repetitions (10-15), a cadence of repetitions execution in 2 seconds concentric and 3 seconds eccentric (2:3) and a passive rest in the sit position between sets (30-45 seconds), following a bi-set protocol method. The first three levels of the Thera Band® System were used. Level one (yellow colour) elastic-bands were used during the first 12 weeks. In the remaining 12 weeks, the increase in the exercise intensity was introduced by changing to the elastic-bands level 2 and 3 (red and green colour). Intensity was measured through the OMINI PES, that comprises a subjective effort scale ranging from 0 to 10 points, with identical intervals and with reference to the quality of effort: (0) extremely easy; (1-2) easy; (3-5) somewhat easy, (6-7) somewhat-hard; (8) hard; (9-10) extremely-hard (Robertson et al., 2003). The goal was to keep the intensity of the exercise activities between 1 to 6 in PES levels. It was expected that the relationship with the real effort would be 55-80% of maximum heart-rate. The session was divided into three parts: 5 minutes of warm-up (PSE 1 to 3, HR_{max} = 45-55%), 35 minutes of muscle-strength elastic-band exercises in PSE 4 to 6 (HR_{max} = 56-75%) and finally, 5 minutes of cool-down (PSE 1 to 2, HR_{max} = 45-50%).

11.3.12 Data analysis

Descriptive data were presented as mean (±) standard deviation or frequencies. The normality of continuous variables was assessed with Shapiro-Wilk tests. In the baseline scores, comparisons between groups were analyzed by one-way ANOVA. Repeated measures ANOVA was used to analyse the effect of time and time versus (*vs*) group interactions for PF total score, disability and hormonal changes over time, followed by Bonferroni *post hoc* test. The magnitude of global effect size (ES) was calculated in the exercise-modulation treatment. For continuous variables, ES were computed using eta-squared (η^2). Magnitude of ES = η^2 > 0.01 corresponds to a small effect, η^2 > 0.06 to a medium effect and η^2 > 0.14 to a large effect (Cooper & Hedges, 1994). McNemar tests were used to compare categorical variables (PF components) between the three time-points intervention treatment following Cochrane's Q *posthoc* test. The ES for PF components reported was Cramer's *Phi* coefficient. In case of interpretability, *Phi* > 0.1 corresponds to a small effect, *Phi* > 0.3, medium effect and *Phi* > 0.5 to a large effect (Alfred P. Rovai, Jason D. Baker, 2012). We used the IBM SPSS Statistics package 24.0 and in R 3.3.1 software's for all statistical procedures. The level of significance adopted was p-value = .05.

11.4 Results

From the 119 participants initially screened, 35 (29.4%) subjects were excluded. Initially, 28 older adults who met the inclusion criteria were simple randomly assigned to each group. In the follow-up phase, 27 subjects withdrew their willingness to participate before or immediately after the beginning of the study and 3 participants were excluded from analyses due to low exercise adherence. None of the drop-outs left the intervention because of injuries or adverse responses to the intervention. A total of 59 participants were analyzed at the completion of the 24 weeks' study. According to Table 11.1, there were no significant differences between all groups for their baseline characteristics at the beginning of the study (p>0.05).

Table 11.1 Characteristics of total sample, experimental and control groups at baseline.

	Total sample (n=59)	**Chair-multimodal exercises (n=24)**	**Chair muscle strength exercises (n=18)**	**Control group non exercise (n=17)**
	M±SD	M±SD	M±SD	M±SD
Chronological age (years)	81.47±7.84	79.92±7.93	84±4.79	80.93±10.1
Stature (centimeters)	1.56±0.31	1.52±0.06	1.64±0.54	1.52±0.08
Body mass (Kilograms)	65.25±14.15	62.44±9.82	65.03±17.76	69.99±4.89
Body mass index ($kg \cdot m^{-2}$)	27.91±6.56	26.98±3.97	27.02±9.09	30.45±6.06
Charlson comorbidity index (score)	7.93±2.1	7.58±1.86	7.78±1.99	7.67±2.53
Medication use, per day (unit)	3.82±0.97	3.71±0.86	4.06±1.11	3.73±0.96
Mini-mental state exam (score)	20±5.57	21.42±5.1	19.28±5.53	21±5.5
Mini nutritional assessment (score)	23.98±2.63	23.33 ±2.68	24.53±2.32	24.37±2.83
Frailty syndrome total score (score)	2.37±1.42	2.14±1.49	2.39±1.46	2.28±1.19

Notes: ** p≤0.01; * p≤0.05; M(SD) = mean (standard deviation). The p-values correspond to comparisons between the three groups and were computed with one-way ANOVA one-way.

11.4.1 Sex steroids hormones

As we see in Table 11.2, there were no effects of time or time vs treatment on cortisol and TT levels during the intervention (p>0.05), despite *post-hoc* analysis with Bonferroni correction showing a small increase in CME between baseline and 14 weeks for TT concentration (p=0.009). Taken the above results together, we saw that no significant effect of time and time versus (*v*s) treatment were observed for cortisol and testosterone/cortisol ratio during the interventions (p>0.05). Despite no effect of time alone on changes in DHEA levels, a significant time *vs* treatment effect with large effect size was observed in this parameter ($F[df$:3.564, 98.005] = 6.009, p=0.000, η^2=.179) and Post-hoc comparisons showed increase in CME after 24 weeks (p=0.01), and decrease in CG_{ne} after the same period (p=0.01).

Table 11.2 Comparison of salivary sex steroids hormones markers between baseline, 14 and 28 weeks of exercise intervention moment.

Groups	Baseline M±SD	12 weeks M±SD	24 weeks M±SD	Interaction effects	*F* test	*p* value	η^2 Effect size	Practical relevance
Cortisol								
CME	0.23±0.10	0.26±0.09	0.36±0.64	Time	2.069	.131	.037	small effect
CSE	0.23±0.13	0.26±0.11	0.21±0.12	TxG	1.203	.344	.043	small effect
CG*ne*	0.25±0.13	0.26±0.14	0.27±0.17					
Testosterone levels								
CME	55.62±25.75	63.02±24.86	67.49±37.43	Time	.509	.750	.009	small effect
CSE	61.49±23.64	63.15±24.46	70.58±42.07	TxG	1.940	.136	.066	small effect
CG*ne*	53.93±27.11	50.66±19.04	52.68±28.34					
DHEA levels								
CME	27.53±29.13	37.96±33.96	47.69±54.53	Time	1.528	.000	.027	small effect
CSE	39.60±32.63	49.59±42.99	49.26±35.23	TxG	6.009	.036	.179	medium efect
CG*ne*	46.99±44.14	38.14±30.99	29.71±14.25					
TT to COR ratio								
CME	0.0061±0.0059	0.0045±0.0018	0.0081±0.0121	Time	1.122	.330	.023	small effect
CSE	0.0036±0.0025	0.0046±0.0029	0.0064±0.0132	TxG	1.233	.302	.050	small effect
CG*ne*	0.0054±0.0030	0.0051±0.0023	0.0055±0.0024					

Notes: ** p≤0.01; * p≤0.05; η^2 = Eta Square effect size (> 0.02 = small effect, > 0.13 = medium effect and > 0.26 = large effect; M(SD) = mean (standard deviation). The p-values correspond to comparisons between the three groups and were computed with following Bonferroni *post-hoc* test, respectively. TxG = time versus group; TT = testosterone; COR = Cortisol; DHEA = D-hydroepiandrosterone

11.4.2 Physical Frailty and disability

The PF total score showed significant time (*F*[*df*: 1.43; 78.75]=7.385, p = 0.003) and time *vs* treatment interactions (*F*[*df*: 2.86; 78.75]=6.765, p=0.000) changes with a medium and large ES, respectively (η^2=.118 and η^2=.197). No significant differences of time and time *vs* intervention were observed on Katz of ADL over 24 weeks (*p*>.05). However, *the post-hoc* comparison showed differences observed after 12 weeks between CME and CSE (CI: -2.367, -0.022 and CI: -2.463, -0.037, respectively, p<.05), as reported in Table 11.3. On the other side, significant effect of time (*F*[*df* =1.7, 93.9] = 20.268, *p*<.01), and time *vs* intervention (*F*[*df*=3.4, 93.9]2.830, *p*=.03), were observed after 28-weeks on FES, with a large and medium ES, respectively (η^2=.270 and η^2 =.093). There were no significant time *vs* treatment interactions in TSB for the three groups, despite changes over time presenting a medium effect on this parameter (*F*[*df*: 1.612; 88.684]=7.609, p = 0.003, η^2=.115) and *Post-hoc* analysis showed that differences between CME and CG_{ne} were only found after 28 weeks of intervention time (*p* = 0.047) (Table 11.3).

Table 11.3 Comparison of frailty status (total score) and functional disability outcomes between baseline, 14 and 28 weeks of experimental design.

Groups variables	Baseline M±SD	14 weeks M±SD	28 weeks M±SD	Interaction effects	*F* test	*p* value	η^2 Effect size	Practical relevance
Physical frailty total score								
CME	2.24±1.49	1.13±1.12	1.04±1.16	Time	7.385	**.003**	.118	medium effect
CSE	2.39±1.46	2.06±1.11	1.56±0.86	TxG	6.765	**.000**	.197	large effect
CG*ne*	2.87±1.19	3.2±1.32	3.27±1.33					
Katz index of IADL								
CME	0.88±1.51	0.75±1.15	1.25±1.78	Time	.289	.750	.005	small effect
CSE	1.54±1.29	1.94±1.82	1.11±1.49	TxG	1.787	.136	.061	medium effect
CG*ne*	1.73±1.87	1.93±1.71	1.87±1.64					
Falls efficacy scale								
CME	59.08±26.66	24.63±16.87	32.08±5.43	Time	20.268	**.000**	.270	large effect
CSE	38.17±21.31	23.28±13.84	18.11±16.3	TxG	2.830	**.036**	.093	medium effect
CG*ne*	45.73±28.73	38.8±19.96	39.67±20.87					
Tandem balance								
CME	2.38±6.02	6.63±9.24	10.3±11.65	Time	7.609	**.002**	.122	medium effect
CSE	2.83±6.91	5.6±6.57	8.46±6.47	TxG	2.078	.104	.070	medium effect
CG*ne*	3.36±4.91	2.54±1.93	3.31±4.36					

Notes: Values of significance ($p<0.05$) are highlighted in bold; η^2 = Eta Square effect size (> 0.02 = small effect, > 0.13 = medium effect and > 0.26 = large effect; M(SD) = mean (standard deviation). The p-values correspond to comparisons between the three groups and were computed with following Bonferroni *post-hoc* test, respectively.

11.4.3 Physical Frailty independent components

Significant positive variations with a large effect size were showed on low levels of PA (CSE, p = <0.001 and CME, p = 0.004). *The post-hoc* comparison showed differences observed after 12 weeks for both exercise interventions (p>0.01). Moderate and statistical significant changes in PF of decrease slowness were observed only for the CME (p = 0.016; Phi_{es} = 0.35). Trends in decrease incidence of weakness with moderate effect size were also found for the CME participants (p = 0.58; Phi_{es} = 0.30). No significant changes in the frailty independent components of controls were found, however, a tendency to increase incidence of slowness with small effect size was found (p=0.08, Phi_{es} = 0.21)

11.4.4 Perceived exertion and adherence

The final minimum, maximum and mean of HR achieved at the end by the CME group was 65.75 (±9.96), 97.56 (±12.40) and 77.27 (±8.21) bpm, respectively. This was equivalent to 57% to 70% of the predicted HRz_{max}. The final mean of PES ranged from moderate (3.14±0.98) to somewhat strong (4.92±1.01). For the CSE, the minimum, maximum and mean of HR achieved at the end was 69.08 (±14.77), 96.24 (±14.13) and 84.48 (±11.52) bpm. This corresponded to 48% to 74% of the predicted HR_{max}. The final mean of PES oscillated from "to somewhat easy" (3.98±1.99) to "somewhat strong" (6,02±2.22), according to the participants self-perception. Regarding exercise engagement, the CSE participants attended an average of 58 sessions (72% of attendance), out of 74 sessions offered in total. In the CME, the participants had 72% of adherence, corresponding to 54 sessions attended.

11.5 Discussion

The main findings of the present study indicated that both CME and CSE had similar effects in decreasing the incidence of low physical activity levels and slowness both independent components of PFS, resulting in a decrease of the PFS total score and disability. Moreover, we revealed that the effect of any exercise-treatment, when compared to the CG_{ne}, was more beneficial for all variables to maintain an appropriate balance through steroids hormones concentrations since DHEA levels decreased in the CG_{ne} and a slight increase of TT and DHEA levels occurred in CME over time. Corroborating with literature review, the participants' adherence to the exercise interventions was considered satisfactory.

A high index of comorbidity, polypharmacy, low cognitive profile and high sedentary behaviour were expected characteristics within all the groups since these health markers are closely associated with the frail condition (Farhat et al., 2012). In general, the two chair-exercise protocols were effective in promoting improvements in some physical functioning indicators, corroborating findings from previous studies (Anthony et al., 2013). A decrease in fear of falling can be explained by the increased proficiency in the balance test. Possible explanations for this result could be that in the present study, both CME and CSE use different systems of progressive muscle-strength exercises, stimulating type II fibers, which assist in the motor skills such as quickness, fast-decision make (time-reaction) and even, empowering the proprioception mechanisms (Ishigaki, Ramos, Carvalho, & Lunardi, 2014).

An interesting finding was the ability of both chair-exercises programs to demonstrate a positive modulation of PF-independent components, reversing the PF status. It was clear that they contributed to increase the levels of PA in their daily living, even if they were classified as octogenarian participants. The most solid explanation for these results is the exercise periodization methodology used for the design of both exercise programs, that included several strategies to develop physical fitness in an integrated way and also, decreasing the sitting time and substantially increasing the time spent in the standing position (Strohacker, Fazzino, Breslin, & Xu, 2015). This seems to have reflected positively on the autonomy for the performance of daily life activities that depend on moderate to high PA levels. Another characteristic that differentiates this study from similar ones is the large total time of the intervention, which may also help to explain the positive results obtained, since the current literature review shows that exercise programs with a longer period (≥ 5months), performed 3 times per week, for 30–45 minutes per session, largely had superior results than other exercise programs (Theou et al., 2011).

In the present study, the potential mechanisms for exercise-induced increases in DHEA levels (reviewed by Heaney et al., 2013) could be explained by an increased secretion rate by the adrenal cortex as a result of adrenocorticotropic hormone stimulation, produced by the anterior pituitary gland. However, hormonal responses in older adults differing between sexes, it appears that women are more sensitive to exercise-induced hormonal modulation (Heaney, Carroll, & Phillips, 2014). This study seems to be in accordance with Heaney and colleagues (2013) suggestions, which encourages the maintenance of chronic exercise (specially muscle-strength routines) to induce the increase in DHEA levels, particularly in older frail adults who experience psychobiological chronic stress (Corazza et al., 2013).

Additionally, increase in DHEA with a simultaneously slight increase in TT levels, showed the effectiveness of exercise as a co-adjuvant therapy to promoting benefits in the musculoskeletal, immune and nervous system in frail older adults since age-related decline in DHEA may play an important role in several degenerative dysfunctions observed in older people (Arlt & Hewison, 2004). Small increases in TT concentrations obtained by the CME participants seem to have promoted muscle strength and endurance in our sample. However, higher increases were reported in other studies, but in these, most of the participants were middle-aged and older men (Hayes et al., 2015). In our study sample, several factors such as age-related hormonal decline, changes in body composition (especially decline of muscle mass) and low mineral density and disturbance in the neuroendocrine system have been shown as concurrent factors in blunting the response to exercise in older females (Copeland et al., 2002).

On the other hand, the response observed for COR and the TT/CORT ratio, corroborates numerous previous studies, although changes in COR levels and consequently variations in the ratios are more perceptible in studies involving acute exercise (Heaney et al., 2014), which was not the case of our study. However, an increase of CORT would be expected if both exercise programs had predominantly continuous aerobic exercise routine, since this type of exercise program does not only promote an increase in CORT secretion by the adrenal gland (Mura et al., 2014), but it can also promote an increase in adrenal gland volume itself (Kjaer, 1998).

In frail older adults, for example, a slight increase in COR levels at non-pathological levels may bring benefits to improve neuroendocrine functions (Sudheimer D. et al., 2014). In general, it appears that older women retain the ability to stimulate an increase in circulating levels of some anabolic hormones via exercise modulation (Copeland et al., 2004) which to a small extent also occurred in our study. Nevertheless, our study sample displays some particular characteristics. Firstly, the frail individuals appeared to have lower hormonal concentrations when compared to non-frail (Wu, Lin, Liu, Tsai, & Shiesh, 2010). The other important condition is multi-comorbidity and subsequently polypharmacy-use. Statins, for example, are a commonly prescribed medicine to reduce cardiovascular disease risk in older adult patients. However, recent studies show that this pharmacological substance attenuates increases in cardiorespiratory fitness and skeletal muscle mitochondrial content when combined with exercise training in overweight or obese patients, promoting strong side-blinding effects (Mikus et al., 2013). Statins could also affect TT and DHEA production, since cholesterol is a precursor to these hormones, blunting the exercise effects.

In conclusion, both exercise treatments used in this study produced similar and significant benefits in order to diminish the physical frail condition, decreased negative perceptions of functional disability domains and also, stimulated satisfactory hormonal responses. in frail older women. Future interventions should attempt to included samples of institutionalized frail-older men since that would allow generalization for both genders.

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CHAPTER 12 (STUDY 10):

THE MEDIATING EFFECT OF TWO DIFFERENT EXERCISE PROGRAMMES ON THE IMMUNE PROFILE OF INSTITUTIONALIZED FRAIL OLDER WOMEN

Authors:

Guilherme Eustáquio Furtado

Matheus Uba-Chupel

Juan Carlos Colado

Eef Hogervorst

José Pedro Ferreira

Ana Maria Teixeira

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12.1 Abstract

Background: Physically frail individuals experience a quicker immunosenescence effect when compared to healthy older individuals. Physical frailty (PF) is characterized by a low physical fitness and exercise has been identified as a coadjutant therapy able to promote a better inflammatory environment and increase physical fitness. Objective: To analyse the effects of 24-weeks of two different exercise protocols on functional fitness and immune profile in institutionalized pre-frail and frail women. Methods: A sample of older frail individuals (n = 59, 81±7.84 years) participated in the study and were divided into three groups: chair-based muscle-strength exercises (CSE, n=18), chair-based multimodal exercise (CME, n =24) and a control non-exercise group (CG_{ne}, n = 17). Both exercise programs consisted of 45 minutes of supervised classes without music, carried out 3 times a week. Multimodal participants performed a progressive circuit-training protocol using static-dynamic balance, walking and body height muscle-resistance exercises. The muscle-strength resistance training with elastic-band exercises following a compound set protocol. The controls did not change their usual lifestyle. The Fried Physical Frailty protocol was used to identify pre-frail and frail groups. Data for anti and pro- inflammatory makers and physical fitness tests were analysed pre and post-interventions. Results: After interventions, a significant effect of time and time by group for IgA and time *by* group for IL-10 levels were found ($p > 0.05$). Within-group analysis showed a significant moderate decrease in the IL-10 to TNF-α ratio for MME and an increase in controls ($p > 0.05$). A substantial improvement in physical fitness in both exercise groups was also found. Conclusion: Both chair-based exercise programs were effective in stimulating positive changes in physical fitness and simultaneous satisfactory responses in immune profile. The controls showed a negative trend towards a decreased physical fitness and slight decreased levels of anti-inflammatory profiles. The evidence regarding the use of systematic and moderate long-term physical exercise as co-adjuvant therapy in promoting better balance on the pro- and anti-inflammatory environment was the most promising results of this study.

KEY-WORDS: Older frail adults, exercise, physical fitness, upper respiratory tract infections, cytokines, immune system

12.2 Introduction

Older frail-adults have a greater intrinsic vulnerability to biological and environmental stressors, increasing the risk for physical decline and adverse health-related characteristics, such as disability and comorbidity when compared to non-frail older-adults (Clegg et al. 2013). Sedentary life styles, chronic stress, vascular, inflammatory, nutritional and metabolic factors have also been shown to have immuno-suppressive effects and to accelerate immunosenescence (Gruver, Hudson, and Sempowski 2007). In older frail individuals, this process occurs more rapidly, leading older people to early hospitalization and death (Collerton et al. 2012). During ageing, there is a decrease in salivary immunoglobulin-A (IgA) secretion, an important ant-bacterial protein involved in the mechanism of defence against pathogens that penetrate the mucosal epithelium, which is also linked to higher URTI incidence (Papacosta and Nassis 2011). Immune function is less impaired in highly conditioned versus non-active older adults (Walsh and Oliver 2016). Immunosenescence is also a part of the aging process and is associated with an increased risk for autoimmune disorders, tumours, infectious disease and inflammatory deregulation (Minciullo et al. 2016).

Recent findings have implicated the inflammatory pathway in increased severity of muscle damage as mechanisms to develop severe physical disorders and fast muscle decline in older frail-subjects (Lu et al. 2016). Very few studies have looked at the effect of regular moderate exercise on salivary makers such as Lys and IgA and none have looked at interferon gamma (IFN-γ) salivary levels in the older participants (Liberman et al. 2017). Peripheral blood concentrations of inflammatory pathway markers, specifically interleukins (IL), will also interact in anti- and pro-inflammatory processes triggered by aging, and affect physical status in older adults (Lu et al. 2016). Some makers, such as IL-1β, IL-6, IL-10, IFN-γ, Tumour necrosis factor alpha (TNF-α), and C-reactive protein (CRP) are important immune markers involved in this process, and some recent studies have shown that hormonal modulation caused by exercise can help maintain the balance within the immune system (Walsh et al. 2011).

Exercise can be a significant factor in ameliorating the deleterious effects of chronic biological and psychological stress, and may positively affect, to different extents, many immune parameters (Kohut and Senchina 2004). However, the type, intensity, duration and frequency of exercise that should be performed in order to effectively improve immune response in very old persons needs to be defined more clearly (Liberman et al. 2017). A review of the literature found that regular exercise has a positive impact on immune status in frail individuals, especially on TNF-α (Theou et al. 2011). Several studies have showed the potential exercise effect on the TNF-α/IL-10 ratio in promoting an pro-anti-inflammatory enviorment/balance in humans (Chupel et al. 2017).

Multimodal exercise programmes seem to be particularly effective in improving general physical fitness, while there is little evidence to date that muscle strength exercises can help achieve the same improvements in frail older adults (Liu, 2017). However, as in the case of the present study, the muscle-strengthening elastic-band exercise system has been offered as a successful method to promote significant beneficial effects on cognition status, physical fitness and immune profile (Chupel et al. 2017). Thus, the aim of this study was to analyse the effect of 24-weeks of two different chair-based group classes exercise protocols on functional fitness and immune profile in institutionalized pre-frail and frail older women.

12.3 Methods

This study consisted of three arms, with controlled trial chair-exercise based interventions, that included a subset of the participants of the previous published study protocol (Teixeira et al. 2016). Participants or their legal tutors signed an informed consent term. This study was approved by the Ethics and Human Subjects Review Board of the University of Coimbra, respecting the guidelines for human research of the Helsinki declaration.

12.3.1 Participants recruitment and allocation

Participants were institutionalized-dwelling pre-frail and frail women living in centres of health and social support in the city of Coimbra, Portugal, aged 75 years and above, with updated medical therapy and who were clinically stable. Not completing the dynamic balance test in 30 seconds, involvement in other exercise programs, use of medications that significantly impaired attention, individuals classified with morbid obesity, who were medical diagnosed with cardiometabolic, respiratory and musculoskeletal dysfunctions, the presence of mental, hearing and vision impairment or involvement in hormone therapy were exclusion criteria.

12.3.2 Sample size calculation and allocation

The sample size was 19 participants per group (power = 0.80), taking into account the comparison of frailty outcomes between treatments in previous studies (de Labra et al. 2015). Further anticipating a dropout rate of 30% (Picorelli et al. 2014), the sample was increased to 28 per group, allocated into three arms. The final sample analysed consisted of 59 participants: a non-exercising control group (CG_{ne}, n = 17), elastic-band muscle strength (CSE, n=18) and multimodal exercises (CME, n =22) programmes.

12.3.3 Assessment procedures

All the tests were applied by an independent assistant who established contact with the participants without reference to the exercise program. The instructor of the exercise sessions did not take part in the data collection procedures. Precaution was taken to avoid interaction of exercise programs between individuals of the two groups by staggering the classes' schedules. The quality of data assessment was made and reported for each of the physical markers through internal consistency reliability scores (ICR).

12.3.4 Physical Frailty (PF)

The Fried PF protocol was used (Fried et al. 2001). Shrinking was assessed by self-report of unintentional weight loss of four kilograms or more in the last six months; Self-reported exhaustion was evaluated by concordance of two questions (7 and 20) of the Center for Epidemiology-Depression (CES-D) scale; Weakness was analyzed using the handgrip strength test, adjusted for gender and body mass index (ICR = .88); Slowness was measured by the 4.6 meters walking test, adjusted for gender and height (ICR = .80); levels of PA were assessed by the International Questionnaire short form (ICR = .78). The prevalence of PF was calculated to generate a PF total score.

12.3.5 Immune and biochemical makers' determination

The sample collection of saliva and blood was done in the morning (between 10:00h – 12:00h). Saliva samples were collected by a passive drool technique, that consisted of allowing the subjects' saliva to collect on the floor of the mouth, then to lean forward and dribble into an high quality polypropylene tube for three minutes. Prior to the saliva collection, the participants were asked to rinse their mouth with water to remove food residues 10 minutes before sample collection. The sample volumes were determined by weighing the collection tubes before and after the saliva collection and the samples were then stored at −20°C until determination of the saliva markers. Salivary concentrations of IL-1β and IL-6 were were analyzed by competitive ELISA kits according to the manufacturer instructions [Salimetrics®, UK]. Blood samples were collected by venepuncture by a registered nurse, and were allocated into serum and kEDTA tubes. Determination of blood counts was done immediately after blood collection, using an automated haematology analyser (Coulter AcT Diff, Beckman Coulter, USA).

The remaining blood samples were centrifuged, serum and plasma aliquoted into several Eppendorf tubes and kept frozen at -80°C until further use. The plasma levels of pro- and anti- inflammatory cytokines, such as TNF-α, IFN-γ and IL-10 were analyzed by ELISA [Invitrogen®, CA] according to the manufacturer instructions. Serum CRP was determined using the Horiba Medical Pentra C200 [Kyoto, Japan].

12.3.6 Functional Fitness

The Senior Fitness Test battery developed by Rikli and Jones (2013) was used. i) Lower body strength was determined with the '30 second's chair-and-stand test' (30s-CS), measuring the number of total full chair-stands that can be completed in 30 seconds with the arms folded across the chest; ii) Upper body strength was assessed with the '30 seconds arm-curl test' (30s-AC) that measures the total number of bicep curls that can be completed in 30 seconds, seated in a chair and holding a hand weight of 5 lbs (2.27 kg) for women. vi) Aerobic resistance was measured through the "2-minutes step test" (2m-ST), that consisted of the number of full steps the subject completed in two minutes performing a stationary gait, with one hand resting on the wall and raising each knee to a midway point between the kneecap and iliac crest. For all the Functional Fitness (FF) tests the best score of the two trials performed was used for final scoring purposes (Rikli,& Jones, 2013).

12.3.7 Health status

The Mini Nutritional Assessment (MNA, k = .74) was used to evaluate the nutritional status categorized as: a predetermined state of malnutrition (< 17 points), malnutrition risk (17 to 23.5 points) and adequate nutritional status of > 23.5 points (Loureiro 2008). The Charlson Comorbidity Index (CCI, ICR = .94) was used to classify comorbid conditions based on the medical register of each individual (Charlson et al. 1994). Systolic and diastolic blood pressure were recorded using a digital device of OMRON model M1 Plus [HEM-4011C-E]® (Viera and Hinderliter 2007). Medication use (MU) was assessed through medical records over one year for each participant. To reduce potential confounding effects, all participants were encouraged to maintain unchanged diets, drugs treatment, and routines across the 24-weeks of the intervention.

12.3.8 Biosocial and anthropometric assessment

Information about chronological age was collected. Body mass was determined using a portable scale (Seca®, model 770, Germany) with a precision of 0.1 kilograms (ICR = .89). Stature was determined using a portable stadiometer (Seca Body meter®, model 208, Germany) with a precision of 0.1 centimetres (ICR = .87). Body mass index (BMI) was calculated according the formula [BMI = weight/stature^2]. Standardized procedures were followed (Lohman, Roche, and Martorell 1988)

12.3.9 Intervention programmes

The chair-based exercise programmes were conducted by exercise specialists. For safety reasons, in both exercise programmes intensity was indirectly calculated using the Karvonen's formula to predict target heart rate (HR), with HR_{max} being calculated using a specific formula for older populations [HR_{max}= 207 beats per minute (bpm) - 0.7 x chronological age] and was monitored using heart rate monitors Polar, RCX5® model (Guderian, Johnson, and Mathiowetz 2013). The classes were offered for 24-weeks, totalling 74 exercise sessions, with two-three sessions per week on non-consecutive days (separated by 48 hours). The percentage of exercise frequency was calculated individually through the total sum of class participation entries recorded in a checklist. A total of 74 (100%) sessions were offered and the values of engagement in different moments were reported as percentages. Based on previous reports, an adherence to the exercise program up to 65% was established as a minimum for each participant to be included in the final data analysis. The CG_{ne} group did not participate in any physical exercise intervention but was encouraged to maintain their normal routine, which included a monthly agenda of artistic and cultural activities.

12.3.10 Multimodal exercises (CME)

The chair CME program was performed with a determined number of exercises (7-9), repetitions (8-16), sets (2-4), the rhythm of execution (1:2) and active rest in a seated position between sets (20-30 seconds) with passive rest between circuits (60-120 seconds). Each session was conducted using a functional circuit training protocol. During the first 12 weeks, the body weight exercises executed in the seat and reach position were used. In the last 12 weeks, the increase of exercise intensity was induced by the inclusion of more difficult and complex exercises and challenge sequences, increasing walking time and placing obstacles along the walking route (cones, floor markers, arcs) to work handedness, changes in direction, static/dynamic balance and coordination. A low to moderate intensity effort around 50-75% of HR_{max} values was attained. Additionally, intensity was measured through the modified BORG

PES, that consists of an arbitrary scale ranging from 0 to 10 points with reference to the quality of effort: (0) nothing at all; (1) very weak; (2) weak; (3) moderate; (4) somewhat strong; (5-6) strong; (7-9) very strong; (10) very, very strong (almost maximal). Each exercise session was divided into three parts: 5 minutes of warm-up exercises for general body mobilization (PSE = 1-3, HR_{max} = 50-55%); 35 minutes of body weight exercises aimed to improve walking proficiency in a sitting and standing position (PSE 3-5, HR_{max} = 56-85%) and finally 5 minutes of cooling down (PSE 1-2, $HR_{max =}$ 45-50%).

12.3.11 Muscle-strength exercises (CSE)

To create a progressive chair MSE program, exercises were performed with a determined number of exercises (8-10), sets (2-3); repetitions (10-15), a cadence of repetitions execution in 2 seconds concentric and 3 seconds eccentric (2:3) and a passive rest in the seated position between sets (30-45 seconds), following a bi-set protocol method. The first three levels of the Thera Band® System were used. Level one (yellow colour) elastic-bands were used during the first 12 weeks. In the remaining 12 weeks, the increase in the exercise intensity was introduced by changing to the elastic-bands level 2 and 3 (red and green colour respectively). Intensity was measured through the OMINI PES, that comprises a subjective effort scale ranging from 0 to 10 points, with identical intervals and with reference to the quality of effort: (0) extremely easy; (1-2) easy; (3-5) somewhat easy, (6-7) somewhat-hard; (8) hard; (9-10) extremely-hard (Robertson et al. 2003). The goal was to keep the intensity of the exercise activities between 1 to 6 in PES levels. It was expected that the relationship with the real effort would be 55-80% of maximum heart-rate. The session was divided into three parts: 5 minutes of warm-up (PSE 1 to 3, HR_{max} = 45-55%), 35 minutes of muscle-strength elastic-band exercises in PSE 4 to 6 (HR_{max} = 56-75%) and finally, 5 minutes of cooling-down (PSE 1 to 2, HR_{max} = 45-50%).

12.3.12 Data analysis

Descriptive data were presented as mean (and standard deviations) or frequencies. In the baseline scores, comparisons between groups were analyzed by one-way ANOVA. Repeated measures ANOVA was used to analyse the effect of time and time by group interactions on the frailty total score, functional fitness and immune profile changes over time, followed by Bonferroni *post hoc* tests, reporting the confidence interval (CI:95%) for the statistically significant results.

Since there was no normality distribution for the TNF-α/IL-10 ratio the pre- and post-interventions comparisons were made using the Kruskall-Wallis test. The percent of change after the interventions was also calculated ([post value/pre value]-1). The magnitude of the global effect size (ES) was calculated by exercise-modulation treatment. For continuous variables, ES were computed using Cohen's (*d*). The effect size was considered trivial ($d \leq .20$), small ($.21 < d < .50$), moderate ($.51 < d < .79$) and large ($d > .80$) (Batterham and Hopkins 2006). The IBM SPSS Statistics package 24.0 and in R 3.3.1 software's for all statistical procedures were used. The level of significance adopted was p-value = .05.

12.4 Results

From the 119 potential participants initially recruited, a total of 29% were excluded for not meeting inclusion criteria and declining to participate in the study spontaneously. In the follow-up phase 6 participants of CME training, 10 of CSE and 9 of CG_{ne} withdrew their willingness to participate before or immediately after the beginning of the study for various reasons. A total of 24 drop-outs was registered during the intervention period because of low exercise engagement, injuries or adverse responses to the intervention. In total, 59 older women participants were examined at completion of the 24 weeks' study. Characteristics of experimental and control groups at baseline are presented in Table 12.1. The statistical analysis showed that no significant differences between the three groups were found (p>0.05).

Table 12.1 Total sample, exercising and control groups characteristics of at baseline.

Variables	Total Sample	Chair multimodal exercises (n=24)	Chair Elastic-band muscle strength exercises (n=18)	Control group non-exercise (n=19)
	M±SD	M±SD	M±SD	M±SD
Chronological age (years)	81.62 ±7.91	80.14±8.19	81.00±4.79	80.93±10.01
Stature (centimeters)	1.51±0.07	1.52±0.61	1.51±0.08	1.51±0.80
Body mass (Kilograms)	64.86±14.06	63.24±8.5	62.03±17.76	64.99±14.89
Body mass index ($kg \cdot m^{-2}$)	28.19±5.71	26.53±3.65	28.35±7.16	28.44±6.06
Charlson comorbidity index	7.93±2.13	7.55±1.92	7.78±1.98	8.67±2.53
Medication use, per day (unit)	6.75±2.34	7.05±1.98	6.95±3.05	6.30±0.95
Systolic Blood pressure	126.09±17.24	124.05±15.01	1131.22±19.37	122,93±17.39
Diastolic Blood pressure	64.85±11.08	64.86±8.07	67.67±13.99	65.87±10.60
Mini nutritional assessment	23.94±2.66	23.18±2.75	24.52±2.32	24.36±2.83

Notes: ** p≤0.01; * p≤0.05; m(sd) = mean (standard deviation). The p-values correspond to comparisons between the three groups and were computed with one-way ANOVA one-way or Kruskal-Wallis, depending the assumption (normality) of variable.

12.4.1 Immune markers

Table 12.2 shows the inflammatory markers changes after the 24 weeks' intervention programs. The results showed that a significant effect of time [F (2,44) = 6.681; p = 0.014)] and time by group for IgA changes over the interventions [*F* (1,44) = 4.661; p = 0.015)]. Bonferroni corrections applied *post hoc* showed a moderate decrease in IgA levels in MSE group (ES = 0.68, Δ% = -26; p<0.01, CI95%: 0.08 to 0.313), while the others remained unchanged over time (p>0.05).

Table 12.2 Comparison of immune profile biochemical makers between baseline and 24 weeks of intervention moments.

Groups	Baseline M±SD	28 weeks M±SD	Interaction effects	*F* test	*p* value	*Cohens' d* effect size	Practical relevance	Δ%
IgA (μg/mL)								
CME	263.34±203.99	155.16±92.13	Time	6.581	**0.014**	0.68	Moderate	- 26
CSE	221.53±134.26	234.77±123.90	Time x Group	4.661	**0.015**	0.10	Trivial	+42
CG*ne*	257.61±172.57	196.92±90.73				0.15	Trivial	- 11
Lysozyme (μg/mL)								
CME	1.42±1.38	1.04±0.84	Time	0.041	0.840	0.33	Small	- 36
CSE	2.97±2.38	2.10±1.41	Time x Group	0.313	0.734	0.44	Small	- 18
CG*ne*	2.89±3.62	2.59±2.03				0.29	Small	- 10
IL-6 (pg/mL)								
CME	20.43±15.50	17.99±10.85	Time	0.048	0.827	0.19	Trivial	- 09
CSE	23.89 ±18.18	25.01±14.95	Time x Group	0.685	0.509	0.06	Trivial	+ 31
CG*ne*	19.15±15.46	20.81±13.80				0.11	Trivial	+ 22
IL-1B (pg/mL)								
CME	77.9±61.34	67.16±56.27	Time	1.402	0.246	0.23	Small	- 130
CSE	76.79±69.55	82.81±55.72	Time x Group	0.643	0.553	0.09	Trivial	+ 83
CG*ne*	73.86±50.23	91.23±62.37				0.31	Small	+ 88
IL-10 (pg/mL)								
CME	13.91±11.09	18.38±12.46	Time	2.769	0.103	0.39	Small	+ 62
CSE	17.63 ±11.28	21.55±10.29	Time x Group	4.514	**0.016**	0.36	Small	+ 46
CG*ne*	14.89±11.03	13.52±10.96				0.12	Trivial	- 03
CRP (pg/mL)								
CME	4.94v5.77	4.16±3.64	Time	0.690	0.410	0.16	Trivial	- 48
CSE	2.91±3.33	2.95±2.87	Time x Group	1.789	0.179	0.01	Trivial	+ 24
CG*ne*	3.19±3.73	5.83±3.08				0.52	Moderate	+ 73
IFN-γ (pg/mL)								
CME	3.48±4.17	4.48±5.49	Time	6.117	**0.018**	0.26	Small	+ 86
CSE	5.04±3.55	6.11±4.61	Time x Group	0.010	0.990	0.25	Small	+ 60
CG*ne*	4.58±5.83	4.82v4.23				0.04	Trivial	+ 91
TNF-α (pg/mL)								
CME	112.55±65.73	122.41±64.12	Time	3.280	0.077	0.15	Trivial	+ 24
CSE	140.23±59.81	153.98±56.22	Time x Group	0.003	0.997	0.23	Trivial	+ 18
CG*ne*	118.11±78.23	131.65±70.22				0.18	Trivial	+ 39
TNF-α/IL-10 ratio*								
CME	9.30±7.76	6.46v8.98	Time	--	**0.011**	0.33	Small	- 43
CSE	11.62 ±9.42	8.98±4.82	Time x Group		**0.068**	0.35	Small	- 30
CG*ne*	8.27 ±7.85	14.40±20.04			**0.021**	0.40	Small	+ 74

Notes: *Cohens' d* = trivial (*d* ≤ .20), small (.21 < *d* <.50), moderate (.51 < *d* <.79) and large (*d* > .80) effect size; M(SD) = mean (standard deviation); Δ% = Delta change percentage; The p-values correspond to comparisons between the two groups and were computed by repeated measure's ANOVA for within comparisons, following Bonferroni *post-hoc* test; TNF-α/IL-10 ratio statistical analysis was made using univariate analysis following within-group Wilcoxon-signed rank test; CME = Chair multimodal exercises; CSE = Chair Elastic-band muscle strength exercises; CG*ne* = Control group non-exercise.

No effects of time or time *by* group were observed for Lys levels (p>0.05). Analysing the results of Table 12.2, we found that effects of time or time *by* group were observed for changes in IL-6 and IL-1β (p>0.05), despite only a small decrease in the CME group (ES = 0.23, Δ% = - 130) and a small increase in the GC_{ne} group (ES = 0.31, Δ% = + 88) in IL-1β levels. Significant interactions were observed for time by group in IL-10 levels [*F* (2,45) = 4.514; p=0.01], where concentrations increased in MME (ES = 0.39; Δ% = + 62; p = 0.023; CI95%: -0.247 to -0.019) and CSE (ES = 0.36; Δ% = + 46; p = 0.029; CI95%: -241 to -013) groups. However, no significant change was observed in controls (p = 0.147). No effect of time or time by group were observed for TNF-α levels (p>0.05), despite a trend for changes over time shown [*F* (1,41) = 3.280, p=0.07].

There was an effect of time for IFN-γ changes [*F* (1, 42) = 6.117, p=0.01)], but no significant interactions with group (p>0.05). No differences were observed for time and time *by* group interaction in CRP levels (p>0.05). Despite a trend for these to be increased in the CG_{ne} group (p = 0.06). Regarding TNF-α/IL-10 ratio, univariate analysis showed no significant differences between groups at baseline and after 24 weeks (p > 0.05). However, within-group analysis using Wilcoxon-signed rank test showed a significant moderate decrease in this ratio for CME (z = -2.551; p = 0.01; ES = 0.33; Δ% = -43), and an increase in controls (z = -2.312, p = 0.02; ES = 0.40; Δ% = +74).

12.4.2 Physical Fitness

Analysing the physical fitness parameters after the 24-weeks intervention programmes, the results showed that there was only an effect of time on CSR-M [*F* (1; 52) = 5.259, p=0.02], but no interactions with group. (Table 12.3) Both CME and CSE group showed increased score with large effect size (ES = 0.40; Δ% = -12 and ES = 0.49; Δ% = -16, respectively). A significant effect of time on 30s-AC was shown [*F*(1;52) = 16.045, p < 0.01). P*ost hoc* analysis showed a decrease in both CME and CSE on 30s-AC with a large and moderate effect-size, respectively (ES = 1.05; Δ% = + 51; p = 0.000 and ES = 0.60; Δ% = + 42; p = 0.021). There was a significant effect of time [*F* (1;52) = 22.675, p < 0.01) and time *by* group interactions [*F* (2;52) = 5.556; p = 0.006)] on the 30s-CS test, and Bonferroni analysis showed an increase for MSE after exercise intervention (p < 0.01).

Table 12.3 Comparison of physical-functional status outcomes between baseline and 24 weeks of intervention.

	Baseline M±SD	28 weeks M±SD	Interaction effects	*F* test	*p* value	*Cohens' d* effect size	Practical relevance	Δ%
Chair Seat and Reach (centimeters)								
CME	28.25±10.59	23.79±11.61	Time	05.25	**0.026**	0.40	small	- 12
CSE	27.53±11.83	22.56±07.80	TxG	00.63	0.850	0.53	moderate	- 16
CG*ne*	24.25±11.27	22.00±10.01				0.12	Trivial	- 08
30-seconds arm curl (reps per time)								
CME	9.09±2.99	12.59±3.45	Time	16.04	**0.000**	1.05	Large	+ 51
CSE	11.56±5.63	14.17±3.42	TxG	00.79	0.456	0.60	Moderate	+ 42
CG*ne*	8.67±4.54	9.20±3.49				0.37	small	+18
Chair-seated and stand (reps per time)								
CME	9.14±3.10	12.36±3.12	Time	22.67	**0.000**	1.03	Large	+ 37
CSE	7.44±3.18	11.94±2.75	TxG	05.56	**0.006**	1.51	Large	+ 82
CG*ne*	6.93±2.81	8.01±3.31				0.19	Trivial	+ 44
Two-minutes step (reps per time)								
CME	39.82±11.83	49.14±14.68	Time	21.43	**0.000**	0.83	Large	+ 35
CSE	29.61±15.63	44.56±12.90	TxG	08.77	**0.001**	1.04	Large	+ 51
CG*ne*	27.92±12.01	24.20±10.54				0.33	small	- 06

Notes: *Cohens' d* = trivial (*d* ≤ .20), small (.21 < *d* <.50), moderate (.51 < *d* <.79) and large (*d* > .80) effect size; M(SD) = mean (standard deviation); Delta change percentage; The p-values correspond to comparisons between the two groups and were computed by repeated measure's ANOVA for within comparisons, following Bonferroni *post-hoc* test; CME = Chair multimodal exercises; CSE = Chair Elastic-band muscle strength exercises; CG*ne* = Control group non-exercise; TxG = time versus group.

Both CSE and CME demonstrated a large magnitude of effect after interventions (ES = 1.05, Δ% = +37 and ES = 1.51; Δ% = 82, respectively). A significant effect of time [*F* (1;52) = 21.739, p < 0.01] and time by group [*F*(2;52) = 8.474, p < 0.01] on the 2M-ST was shown after the intervention program. P*ost hoc* analysis showed an increase in both CME and CSE on the 2M-ST (p < 0.01), with moderate (ES = 0.70, Δ% = +30) and large effects (ES = 1.04; Δ% = +51), respectively. The CG*ne* remained unchanged over time (p>0.05).

12.4.3 Exercise effort and engagement

The final scores of minimum, maximum and mean HR achieved at the end by the CME group was 65.75 (±9.96), 97.56 (±12.40) and 77.27 (±8.21) bpm, respectively. This corresponded to 57% to 70% of the predicted HRz_{max}. The final mean of PES ranged from moderate (3.14±0.98) to somewhat strong (4.92±1.01). For the CSE group, the scores of HR achieved at the end were 69.08 (±14.77), 96.24 (±14.13) and 84.48 (±11.52) bpm. This corresponded to 48% to 74% of the predicted HR_{max}. The final mean of PES oscillated from somewhat easy (3.98±1.99) to somewhat strong (6,02±2.22), according to the participants self-perception. Regarding adherence, the CSE participants attended an average of 58 sessions (78% of attendance), out of 74 sessions offered in total. In the CME, the participants had a 72% adherence, corresponding to 54 sessions attended.

12.5 Discussion

The goals of this study were to assess the impact of two different structured exercise programmes, CSE and CME, in older frail women on immune profile and physical fitness. The assumption was that including regular exercise as a co-adjuvant therapy would be effective for reducing chronic inflammation, since this population suffers, more prominently age-effects, which tend to accelerate the immunosenescence process. The main results of this study were that both CSE and CME programmes could increase physical fitness and also simultaneously increase anti-inflammatory cytokine concentrations to promote a better inflammatory balance in institutionalized older frail women after 24 weeks of systematic exercise. However, CSE and CME programs promoted a different response for some of the analysed variables, even though the participants of the study had a similar intensity of effort and similar values in adherence to the exercise programmes.

12.5.1 Immune Makers

It is generally understood that immune function declines with age, and, compared with young people, older people are less resistant to pathogenic microorganisms (Senchina DS1; Kohut ML. 2007). In the case of frail individuals, the susceptibility to increased episodes of the upper respiratory tract infector (URTI) appears to be greater (Compté et al. 2013). Several exercise intervention have examined markers of mucosal immunity, including salivary antimicrobial proteins, such as IgA (Allgrove et al. 2008; Shibuya et al. 2015; Silva et al. 2009). However, results showed a slight conflict in the interpretation of results, especially in short-term programs (up to 12 weeks) (Senchina DS1; Kohut ML. 2007).

In the results of Akimoto and colleagues, regular moderate exercise seemed to enhance mucosal immune function (salivary IgA) in elderly subjects after 12-weeks of combined training (Akimoto et al. 2003). But, this study reveals another important question in the comparison with our results, although the exercise program used shows some similarity with the CME used in this study, his sample had a younger age group living in the community and for this reason the authors may have observed better results. In the other study which aimed to investigate the effects of aerobic conditioning in a very similar population, salivary IgA concentration was unchanged, suggesting that alterations in salivary IgA levels in response to exercise may also be related to age (Martins et al. 2009). In another recent study, no change was observed in IgA after 28 weeks of Yoga, however, a trend towards an moderate increase in both IgA (ES = 0.20, Δ%= 26) and Lysozyme (ES = 0.48, Δ% = 87) secretion rates were found, while in the control group a trend towards a decrease in the IgA secretion rate was found (Marques et al., 2017).

In our study, unlike these studies cited above, there was a trend to reduced IgA, except for the CSE group, which is in line with the results of the previous studies using strength training (Neves et al. 2009). Unlike data on IgA, there is little data available regarding the changes in salivary Lys concentrations with acute or chronic exercise in this type of population. A recent study described that salivary Lys secretion increased after moderate intensity exercise and increased further after high intensity exercise, which implies that Lys levels may be related with exercise intensity (Papacosta and Nassis 2011). Despite the lack of research involving modulating effects of exercise on Lys, the studies showed that Lys and IgA and others salivary markers, such as α-amylase, seem to demonstrated a similar behaviour during and after physical exercise, because they share the same control and activation that is regulated by the autonomic nervous system (Allgrove et al. 2008). The subjacent mechanisms involving the inflammation process is one such potential pathophysiological change which may be closely linked with the physical frailty condition (Soysal et al. 2016). However, it is consensual that chronic subclinical inflammation contributes to impaired physical functioning in older adults (Brinkley et al. 2009).

The concept of a beneficial ‘anti-inflammatory exercise-effects’ in older populations who participate in regular programs seems to justify the possible beneficial increase that occurred in IL-10 in both CSE and CME programs, while in the CG_{ne} a slight decrease ocurred, taking into account the magnitude of effect size. TNF-α and IL-6 are important pro-inflammatory markers and have previously been found to be elevated in cases of frail individuals in comparison to healthy age-matched controls (Hubbard et al. 2009). In the present study, the increase in IL-10 levels may partly justify the behaviour of inflammatory markers observed, since this marker promotes the reduction of TNF-α, IL-1β, and IL-6 mRNA levels of in skeletal muscle of older adults (Nicklas and Brinkley 2009). In similar research with obese frail older patients, a combined exercise program (strength plus muscular resistance training) led to a significant decrease in IL-6 and TNF-α mRNA expression, despite having no effect on weight loss (Lambert et al. 2008). In another intervention study, significant decreases in TNFα mRNA and protein expression were reported after 12-weeks of resistance training in frail older men and women (Lambert et al. 2008).

Our results showed, after 24-weeks of systematic exercise, a slight reduction in inflammatory IL-6 and IL-1β concentrations in the CME participants, while in the controls a trend for an increase in levels of these markers was seen. Changes in TNF-α levels appear to be inconclusive, but when analysing the TNF-α to IL-10 ratio, a decrease of this ratio was observed which could be seen as the effect of exercise on the inflammatory balance, an immune physiological phenomenon recently observed by our research group in a study with a very similar population (Matheus U. Chupel et al. 2017). The mechanism explaining this balance is associated with the attenuated-effect triggered by IL-10 on TNF-α receptors expression, stimulating release of their extracellular domains into the systemic circulation. Additionally, IL-10 also downregulates cell-mediated immune responses and cytotoxic inflammatory responses, the imbalance in these cytokines appearing to be associated with coronary heart disease (Kumari et al. 2018). Similar to TNF-α, several cross-sectional studies have associated high levels of CRP to abnormal cardiovascular risk and stroke. Results from these studies are consistent in showing that low general physical function (gait speed, muscle mass, muscle strength and self-reported functional ability) are associated with high inflammatory marker concentrations (Nicklas and Brinkley 2009).

Therefore, low concentrations of these inflammatory markers are essential for the maintenance of better neuromuscular performance. In this study, the results showed no significant alterations in CRP levels, although the CG*ne* did show a trend for a moderate increase (ES =0.47; Δ% = 87) which could indicate that exercise was able to prevent further CRP increase with time/aged. However, in two other similar studies conducted with postmenopausal women, between14 and 20 weeks of aerobic exercise intervention decreased CRP by 15% and 25%, respectively (Greine 2001; Giannopoulou et al. 2005).

Comparable to the present study, the exercise-mediated effect on the increase of anti-inflammatory makers (IL-10 and IFN-γ) was the plausible explanation given for these results. Similar to the increase in IL-10, the concurrent small increase of IFN-γ in both the MME and MSE exercise groups (and unchanged in the controls) seems to be beneficial, since this biomarker is considered as an anti-inflammatory cytokine in low concentrations. it is secreted by Th1 cells and has an essential role in maintaining immune function by preserving the Th1/Th2 balance that is usually altered towards a more Th2 cytokine secretion profile with age (Gage et al., 2004). Regular moderate exercise (as was the case in this study) and not intense exercise, has beneficial effects on health by way of increasing satisfactory plasma IFN-γ levels (Vijayaraghava et al., 2014).

12.5.2 Physical Fitness status

Analysing the physical fitness data, we observed that the large and beneficial improvements achieved by the exercise groups were quite similar after the 24-week programmes, despite the fact that the design characteristics of CSE and CME exercise programs were quite specific and different. According to the American College of Sport Medicine (ACSM), multimodal exercises are categorized as a group class where the instructor uses aerobic exercises interspersed with endurance, strength, balance and other types of exercises (De La Cabra et al., 2015).

The main purposes of multimodal exercise program is to encourage older people to work on muscle strength and endurance, integrating other physical fitness domains, such as time reaction, gait performance, static balance and improved stability in dynamic balance (Baker et al., 2007). Although ACSM classifies the evidence level of multimodal as C or moderate (on a scale ranging from A to D) (Antunes et al., 2006), most current studies have demonstrated a general health benefit of multimodal exercise in older patients with physical and cognitive frailty conditions when compared to other programs or controls, especially in increasing cognitive functions, decreasing falls incidence and improving physical fitness related to daily tasks autonomy (Lopez et al., 2017). The most probable explanation for the results similarities between the CME and CSE groups, was the progressive increase in difficulty (effort) of the muscle resistance body weight exercise components over time (i.e. chair muscle up and seat to chair muscle up and stand), which demonstrated beneficial effects on muscle strength after 24 weeks.

A complete and comprehensive review indicated that longer-term (intervention time over 16 weeks) MME interventions with shorter-duration sessions (30 to 45 minutes) might be a better option for this population, especially for the prevention of adverse health consequences (Theou et al., 2011). In this sense, the results of our study are in agreement with the current literature. Unlike the CME programs, the CSE programs are classified as evidence level A (strong), and its benefits are also well researched and scientifically proven. Current evidence indicates that supervised and controlled trials of CSE represent an effective intervention in physical frailty treatment (Lopez et al., 2017). Unlike the traditional MSE program, which opts for the use of free weights and machines, our program used a workout with gradual increases in elastic bands resistances. Recent studies have demonstrated the effectiveness of exercise interventions with elastic bands in improving muscle strength and functional capacity in older adults (José & Del Corso, 2016).

In addition to the fundamental characteristics such as ergonomics, practicality, and gradual control of the effort (Andersen et al., 2010), some studies with older participants have proven that some physiological adaptations (including changes in immunological parameters) inherent to the traditional strength exercises, can also be achieved using the gradual system of elastics bands (Chupel et al., 2017; Colado e Triplett, 2008). One other hypothesis, that could explain the substantial physical fitness improvements in this sample refers to the gains most evident in older people with low levels of physical functioning, as was the case in this sample.

The control group, as expected, did not shown any improvements in these study variables, on the contrary a decreased performance in almost all of the physical fitness tests used in this study was seen, emphasizing the importance of being and staying active across the life span. Lack of exercise/physical activity is a well-known risk factor for the loss of independence of older adults.

12.5.3 Limitations

Despite the interesting results, this study presented some limitations. Firstly, we must interpret the results carefully, since the degree of multi-comorbidity and the use of drugs may influence the variation of biochemical markers. In our study sample, for example, there was a high prevalence of hypertension (78%), dyslipidemia and metabolic syndrome (64%), heart failure (37%), rheumatic or connective tissue disease (48%) and diagnosed mental disorders, such as depression, anxiety and chronic stress (28%). Some of these diseases are treated with beta-blockers that may have interfered with autonomous nervous system functioning (49); Statins, the commonly prescribed drug to reduce cardiovascular disease risk has been linked to skeletal muscle myopathy and attenuates increases in cardiorespiratory fitness and skeletal muscle mitochondrial content when combined with exercise (50).

The pragmatic treatment for rheumatic disorders included medication for pain and inflammation (methotrexate and leflunomide) or biologic drugs (infliximab, adalimumab, etanercept, golimumab and certolizumab), and while improving pain, mood disorders, and fatigue, these drugs also act as inhibitors of IL-6 and TNF-α (49). Secondly, we opted for a naturalistic controlled trial, due to the very poor physical-functional condition of the sample, that would have made moving to an exercise center unlikely. However, it is essential to mention that participants of this study started the exercise programmes under the same conditions. Another interesting question is that unlike some studies, this one choose to also discuss the results taking into account the size of the effect of the changes, which may reveal clinically or biologically relevant effects for all the variables in question.

12.6 Conclusion

Our study described important evidence regarding the use of systematic and moderate long-term physical exercise as co-adjuvant therapy in achieving a better balance/environment between the pro- and anti-inflammatory environment. Also, these findings revealed the expected capability of multimodal or elastic-band strength exercise programmes to substantially increase physical fitness in the older frail women that can substantially promote independence. The chair-based exercise method in groups used does not appear to have negatively influenced the results.

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CHAPTER 13 (STUDY 11):

EFFECTS OF MULTIMODAL AND MUSCLE-STRENGTH CHAIR-EXERCISE PROGRAMMES ON PSYCHOLOGICAL WELL-BEING AND SALIVARY STRESS HORMONES IN PRE-FRAIL AND FRAIL OLDER WOMEN

Authors:

Guilherme Eustáquio Furtado

Matheus Uba Chupel

Eef Hogervorst

Ana Maria Teixeira

José Pedro Ferreira

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13.1 Abstract

Background: In recent years, the role of different types of physical exercise programmes in improving the overall factors of global health, such as immune profile, functional fitness status, psychological well-being has been highlighted together with its positive mediation effect on stress hormones. **Goals:** Thus, the aim of this study was to analyse the effects of 24-weeks of two different exercise protocols on functional fitness and stress hormone levels in institutionalized pre-frail and frail women. **Methods:** A sample of older frail individuals (n = 59, 81±7.84 years) participated in the study and were divided into three groups: chair-based muscle-strength exercises (MSE, n=18), chair-based multimodal exercise (MME, n =24) and a control non-exercise group (CG_{ne}, n = 17). Both exercise programs consisted of 45 minutes of supervised classes without music, carried out 3 times a week. The multimodal exercise group performed a progressive circuit-training protocol using static-dynamic balance, walking and body height muscle-resistance exercises. The muscle-strength resistance training with elastic-band exercises followed a compound set protocol. The controls did not change their usual lifestyle. The Fried Physical Frailty protocol was used to identify older-frail participants. Data for functional fitness, stress hormones and mucosal immune makers were analysed pre and post- interventions. **Results:** After interventions, a significant effect of exercise in time versus group for IgA levels ($p>0.05$) was found. A substantial improvement in psychological well-being and functional fitness in both exercise groups was also found while the controls had a substantial decrease ($p > 0.05$). Overall, the multimodal exercise group presented better improvements for all variables. **Conclusion:** Present results clearly evidence a positive effect of exercise in improving individual feeling, preventing a psychological and physical frail status. The slight variation seen in the stress hormones also indicated a beneficial mediation of exercise, with the different types of exercise showing satisfactory results. Further studies involving the same markers should be performed, in order to prove their real adaptation to this makers of the chronic exercise.

Key-words: Older-frail adults, psychological well-being, cortisol, alpha-amylase.

13.2 Introduction

Muscle strength, gait speed, low cardiorespiratory capacity and levels of physical inactivity characterizes a central partner of Physical Frailty (PF), a current concept that designates a frail state in older individuals associated with poor physical-performance (Fried et al. 2001). However, recently studies have revealed that other geriatric outcomes, such as psychological domains have a significant association with PF status (Freitag and Schmidt 2016). The term psychological frailty is relatively new and encompasses cognitive, mood, and motivational components (Andrew, Fisk, and Rockwood 2012). The concept is intended to consider brain changes that occur beyond normal aging, but not necessarily inclusive of disease, that result in decreased cognitive or mood resilience in the presence of modest stressors, and may eventually lead to negative health outcomes in a manner parallel to physical frailty, an entity well known to clinicians (Fitten 2015).

In oldest age, losses of social, mental and physical status are expected to have an intrinsic relationship that is maintained across the life (Clegg and Trust 2011). Levels of negative mood and feelings appear to increase faster in the elderly-frail when compared to non-frail subjects (Lohman, Dumenci, and Mezuk 2016). Stress is often recognized as a latent variable in studies involving older populations and it plays a crucial role in late-life depression (Jeon and Dunkle 2009). Stress is well-defined as a state in which an organism's internal controlling homeostasis is disturbed by real or perceived tasks in its situational demands (Souza-Talarico et al. 2009). It refers to a cognitive-affective response involving appraisal of threat and increased physiological arousal. However, feelings of stress have a proven relationship with other emotional states such as, anxiety, self-esteem and well-being (Steptoe, Deaton, and Stone 2015). Psychosocial and biological stress do not always trigger similar responses, however both have closeness and affect the physical performance (Takai et al. 2004).

Some physiological systems have a close involvement with changes in the biological and psychological stress response (van Stegeren, Wolf, and Kindt 2008). The survival and well-being of all species requires appropriate physiological responses to environmental and homeostatic challenges (Urs Markus Nater et al. 2006). The hypothalamic–pituitary–adrenal (HPA) axis and the autonomic nervous system (ANS), especially the sympathetic nervous system (SNS) are the systems that provide the most immediate response to stressor exposure (U. M. Nater and Rohleder 2009). Variations in these two systems have been related to several (psycho) pathologies (Urs Markus Nater et al. 2006). The biochemical makers of Alpha-Amylase (α-amylase) and Cortisol (COR) are the biochemical makers involved in the regulation and homeostasis of the both HPA and SNS systems as well as in the regulation of the mucosal immune system (U. M. Nater and Rohleder 2009).

Both α-amylase and COR has been shown can be sensitive in detecting changes related to adaptive responses to stress and can be (non-invasively) detected in saliva (Bosch et al. 2011), It was recently found that the salivary α-amylase/COR ratio could be used as marker to evaluate dysregulations in the stress systems (Ali and Pruessner 2012). In addition, -amylase also play an important role in the immune response, integrating the defence mechanism against pathogens trying to enter through the oral mucosa by preventing their adherence and penetration of the mucosal epithelium (van Stegeren, Wolf, and Kindt 2008).

Exercise in general triggers a series of changes in the body regulated by the ANS (Fu and Levine 2013). Several studies have revealed that α-amylase levels increase under conditions of physical and psychobiological stress (Rashkova et al. 2012). Unlike α-amylase, CORT has been well studied over many years and there are several studies that relate its increased levels to exercise practice, but the results of these evidences may not be generalized, especially because the studies showed diversity in the outcomes and approaches (Corazza et al. 2013). Additionally, little evidence on the chronic exercise-effect studies relating to α-amylase and CORT concentrations in frail-older adults has been found, with most exercise studies focusing in adults or athletes (Schipper, Silletti, and Vingerhoeds 2007).

A few studies aimed at testing the modulatory effect of exercise on stress hormones have reported a simultaneously positive improvement on health psychological outcomes in older subjects experiencing chronic exercise (de Labra et al. 2015). Recent studies have also demonstrated the effectiveness of both aerobic and strength exercise with elastic bands in improving physical fitness, and reversing the physical frailty and improve some psychological correlates of frailty in older adults (Theou et al. 2011). The types of exercise program and the approaches used can establish the level in exercise involvement and the results attained, especially in populations with special needs conditions, as is the case in this study. Thus, the purpose of this study was to analyse the effects of 24-weeks of two different chair-based circuit exercise protocols on changes in psychological well-being, frailty status and biochemical stress markers in institutionalized pre-frail and frail women.

13.3 Methods

13.3.1 Initial procedures and ethics

The legal tutors, directors of social and health care support centres and all subjects, were required to give full statement consent, where the confidentiality was also assured. This research was approved by the Multidisciplinary Research Ethical Committee of the University of Coimbra; comprehending the Portuguese Statement on ethics in human studies and conforming to the guidelines of the Helsinki Declaration (Petrini 2014).

This study consisted of a naturalistic controlled trial chair-exercise based intervention. The first phase included the recruitment and assessment of the participants before interventions. The second phase involved 24-weeks of two types of exercise-based interventions and phase three comprised the final assessment of the participants.

13.3.2 Participants characterisation and recruitment

Participants were institutionalized-dwelling women living in the city of Coimbra, Portugal, that were living in three different SHC with similar characteristics. Participants who were taking medications including aspirin and statins maintained unaltered posology during the study. All participants were provided with similar diets, in terms of caloric intake and nutrients, controlled by a local nutritionist and clinical staff. The diet was preserved unaltered across the intervention time.

13.3.3 Criteria of sample selection

The inclusion conditions for the older participants were: participants had to be aged over 65 years; medication therapy needed to be controlled and updated; if the participant had a clinical condition or severe comorbidity, it had to be stable and enable participation in exercise classes as decided by local medical staff. The exclusion criteria were: withdrawing or not completing the 8-foot-up and go test in the maximum time of 30 seconds, since scores above this value indicate severe physical conditions in institutionalized older adults (Furtado, Patrício, Loureiro, Teixeira, & Ferreira, 2017); involvement in other structured PE program; presence of severe cardiopathy, uncontrolled hypertension or asthmatic bronchitis, musculoskeletal dysfunctions (i.e. osteoarthritis, recent fractures), mental disorder, hearing and vision impairment, morbid obesity or the use of medications that significantly impair attention.

13.3.4 Sample calculation and allocation

The sample size (SS) estimation was performed by comparison of physical fitness outcomes between pre- and post PE intervention (de Labra et al. 2015). For different combinations of power and effect size (ES), the SS was computed with G*Power 3.1.9.2, with paired samples t-Student tests (Faul et al. 2007). The SS was seen to range between 5 and 44. Previous publications have reported high ES for frailty total score, up to 0.5 (large effect). Assuming a minimum power of 0.80 as acceptable and that we may realistically but conservatively expect the ES to be at least 0.3 (medium ES), the SS of the study was 19 per group. Further assuming a dropout rate of 25 to 35% (Picorelli et al. 2014), the SS increases to 28 per group, to a total of n = 84 participants. To guarantee an initial equal distribution [1:1] and the non-influence of the researchers in the assignment of the groups, participants were allocated into 3 groups: a chair based exercise (CBE) elastic-band muscle strength group (CSE, n=23), a CBE aerobic improved walking group (CAE, n =24) and a control non-exercising group (CG_{ne}, n = 15). The allocation to treatment was randomized according to CONSORT statement extension for controlled trials and was used this study (Des Jarlais, Lyles, and Crepaz 2004).

13.3.5 Masking effect

All the tests were applied by an independent assistant who established contact with the participants without reference to the exercise program. The instructor of the exercise sessions did not take part in the data collection procedures. Precaution was taken to avoid interaction of CEB programs between individuals of the two groups by staggering the classes schedule.

13.3.6 Measurements

All dimensions' measures were done by the same expert technicians in all participants, to diminish differences in data collection procedures. The data quality was done in the pilot study and reported for each physical-functional fitness and anthropometric markers through scores of internal consistency reliability (ICR). In the psychometric rate scales the Cronbach's alpha (C-α) or Cohen's kappa coefficient (*k*) were reported.

13.3.7 General health status

The Charlson Comorbidity Index (CCI) is a method of predicting mortality by classifying or weighting comorbid conditions based on the registry of each individual comorbidity. This score can be combined with age and gender to form a single index. CCI was validated by medical records over one year for each participant. (Charlson et al. 1994). Medication use (MU) was assessed through question number six (6) of the Mini Nutritional Assessment (MNA) scale, that asks the participants how many prescription drugs they take per day. CCI and MU was validated by medical record over one year for each participant. Medications for all the study participants did not change during the intervention program. The MNA was used to evaluate the nutritional status and comprised 18 questions for a maximal score of 30 points, and classifies older subjects as well-nourished, malnutrition risk, or malnourished (*k* = .74) (Loureiro 2008).

13.3.8 Biosocial and anthropometric evaluation

Information about chronological age was collected. The standardized procedures described by Lohan and colleagues (Chumlea, W., Baumgartner and Baumgartner 1989) for anthropometric measures were followed. Body mass was determined using a portable scale (Seca®, model 770, Germany) with a precision of 0.1 kilograms (IC = .89). Stature was determined using a portable stadiometer (Seca Body meter®, model 208, Germany) with a precision of 0.1 centimetres (IC = .87). Body mass index (BMI) was calculated according the formula [BMI = weight/stature^2].

13.3.9 Physical Frailty assessment

Assessment of physical frailty was evaluated according to the five criteria of the Fried frailty phenotype index (Fried et al. 2001). Shrinking was assessed by self-report of unintentional weight loss of four kilograms or more in the last six months, validated by medical records over one year for each participant; Self-reported exhaustion was evaluated by concordance of two questions (7 and 20) of the Center of Epidemiologic Studies for Depression (CES-D) scale (Gonçalves et al. 2014); Weakness, was analyzed using the handgrip strength test, adjusted for gender and BMI (Syddall et al. 2003); Slowness, as measured by the 4.6 meters walking test, adjusted for gender and height (ICR = .80) (Newman et al. 2003); low levels of PA were assessed by the International PA Questionnaire short form (ICR = .78) (Pitanga et al. 2012; Guessous et al. 2014). The prevalence of this criteria was calculated to generate a FS combined score.

13.3.10 Psychological well-being screen

The psychological tests described below were chosen because they had been validated in the Portuguese population and characterize the main psychological domains described in the concept of Psychological frailty as defined previously (Fitten 2015).

i) Cognitive status: The Mini-Mental State Examination (MMSE) was used to assess cognitive state (Cr-α = 0.71) The MMSE assesses five areas of cognitive function: orientation, immediate recall, attention and calculation, delayed recall, and language. The maximum MMSE score is 30 points, and a score below 24 points is considered abnormal and used for dementia and cognitive impairment screening (Macuco et al. 2012).

ii) Mood states: Depression was assessed using the Center for Epidemiologic Studies for Depression (CES-D) scale reflecting major facets of this state (Cr-α = 0.89). The 20-items are given on a four-point Likert scale, with scores between 0 and 60 in which the highest scores correlate with more depressive symptoms for the last week (Gonçalves et al. 2014). The Perceived Stress Scale (PSS) assesses the perception of stressful experiences. Seven out of the 14-items are considered negative and seven as positive. Final scores can vary from 14 to 70 points, a higher score indicating greater feelings of stress (Taylor 2015).

iii) Self-perception: The Rosenberg Self-esteem Scale (RSES) analyses global self-worth (Cr-α = 0.85). The sum of all 10-item scores gives results between 10 and 40 points, where higher values represent higher levels of self-esteem (McKay, Boduszek, and Harvey 2014). The General Self-Efficacy Scale (GSES) was used to assess optimistic self-beliefs related to efficacy to cope with a variety of difficult demands in life (Cr-α = 0.75). Responses sum up to a composite score with a range from 10 to 40 points, where higher values represent higher levels of GSES (Edward McAuley et al. 2005). The Attitudes to Aging Questionnaire (AAQ) was used to assess attitudes toward the ageing process as a personal experience from the perspective of older people (Cr-α = 0.67). The AAQ contains 24 items and total scores range from 8 to 40 points. The higher the score the more positive the attitude towards one's own ageing process (Low, Molzahn, and Donald Schopflocher 2013).

iv) Emotional well-being: The Satisfaction With Life Scale (SWLS) measures global cognitive judgments of satisfaction with one's life (Cr-α = 0.89). The 5-item scale results in scores between one to 35 points, with higher values representing higher levels of life's satisfaction (McKay, Boduszek, and Harvey 2014). The Happiness Face Scale (HFS) consisted of a graphical scheme where for each face is assigned one letter, in which the letter A (seven points) is considered the maximum and the letter G, the minimum of one point (Cr-α = 0.78). The participant has to identify with one of the faces, depending on his/her state of happiness (Andrews and Withey 1976).

13.3.11 Stress hormones assessment

Saliva samples to measure salivary COR, IgA, Lys and α-amylase levels, were collected by passive drool always at the same time in the morning (between 10:00h to 11:30h) to minimize circadian effects. Individuals salivated without any orofacial movement into high quality polypropylene vials to avoid problems with analyte retention or the introduction of contaminants that could interfere with the immunoassays. The tubes containing the saliva samples were then frozen (-20ºC), until the day of analysis. defrosted and centrifuged in order to obtain a clear sample. Cortisol concentrations were determined by competitive enzyme linked immunosorbent assay (ELISA) [Salimetrics, USA], according to the manufacturer instructions (Miller et al. 2013). Alpha-amylase activity was determined by enzyme kinetic enzymatic assay (Salimetrics, USA) according to the manufacturer instructions. The reference values (RV) and serum saliva-correlation (r) for salivary CORT (RV = <0.007 ug/dL, r = .91) and α-amylase (RV = 0.4 U/mL, r =.86) were reported by the manufacturer, in terms of sensitivity and their respective correlation with serum samples.

13.3.12 Characterization of chair-exercise protocols and adherence

The CBE programmes were conducted by exercise specialists, and consisted of structured and progressive exercises performed with a chair for support guarantying the individual's security and stability during the session, respecting individual limitations without discouraging individuals to reach beyond their limits (Anthony et al. 2013) Additionally, both CME and CSE respected the guidelines of integrated exercise periodization and ACSM guides of prescription exercise for non-active older adults (Strohacker et al. 2015; Nelson et al. 2007). The two types of CBE programs were offered for 28-weeks, with two-three sessions per week on nonconsecutive days (separated by at least 48 hours). The percentage of exercise frequency was calculated individually through the total sum of participation and entries were recorded in a checklist. When a participant had two consecutive absences, she was contacted to return to the group classes. An adherence to the exercise program between of 65% - 75% (Picorelli et al. 2014), was established as minimum for each participant to be included in the study results analysis.

13.3.13 Chair multimodal exercises (CME)

In order to establish a progressive endurance training program aimed to improve the walking capability, specific exercises were performed with a determined number of exercises (7-10), repetitions (6-10), sets (2-3), cadence of execution (1:2) and rest between sets (45-60 seconds), following a circuit training protocol. Intensity was indirectly calculated using the Karvonen´s formula to predict target heart rate (HR), with HR_{max} being calculated using a specific formula for older population [HR_{max}= 207 (beats per minute, bpm) - 0.7 x chronological age] (Guderian, Johnson, and Mathiowetz 2013) and was monitored using heart rate monitors (Polar, RCX5®) randomly distributed among participants. A low to moderate intensity effort around 50-75% of maximum heart rate zone (HRz_{max}) values was attained as recommended by the ACSM (Nelson et al. 2007). Additionally, intensity was measured through the modified BORG scale of perceived exertion (PSE), that consists of an arbitrary scale ranging from 0 to 10 points, with identical intervals and with reference to the quality of effort: (0) nothing at all;

(1) very weak; (2) weak; (3) moderate; (4) somewhat strong; (5-6) strong; (7-9) very strong; (10) very, very strong (almost maximal). Each session was divided into three parts: 10 minutes of warm-up and body mobilization (PSE = 1-3, HRz_{max} = 50-55%); 40 minutes of elastic-band exercises (PSE 3-4, HRz_{max} = 56-70%) and finally 10 minutes of stretching exercises targeted to encourage cool-down (PSE 1-2, HRz_{max} = 45-50%).

13.3.14 Chair elastic-band muscle-strength exercises (CSE)

To create progressive strength training, specific exercises were performed with a determined number of exercises (4-8), sets (2-3), repetitions (12-15), cadence of execution (2:2) and rest between sets (30-45 seconds), following a circuit training protocol. The first three levels of the Thera Band system (Thera Band®, Akron, Ohio, US) were used. Intensity was measured through the OMINI PSE, that consists of an arbitrary scale ranging from 0 to 10 points, with identical intervals and with reference to the quality of effort: (0) extremely easy; (1-2) easy; (3-5) somewhat easy, (6-7) somewhat-hard; (8) hard; (9-10) extremely-hard (Robertson et al. 2003). The goal was to keep the intensity of the exercise activities between 1 to 6 in PES levels. It was expected that the relationship with the real effort would be 55-80% of maximum heart-rate (Garber et al. 2011). For safety reasons, the participants of CSE were using heart rate monitors. The session was divided into three parts: 10 minutes of warm-up exercises for general body mobilization (PSE 1 to 3, HRz_{max} = 45-55%), 40 minutes of strength elastic-band exercises in PSE 4 to 7 (HRz_{max} = 56-75%) and finally, 10 minutes of cool-down stage, through easy-walking and static flexibility exercises for ´breath´ control, PSE 1 to 2 (HRz_{max} = 45-550%). During 24-weeks the CG_{ne} did not participate in any exercise protocols intervention. The participants were encouraged to maintain their usual life style, within the monthly agenda of the CSHS which comprised several sociocultural activities and external tours.

13.3.15 Data analysis

Descriptive data were presented as mean (and standard deviations) or frequencies. In the baseline scores, comparisons between groups were analysed by one-way ANOVA. Repeated measures ANOVA was used to analyse the effect of time and time by group interactions on the frailty total score, functional fitness, psychological well-being and stress hormone changes over time, followed by Bonferroni *post hoc* tests, reporting the confidence interval (CI95%) for the statistically significant results. The percent of change after the interventions was calculated ([post value/pre value]-1).

The magnitude of the global effect size (ES) was calculated by exercise-modulation treatment. For continuous variables, ES were computed using Cohen's (*d*). The effect size was considered trivial ($d \leq .20$), small ($.21 < d < .50$), moderate ($.51 < d < .79$) and large ($d > .80$) (Batterham and Hopkins 2006). The IBM SPSS Statistics package 24.0 for all statistical procedures were used. The level of significance adopted was p-value = .05.

13.4 Results

Characteristics of experimental and control groups at baseline are presented in Table 13.1. The analysis of statistical comparisons shows that no significant differences between the three groups were found ($p>0.05$). In terms of adherence, the CSE participants attended an average of 58 sessions (78% of attendance), out of 74 sessions offered in total. In the CME, the participants had 72% of adherence, corresponding to 54 sessions attended. From the 119 potential participants initially recruited, a total of 29% were excluded for not meeting inclusion criteria and declining to participate in the study spontaneously. In the follow-up phase, 4 participants of CME, 2 of CSE and 12 of CG_{ne} withdrew their willingness to participate before or immediately after the beginning of the study for various personal reasons. A total of 3 drop-outs were registered during the intervention period because of low exercise engagement, injuries (not related to the exercise program) or adverse responses to the intervention. In total, 57 older women participants were examined at completion of the 24 weeks' study. No differences regarding any variables of sample characteristics were found among the 2 exercise and controls groups who completed the trials ($p > 0.05$).

Table 13.1 Characteristics of total sample, exercise and control groups at baseline.

	Total sample (n=57)	**Chair multimodal exercises (n=24)**	**Chair muscle strength exercises (n=18)**	**Control group non-exercise (n=15)**
	M±SD	**M±SD**	**M±SD**	**M±SD**
Chronological age (years)	83.93 ±10.10	79.92±7.83	81.15±4.89	80.93 ±10.10
Stature (centimeters)	151.47±0.30	152.13±0.06	153.89±0.51	152.67±0.08
Body mass (Kilograms)	66.01±13.91	63.44±9.82	65.03±16.80	64.99±14.89
Body mass index ($kg \cdot m^{-2}$)	28.04±6.84	26.98±3.97	27.03±8.67	27.45±6.06
Charlson comorbidity index	8.05±2.53	7.58±3.97	7.65±1.93	7.67±2.53
Medication use, per day (unit)	6.75±2.34	7.05±1.98	6.95±3.05	6.30±0.95
Mini nutritional assessment	25.03±2.60	23.33±2.68	24.58±2.37	24.37±2.83
Physical Frailty index	2.02±1.32	2.35±1.42	2.38±1.72	2.37±1.19

Notes: ** $p\leq0.01$; * $p\leq0.05$; M(SD) = mean (standard deviation). The p-values correspond to comparisons between the three groups and were computed with one-way ANOVA one-way or Kruskal-Wallis

The baseline comparisons show that no significant differences exist in the salivary hormones and physical fitness variables before to start the interventions (p > 0.05). Table 13.2 shows the salivary stress hormones biomarkers changes after the 24 weeks' intervention programs. No effect of time or time versus group was observed in the COR levels, however, a moderate ES in the CME group (ES = 0.51, Δ% = +104%) and a large increased in the controls (ES = 1.13, Δ% = +102%) were observed. Significant value of time treatment was observed in salivary α-amylase [F(1.53) = 0.48; (p<0.01)] with a trend to significant differences in the time versus group [F(2.53) = 0.25; (p=0.052)].

Table 13.2 Salivary stress hormones and functional fitness comparisons between pre- and post- intervention and control group (non-exercise) after 24-weeks.

Salivary stress hormones	**Baseline M±SD**	**24 weeks M±SD**	**Interaction effects**	***F* test**	***p* value**	***Cohens' d* effect size**	**Practical relevance**	**Δ%**
Cortisol (µg/mL)								
CME	0.21±0.11	0.44±0.65	Time	9.11	0.147	0.51	moderate	+104
CSE	0.22±0.13	0.20±0.14	TxG	1.60	0.057	0.14	small	+5
CG*ne*	0.23±0.14	0.46±0.25				1.13	large	+102
Alpha-amylase (U/mL)								
CME	68.06±126.34	57.28±71.08	Time	0.48	**0.009**	0.10	small	-16
CSE	43.57±86.35	50.54±100.13	TxG	1.43	0.052	0.07	trivial	+16
CG*ne*	38.65±29.17	51.7±70.57				0.48	small	+33

Notes: *Cohens' d* = trivial (*d* ≤ .20), small (.21 < *d* <.50), moderate (.51 < *d* <.79) and large (*d* > .80) effect size; M(SD) = mean (standard deviation); Delta change percentage; The p-values correspond to comparisons between the two groups and were computed by repeated measure's ANOVA for within comparisons, following Bonferroni *post-hoc* test; CME = Chair multimodal exercises; CSE = Chair Elastic-band muscle strength exercises; CG*ne* = Control group non-exercise

Table 13.3 shows the results for the functional fitness tests. The baseline comparisons show that no significant differences exist in the physical fitness variables before the start the intervention (p > 0.05). Statistical differences in the time versus groups after intervention [F(2.53) = 0.25; (p=0.000)] in the HGT test was found. Bonferroni corrections applied *post hoc* indicating a statistical significant small increase in the CME (ES = 0.30, Δ% = +16%; p<0.01, CI:95% = -5.10 to -1.38), a large addition in the CSE (ES = 0.90, Δ% = +24%; p<0.01, CI:95% = 1.39 to 5.01) and a moderate decreased in the GC*ne* (ES = 0.69, Δ% = -22%; p<0.01, CI:95% = 1.38 to 6.08). Significant effect of time in the 4.6 walking test was found [F(1.53) = 12.96; p = 0.001)]. *Post hoc* tests indicated that significant moderate decrease on time of execution in the CME (ES = 0.62, Δ% = -23%; p<0.01, CI:95% = 0.228 to 4.75) and CSE (ES = 0.69, Δ% = -22%; p<0.01, CI:95% = 2.09 to -0.22) was found.

Table 13.3 Functional fitness comparisons between pre- and post- exercise and control group after 24-weeks.

Physical Fitness	**Baseline M±SD**	**24 weeks M±SD**	**Interaction effects**	***F* test**	***p* value**	***Cohens' d* effect size**	**Practical relevance**	**Δ%**
Hand grip strength test								
CME	19.91±11.18	23.12±10.47				0.30	small	+16
CSE	14.30 ±5.12	18.50±2.28	Time	2.96	0.091	0.90	large	+24
CG*ne*	17.75±7.45	13.20±4.45	TxG	13.82	0.000	0.69	moderate	-22
4,6 meters walking test								
CME	12.63±4.81	10.13±3.04				0.62	moderate	-23
CSE	17.52v8.31	13.05±4.43	Time	12.96	0.001	0.67	moderate	-25
CG*ne*	16.17±7.86	15.24±5.21	TxG	1.99	0.070	0.13	small	-9

Notes: *Cohens' d* = trivial (*d* ≤ .20), small (.21 < *d* <.50), moderate (.51 < *d* <.79) and large (*d* > .80) effect size; M(SD) = mean (standard deviation); Delta change percentage; The p-values correspond to comparisons between the two groups and were computed by repeated measure's ANOVA for within comparisons, following Bonferroni *post-hoc* test; CME = Chair multimodal exercises; CSE = Chair Elastic-band muscle strength exercises; CG*ne* = Control group non-exercise

Table 13.4 presents the results of psychological well-being (PwB) dimensions before and after the intervention programs. The baseline comparisons show that significant differences exist in the PwB variables before the start the interventions for MMSE (CME to CSE group), CES-D (CG*ne* to both exercise intervention groups); RSES (CG_{ne} to both exercise intervention groups) and SWLS (MME to CSE group (p > 0.05). After de intervention program, statistical differences in the time versus group treatment was found for MMSE (F(2. 56)=5.42; p=0.007) and Bonferroni corrections applied *post hoc* indicating a small increase in the CME (ES = 0.48, Δ% = +16%; p<0.01) and moderate decreased for GC*ne* (ES = 0.58, Δ% = -14%; p<0.01), with the CME group also presenting a small increase (ES = 0.47, Δ% = +18%). There was an effect of time versus group interaction in CES-D changes (F(2. 56)=6.452; p=0.003) with the *Post hoc* test showing a statistical significant large decrease in the CME group (ES = 1.16, Δ% = -14%; p<0.01; CI:95% = 4.97 to 13.92).

Statistical differences in the time versus group treatment was found for GSES (F(2. 56)=5.42; p=0.007). *Post hoc test* showed a statistical significant large increase in the CME group (ES = 0.87, Δ% = +14%; p<0.005), and the CSE presented a trend for statistical differences with moderate effect (ES = 0.62, Δ% = +10%; p<0.060). The GC_{ne} presented a moderate decrease (ES = 0.55, Δ% = -9%). There was significant statically differences in the time versus group (F(2.56)=12.08; p=0.000) for the GSES. After intervention program, post analysis showed a statistical large increase in CME (ES = 0.86, Δ% = +14%, p = 0.001; CI:95% = -6.12 to -1-71), moderate increase in the CSE (ES = 0.76, Δ% = -9%, p = 0.006; CI:95% = -5.86 to -1.04) while a moderate decrease in the controls occurred (ES = 0.57 Δ% = -15%; p = 0.004; CI:95% = 1.41 to 6.98).

Table 13.4 Psychological well-being comparisons between pre- and post- intervention and control group (non-exercise) after 24-weeks.

Psychological well-being	Baseline M±SD	24 weeks M±SD	Interaction effects	*F* test	*p* value	*Cohens' d* effect size	Practical relevance	Δ%
Mini-mental state examination								
CME	21.42±5.09	23.12±4.62	Time	0.58	0.448	0.47	small	+8
CSE	16.95±5.33	19.70±20.70	TxG	5.41	**0.007**	0.48	small	+16
CG*ne*	21.0±05.50	18.13±4.32				0.58	moderate	-14
State of depression scale								
CME	43.42±9.21	41.00±8.06	Time	3.23	0.077	0.27	small	-6
CSE	42.35±9.31	33.20±8.53	TxG	0.03	**0.003**	1.16	large	-22
CG*ne*	33.20±8.44	37.13±5.97				0.15	small	+12
Perceived stress scale								
CME	28.54v8.01	24.54±6.03	Time	1.32	**0.023**	0.51	moderate	-14
CSE	25.19±6.12	24.95±5.51	TxG	3.34	0.107	0.04	trivial	-1
CG*ne*	28.73±5.83	29.87±7.06				0.17	small	+4
Global self-esteem scale								
CME	20.83±2.82	23.79±4.01	Time	2.05	0.157	0.85	large	+14
CSE	20.75±2.85	22.85±4.75	TxG	5.22	**0.008**	0.62	moderate	+10
CG*ne*	24.40±4.45	22.20±3.07				0.55	moderate	-9
General self-efficacy scale								
CME	28.42±4.75	32.33±4.25	Time	2.18	0.145	0.86	large	+14
CSE	28.35±5.01	31.81±4.65	TxG	12.08	**0.000**	0.59	moderate	+12
CG*ne*	28.52±5.77	24.67±7.98				0.62	moderate	-15
Attitudes to aging questionnaire								
CME	28.46±4.63	31.43±3.96	Time	1.83	0.381	0.68	moderate	+10
CSE	26.65±4.66	29.85±3.66	TxG	7.91	**0.001**	0.76	moderate	+12
CG*ne*	25.21±6.52	21.87±5.08				0.57	moderate	+13
Satisfaction with life scale								
CME	24.96±5.97	26.63±6.14	Time	0.37	0.541	0.27	small	+9
CSE	19.40±5.77	22.35±7.12	TxG	7.83	**0.001**	0.45	small	+15
CG*ne*	21.93±6.18	18.13±3.58				0.59	moderate	-17
Happiness face scale								
CME	2.81±1.29	3.33±1.09	Time	2.67	0.108	0.43	small	+19
CSE	3.03±1.30	3.48±1.04	TxG	0.97	0.409	0.38	small	+15
CG*ne*	3.27±1.94	3.20±1.15				0.04	trivial	-17

Notes: *Cohens' d* = trivial ($d \leq .20$), small ($.21 < d < .50$), moderate ($.51 < d < .79$) and large ($d > .80$) effect size; M(SD) = mean (standard deviation); Delta change percentage; The p-values correspond to comparisons between the two groups and were computed by repeated measure's ANOVA for within comparisons, following Bonferroni *post-hoc* test; CME = Chair multimodal exercises; CSE = Chair Elastic-band muscle strength exercises; CG*ne* = Control group non-exercise; TxG = time versus group

In the AAQ, statistical variations in time versus group were found (F(2. 56)=5.42; p=0.007). Post hoc test showed significant and moderate increases in the CME (ES = 0.68 Δ% = 10%; p = 0.010; CI:95% = -5.17 to -0.74) and CSE (ES = 0.76; Δ% = 12%; p = 0.009; CI:95% = -5.73 to -0.87), while GC_{ne} showed a moderate decrease (ES = 0.57 Δ% = -15%; p = 0.004; CI:95% = 0.53 to 6.14). In the SWLS, significant statistical changes in time versus group was found (F(2. 56)=7.83; p=0.001). Post hoc test showed a significant and small increase in the CSE (ES = 0.27; Δ% = 9%; p = 0.017; CI:95% = -5.36 to -0.53), and CSE showed a not significant but small increase (ES = 0.45; Δ% = 15%), while GC_{ne} showed a moderate decrease (ES = 0.57 Δ% = -17%; p = 0.008; CI:95% = 1.01 to 6.58). No significant time and time versus treatment was observed for HFS, however, Both CME and CSE presented a small increase (ES = 0.43; Δ% = 19% and ES = 0.45; Δ% = 15%, respectively).

Additionally, the final values of exercise engagement and adherence were also registered. The final scores of minimum, maximum and mean of HR achieved at the end by the CME reported were 65.75 (±9.96), 97.56 (±12.40) and 77.27 (±8.21) bpm, respectively. This corresponded to 57% to 70% of the predicted HRz_{max}. The final mean of PES ranged from moderate (3.14±0.98) to somewhat strong (4.92±1.01). For the CSE group, the same HR scores achieved at the end were 69.08 (±14.77), 96.24 (±14.13) and 84.48 (±11.52) bpm respectively. This corresponded to 48% to 74% of the predicted HR_{max}. The final mean of PES oscillated from somewhat easy (3.98±1.99) to somewhat strong (6,02±2.22), according to the participants self-perception.

13.5 Discussion

In this study, the goals were to assess the impact of two different structured exercise programs of CSE and CME in older frail women on biochemical markers related to stress as well as to verify simultaneously changes in psychological well-being and functional fitness. The assumption was that including regular exercise as a co-adjuvant treatment would be important for positive modulation of salivary stress hormones, since this population suffers, more prominently age-effects (e.g. biological stress and psychological stress), which tend to affect mental health and psychological well-being. The main results of this study were that both CBE programs increased functional fitness, and promoted important changes in the PwB state in institutionalized older frail women after 24 weeks of systematic exercise. Despite participants of the two different exercise program registering a similar adherence and intensity of effort, CSE and CME programs induced a different response for some of the analysed variables.

13.5.1 Salivary stress hormones

Despite the variations was found in the salivary α-amylase and COR levels, we should be cautious when taking conclusions, since these two hormones may be influenced by external factors, such as psychological stress, medication use or even by the acute response to physical exertion (Maruyama et al. 2012). Another question would be the small number of studies that looked at the chronic response of these markers in frail and pre-frail older individuals. Alpha-amylase was recently identified as a potential marker of sympathetic activity while salivary cortisol seems to be a valid measure for the HPA axis activity and also, related to the biological stress response (Papacosta and Nassis 2011).

Alpha-amylase is an enzyme that breaks down starch into maltose and can be important to host defence by inhibiting the adherence and growth of certain bacteria (Maruyama et al. 2012). In this study there was a substantial decline in α-amylase values in the CME and increase in CSE and controls. Some studies involving analysis of the sAA reveal considerable variation in the activity of this enzyme across populations (Mandel et al., 2010). The patterns of between population differences have been linked to the number of AMY1 copies, which is seen as an adaptive response to the intake of dietary starch (Perry et al., 2006). It can also reflect a decrease in mucosal immunity since α-amylase is also used as a first barrier to bacterial colonization in the mouth. At the same time, a small increase of the salivary COR levels in both exercise groups and a large increase in the controls were found in our study. Although this evidence explains a variation of these hormones, in our study it seems much more clear that this variation may be associated to the different intensities promoted by the different exercise programmes. While CSE promotes intermittent stimuli, CME participants underwent a more continuous effort with very short rest intervals, and the subsequent adaptation-response to the effort may have influenced the results of both markers.

This result was expected, since exercise has been shown to increase adrenal glands volume and cortisol secretion (Papacosta and Nassis 2011). Based on the assumption that the older-frail population has a usually sedentary lifestyle and suffer side effects from polypharmacy use, this small and no pathological increase of cortisol levels over time may be beneficial, since it may be associated with a small increase in autonomy for the motor activities of everyday life. However, the large increase found in the control group in the both stress hormones may reflect a response to increased biological (ex: inflammaging) and psychological stress (Ali and Pruessner 2012).

13.5.2 Psychological well-being

In the last decades health professionals have been increasingly interested in the potential of exercise to prevent and treat mental health disorders and to improve the levels of psychological well-being of the older population (Windle et al. 2010). In this study, the results show that regular exercise improved or maintained satisfactory PwB across the time-intervention. However, it is important to note that the slight decline in the subjective perception of PwB in the control group is equally important as the findings described above. Within the exercising groups, other factors may have been responsible for this improvement, such as the benefits of regular exercise in increasing social interaction that may reflect positively on dimensions such as attitudes, subjective happiness and depressive state. (Ko and Lee 2012)

In this study, older-frail participants exposed to exercise, especially in the CME group, showed a substantial increase in their levels of functional fitness (gait speed and grip strength test), contributing positively, according to classical theories of the physical self-perception, in the improvement of general self-efficacy, exercise efficacy and physical and global self-esteem (Opdenacker, Delecluse, and Boen 2009). Positive effects of exercise participation have been reported suggesting increases on older adult's self-efficacy that might improve more positive perceptions of well-being and effectively enhancing mood states' (Edward McAuley et al. 2006). Recently, a longitudinal descriptive study suggested that CME exercise programs may be effective in preventing psychological declines, such as depression, anxiety, cognitive decline and other psychological events (50,51), associated with improvements on strength and cardiorespiratory fitness, even in the populations over 60 years of age (9,51).

Recent studies showed a positive correlation between high levels of physical activity or participation in regular exercise programs and the satisfaction with life domain (18). These studies, as well as ours, support the hypothesis that increased proficiency on motor tasks via structured exercise, even in women over 75 years of age, can contribute to improvements in their subjective well-being (14). Unlike other studies, our results revealed changes in the subjective perception of psychological stress, which satisfactory reduction of PSS in the CME group that could be related to increased social interaction and improved well-being perception associated with the physiological effects of exercise.

Systematic reviews have examined the sizable empirical literature testing the effect of multimodal interventions on subjects with cognitive impairments (9). Unlike others studies, the participants of CSE program, but not CME presented improvement in their cognitive status. Recently, there is a growing body of evidence indicating the positive impact of exercise on individuals with cognitive impairment, one particular facet of mental health. The MMSE is an instrument that verifies the proficiency of the elderly in performing tasks that require the executive function (Okun et al., 2006). The executive functions require higher level cognitive processes associated with the frontal lobe of the brain that control and coordinate more fundamental processes in the effortful pursuit of goals (Atlantis et al., 2004). Several studies investigated the effects of exercise programs on older adults and found improvements for both older men and women on executive processing (Windle et al., 2010). As was found in our results, Poor performance on executive function tasks has also been shown associated to prospectively low levels of physical activity in all components of physical fitness (Okun et al., 2006). The other factor that can contributed to the results is the attenuation of subjective perception of depressive state and psychosocial stress.

The hypothetical conclusions that associate the variation effects of the stress hormones involved in this study with the effects that were found in PwB are somewhat limited, since there was no response considered linear in these markers. However, the assumption mentioned above, that the cyclical increase of stress hormones at levels not harmful to health can bring psychological benefits seems promising, since these hormones can act as starting signals to the use of glucose in the physical and brain activities, which to a certain extent can bring benefits for mental well-being.

13.6 Conclusion

In summary, our results clearly evidence a positive effect of exercise on improving individual feelings of psychological well-being and functional fitness. Interpreting the slight variation of the hormones as beneficial, we can see that although to a different extent, both types of exercise have shown satisfactory results. These however, should be interpreted carefully due to the small sample size. Further studies involving the same hormonal markers should be performed, in order to prove that they represent a real adaptation to chronic exercise (ex: biological stress caused by the exercise), and their relationship with the variation in the psychological well-being and mental health found.

13.7 References

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SECTION V

Final considerations: discussion, conclusion and directions for the future researches

CHAPTER 14:

GLOBAL DISCUSSION AND FINAL CONSIDERATIONS

14.1 Summary of findings

The present chapter presents the main findings found in the studies carried out, taking into account the three phases of this PhD thesis. Firstly, some of the results found in the preliminary studies will be discussed. Secondly, we will discuss the results of the cross-sectional studies and finally, we will present the general discussion of the findings related to the intervention-exercise studies. However, this sequence of the discussion does follow a linear path (according to the types of study), but taking into account that the results of the different studies have an intrinsic relation between them. As it was previously started, this PhD thesis presents a multidimensional approach in the study of PF and its connections with other global health variables, through correlational data analysis. Subsequently, it sought to test the impact of different exercises on the modulation of global health markers related to PF.

The main results found in this preliminary studies pointed to the following questions: i) in study 01, we found a strong association between the decline in the cognitive profile and PF, which presents a similar pattern in countries from several regions of world; ii) study 2 confirmed through numerous systematic review studies that there is concrete evidence of a promising effect for the different types of physical exercise on different global health variables, as well as its ability to attenuate and reverse the PF in the elderly. It seems that a multimodal exercise with a long-term duration (more than five months) and a weekly frequency variyng between 3-5 times per week seems to have a superior effect when compare to other types of exercise; iii) in study 3, it was possible to verify, using a preliminary exercise intervention programme with yoga-flexibility chair-based exercise, as an method integrated method with the conventional exercise group classes, also promotes promising results in the modulation of some parameters of global health, namely in the subjective perception for the execution of daily living tasks, functional fitness and salivary stress hormones (1). However, we verified that the intensity of the exercise was determinant for the impact of the results, since it was verified that the light exercise intensity did not promote substantial changes in all analyzed variables, namely physical-functional fitness.

The cross-sectional studies presented interesting evidence regarding the identification of new variables related to PF in the elderly, as well as the power of some of these variables to explain the variance associated with frailty status in the institutionalized old women, which are as follows: i) study 4 demonstrated that the cognitive status was the variable that has the strongest power of explanation of the PF condition when compared to several other global health markers, corroborating the findings pre-announced in the preliminary systematic review study (2); ii) in study 5, it was demonstrated that the agility-dynamic balance test can be used as a simple and fast tool for the detection of physical frailty in the elderly (3); iii) in study 6, it was clear that low activity levels and slow gait are independent dimensions of Physical Frailty that contribute to functional disability in the elderly; iv) study 7 revealed that attitudes towards aging and the subjective perception of happiness were highlighted as new psychological dimensions that may explain the variance associated with PF; v) in study 8, the results pointed to salivary α-amylase as a promising marker for prognosis of PF the condition.

Intervention studies with different types of multimodal (CME) and muscle strength elastic bands exercise (CSE) presented as important results: i) in study 9 it was possible to verify the positive effect of exercise modulation on the independent components of PF; in several domains of physical function, namely in the reduction of the subjective perception of the risk of falls and in the proficiency to perform daily life activities in addition to the small increase in sex hormones such as DHEA and testosterone; ii) Study 10 demonstrated the effect of exercise on the positive mediation of immune markers, specifically in the IL-10 / TNF alpha ratio and salivary IgA; iii) In study 11, the effect of exercise on the maintenance and improvement of psychological well-being and cognitive abilities of exercise practitioners was verified, as well as the effect of exercise on the modulation of biological stress markers (COR and γ-amylase).

14.2 Inferences based on key results

Despite the numerous frailty evaluation protocols available, Fried's PF phenotype has clearly demonstrated its robustness, as found in study 1, the systematic review of metanalysis (2). As pointed out by several studies, its easy application and access allowed the evaluation of large samples and to confirm that PF respects a temporal pattern associated with age and other aspects of aging that transcends particular characteristics of some samples (e. g. community elders or living in a hospital setting). On the other hand, some recent research has also shown that, regardless of the size of the sample (whether small or large), the use of the five independent components of PF for the creation of the three subgroups has been replicated in several studies (4). In the Portuguese population of institutionalized older individuals, as in the case of our study 4, the results revealed a significant incidence of PF, highlighting the Linda Fried construct as a phenotype associated with the elderly that has the accuracy and reliability to detect what is proposed in samples of institutionalized elderly, corroborating with findings in other European countries (5,6). In addition, subsequent cross-sectional studies revealed that, as the literature points out, PF has several dimensions of global health that have a more closed relationship, highlighted in cross-sectional studies 5, 6, 7 and 8 that pointed out significant differences for some variables (i.e., d and the frail subgroup participants presented the most negative outcomes for most of the variables framed in the different dimensions.

However, when were explored the associations between PF and the several dimensions of global health in some cross-sectional studies (i.e. studies 6 and 8), we opted to perform the correlations analisys between the variables included in the statistical model and each independent components of the physical frailty, following the rationale of previous studies (7,8). Although the different markers did not present consistent associations with PF total score, some variables demonstrated a closed link with different independent components of PF, like in study 6, that linear regressions analysis showed that in the two models tested, Low physical activity levels and Slowness were the frailty independent components most associated with disabilities, and study 8, revealed that weakness and exhaustion were the PF components most associated with immune profile makers.

The option for using ROC analysis in study 4, for example, allowed us to verify that the MMSE questionnaire of cognitive status can be used to predict a possible PF associated to cognitive impairment, being a result that is in line with several recent studies (9–11); to verified the power of estimation of a simple applicable functional-fitness test (i.e. agility-dynamic balance test) for the use to detect PF in institutionalized older people, corroborating previous studies (12,13); and also, identifying that salivary α-amylase was the 'novel' biomarker that better explained the physical frail condition.

In this sense, the set of cross-sectional studies were able to prove the existence of a significant independent and combined relationship of several variables with the PF status, help us achieve some important conclusions, taking into account the current state of art about frailty and their correlates (14): in this sample was showed the presence of a new phenotypes associated with physical frailty status: Disability of Frailty characterized by the high loss of proficiency to perform activities of daily living (15); Cognitive Frailty, defined as a form of pathological brain-aging and a precursor to neurodegenerative processes, that is characterized by concurrent PFS and potentially reversible cognitive impairment (16); Psychological Frailty defined by the decline in subjective perception of psychological well-being (e. g. emotional well-being, mood and resilience) associated with worsening physical condition (17); Poor functional fitness of Frailty, characterized by a fast deterioration in other motor skills and functional-physical tasks; the frailty endocrine-immune system, with evidence suggests inflammation process has a major role in the pathophysiology of frailty through an abnormal, low-grade inflammatory response that is hyper-responsive to stimuli and that persists for a long period after removal of the initial inflammatory stimulus (18).

Looking at the interconnection between studies, we can see that lower physical fitness in frail individuals, accompanied by a physical inability to perform daily tasks and the high fear of falling makes sense (19); also a link between the low profile of psychological and cognitive state and a lower functional fitness, since the literature points out a relationship between a satisfactory executive function and a greater capacity to solve physical tasks and daily problems, also including the management of the stress for problem solving (20,21); and the relationship between the satisfactory hormonal balance and the good functioning of the skeletal muscle system (22).

Despite the objectives proposed in each cross-sectional study, it is important to highlight that notwithstanding the associations demonstrated in the different studies, some of them where dependent on the cognitive profile (MMSE) and the multiple comorbidities (CCI), characterized as a central co-variates in this type of study. Some findings have shown the existence of a PF associated with cardio metabolic diseases, whose incidence in our study sample is high (48% of the total sample). Recently, the term 'Diabetes of Frailty' and Sarcopenic obseity has been suggested comprehended as a two new frailty phenotype (23), which associates this disease with PF. The precise relationship between incidence of cardiometabolic diseases and physical frailty could be explored in future studies.

It is important to highlight that the cross-sectional studies helped us create a greater affinity and specific knowledge of the study variables include in the experimental study design. The most interesting was to observe the effect of the exercise modulation in those variables that presented some degree of correlation with the PF status. The intervention studies were performed with the same participants of the cross-sectional studies and this factor allowed us to look for this variables from a specific point of view. Considering the closed interconnection between the different study variables and PF on this sample, our interest was to observe the impact of the exercise in the static and dynamic balance, cognitive status, attitudes toward aging and subjective perception of happiness and fear of falling; and particularly biochemical markers of α-amylase, cortisol, and Interleukins (IL-10, IL-6 and IL-1ß), because these variables presented a more closed relation with PF. However, our decision was to organized the three intervention studies observing the modulating effect of exercise on a greater number of variables, without disregarding a logical and coherent organization of the intervention studies, which took into account the physical-functioning, psychobiological and the immunity profile dimensions.

When analyzing the effects of exercise in some of these variables, it is appropriate to identify the reasons for choosing the different exercise programs (PEP). In a preliminary phase study, the choice of Yoga type-flexibility was based on the hypothesis that a low-impact exercise program would not promote satisfactory results in the positive modulation of some variables in study, which was partially supported by the results. Another factor was the need to test some methods for driving exercise programs (e.g. chair and stand exercises, heart rate control) and the effect on some variables in study. In a subsequent phase of the study design, we decided to select two exercise programs, based on the findings of the previous systematic review of reviews study and the guidelines the of American College of Sport Medicine (ACSM) (24,25).

The Muscle-strength exercise is considered by ACSM a gold standard, of high evidence (level A) of exercise-type recommended to older populations (24). In the case of our study, we chose to use a more economical solution, strength training with elastic bands, which recent literature points to similarly satisfactory results for this type of population, when compared to a group of elderly people who performed traditional strength training using dumbbells, free weights and machines (26). The CME was considered of moderate evidence, level C. However, our SR presented results that can be considered as contradictory to what is presented by the ACSM, since it evidences the CME as the one that most impacts on the overall health of the older person (25). However, we should consider that our SR of study 2 clearly was displayed that this type of training has benefits for the older classified as (pre)frailty or with low physical-functional fitness, while the ACSM guidelines does not fit the different classifications of the older population.

Our option was to select two types of exercise program (CME and CSE) and integrate them in chair-based exercise, that literature points out as appropriate to integrate with the conventional methods of exercise prescription in the older-frail individuals (27). Subsequently, we tested the hypothesis that the different types of program would present different results in the modeling of the different variables included in the intervention. Taking into account the overall outcomes of the three different intervention studies (10, 11 and 12) and when compare the impact of different exercise programs the results showed similar findings. This can be justified by some aspects. First, we verified that two exercise programs had the same average exercise intensities. However, looking at the heart rate behaviour during the different programs, the graphs obtained through the measurement of the MME training showed a curve that characterizes the exercise program as extensive interval training, that is, there were variations of effort with peaks of moderate intensity moments of medium-low intensity.

In the muscle-strength elastic bands exercises, the interposition of the graphs clearly assumed an interval design, with peaks of moderate-high intensity, followed by moments of very low-intensity of active and passive recovery. In this case, the mean of the results obtained in the monitoring of HR masks these results. The other reason that justify the similarities of results was the percentage of exercise adherence in the CME and CSE programs was similar. Both exercise programs were conducted by experienced professionals, who assisted in the design and development of more attractive types of programs for this type of population. In addition, the exercise programs were conducted in the very places where the elderly lived, characterizing the interventions as 'naturalistic' controlled trial. These strategies seem to have positively influenced the satisfactory adherence to both exercise programs (28,29).

Another relevant aspect that seems to have influenced the similarity of the results achieved may be related to the fact that one of the main components of the CME was the integration of neuromuscular strength exercises with body weight, which seems to have promoted similar adaptations to the CSE or traditional strength programs, according recent findings. Looking at the results we can observe that the CME also obtained satisfactory results also in the improvements of upper and lower body strength. In spite of similarities of the findings, it appears that multimodal exercise program was able to promote a slightly more pronounced impact on steroid sex hormone markers, improvements of the immune profile, and also triggered substantial alterations in stress hormones when compared to the CSE program. However, the CSE program promoted slight higher benefits in the functional-physical fitness, physical frailty and psychological well being variables. The two programs were equally effective for the variables of physical function associated with disabilities.

Despite the different results presented in the intervention studies, we could see that: i) different types of physical exercise positively influenced the improvement of levels of physical activity (independent component of PF) and muscular endurance (*2 minute step test)* of the participants, which may be related to an improvement in subjective perception of fear of falling and proficiency in daily life activities; ii) the improvement of the physical performance outcomes mentioned above and the scores of the muscular strength test seem to have influenced attitudes toward aging, global self-esteem and general self-efficacy, which the previous studies already reporting correlations through physiological well-being and some physical-functional fitness components; ii) although not directly assessed the social interaction component promoted by both exercise programs, may have a positive influencing on the improvement of emotional well-being and mood state of participants, since similar results were not shown in the non exercising controls.

Overall, this study highlighted the benefits of regular exercise in terms of physical-functional fitness improvment, dimished sedentary behaviour, reversed frailty status, increased psychological well-being and cognitive status, as well as knowledge on the response of biochemical makers of neuroendocrine and immune systens. However, the exercise frequency of 2-3 times per week, using an integrated pediodization model as a form of organizing long-term exercise programs, with special attention for adherence and control of effort, seems to be an effective solution. The findings could provide evidence suggesting the need to augment the standard exercise practice prescribed at nursing homes for the frail older population. It is expected that the findings of this research will guide clinical practice in centers for social and health support, so that physicians togheter with physiotrapeuts, exercise specialists and policymakers can provide more evidence based practice for the management of institutionalized older people. It is also critical to highlight the importance of considering the possibility of integrating different types of frailty assessments to detect frailty and their main correlated dimensions. Despite the proven robustness of Fried's construct, our study demonstrated that some psychological, biological, and behavioral dimensions seem to have an equal or greater contribution to frailty. In this sense, multidimensional assessement is recommended.

14.3 General limitations

Although this PhD thesis presented a well-defined topic of study and a logic sequence of different studies, we did find several methodological limitations. Notwithstanding the study limitations described earlier in chapter one of this thesis, we have outlined some limitations that were during the development of the study. Contrary to our expectations, adherence to exercise programs was satisfactory. As already predicted, we did not obtain authorization to transport the elderly to the FCDEF laboratory facilities to perform of anthropometric and physical fitness assessment. Then, we set up the physical assessements stations in each institution. In addition, exercise programs were also conducted on-site, as previously mentioned and predicted. Considering the characteristics of the populations and the outcomes measurements, we observed great variability among the different study variables especially in the biochemical of salivary and blood makers.

Comparing our study with the international literature, we found similar results for some variables. However, studies with higher samples of the population in question (in the case of the cross-sectional studies), would solve the problem of intra-individual variability in some markers. This increase in the initial study sample would have increase the number of participants in the exercise intervention study design. Additional limitations were the few cross-sectional studies performed in institutionalized settings, that made it impossible for us to perform significant and strong comparisons with them. Lastly, the small sample sizes of the trials, despite the application of power calculation, limited the strength of the conclusions.

14.4 Directions for the future studies

Based on our cross-sectional studies as a pilot trial, we can recommend future studies that extend to the older populations (e.g. hospitalization, community, social vulnerability). In addition, a longitudinal design that focuses in the study of the time-life course, starting at age 40 and above (middle-age) may produce clues about how the physical Frailty phenotype develops across the time. This was the maximal recommendation from the World Health Organization Scientific Committee on the International Conference on Frailty and Sarcopenia 2017 (Barcelona). Exercise as adjunctive therapy may be combined with other therapies (e.g. Supplementation) to improve its beneficial effects, and these are also studies that need further implementation.

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ANNEXES

Essential elements of research activities

ANNEX I:

CONSENT FORMS

Termo de consentimento dirigido à Instituição

Obrigado por ter demonstrado interesse neste projecto. Por favor leia cuidadosamente esta folha informativa antes de decidir participar. Desde já agradecemos a sua adesão, no entanto não existirá qualquer tipo de desvantagem se a sua decisão for contrária e agradecemos de qualquer modo, o facto de ter ponderado a sua participação. Em qualquer altura poderá abandonar este projecto sem qualquer desvantagem. Este projecto de estudo insere-se no âmbito das Ciências do Desporto e tem por objectivo verificar se diferentes programas de exercício físico moderado são capazes de modificar o "ambiente" hormonal em idosos e se se correlacionam com variáveis cognitivas, imunes e de stress, podendo o exercício funcionar como um factor protector contra as doenças crónicas próprias do envelhecimento.

Ao integrar este projecto, será pedido aos participantes que autorizem a recolha de amostras de sangue venoso, saliva, medidas corporais, o preenchimento de vários questionários destinados a avaliar o seu nível de stress, a realização de vários testes de cognição, testes de avaliação funcional/condição física e dados biográficos. Todos os dados recolhidos serão confidenciais e só a equipa de avaliação terá acesso a eles. Os resultados deste projecto poderão ser publicados mas jamais permitirão a identificação de qualquer elemento. Se for o seu desejo os responsáveis pelo projecto prontificam-se a disponibilizar os resultados obtidos. Os dados recolhidos serão armazenados em segurança e só os que foram mencionados poderão ter acesso a eles. No final todas as informações recolhidas serão destruídas, excepto aquelas que por política de investigação tenham implicações relativamente às conclusões deste projecto, que serão armazenadas em segurança. Se tiver dúvidas acerca do projecto agora ou no futuro não hesite em colocá-las aos responsáveis do projecto.

O investigador responsável: Doutora Ana Maria Teixeira
e-mail: ateixeira@fcdef.uc.pt

Termo de consentimento

Li a folha de informação relativa a este projecto e compreendi o seu âmbito e o que a participação nele envolve. Todas as minhas dúvidas foram esclarecidas. Compreendi que posso pedir informações adicionais em qualquer altura.

Sei que:

1. a participação é totalmente voluntária.
2. posso abandonar o projecto em qualquer altura sem qualquer desvantagem.
3. os dados recolhidos serão destruídos quando o projecto terminar, excluindo aqueles dados necessários para sustentar as conclusões do estudo que serão conservados em segurança.
4. sei os riscos que envolvem a recolha de dados prevista.
5. os resultados deste estudo poderão ser publicados mas o anonimato será preservado.

Concordo em participar neste estudo

....

(assinatura) (data)

Este estudo foi previamente aprovado pelo Comitê Multidisciplinar de Ética da Faculdade de Ciências do Desporto e Educação Física da Universidade de Coimbra, integrado numa linha de pesquisa denominada PRO-HMECSI: Mediação hormonal do exercício no estresse, cognição e imunidade [FCT-PTDC/DTP-DES/0154/2012].

Termo de Consentimento dirigido ao participante ou ao seu responsável

Obrigado por ter demonstrado interesse neste projecto. Por favor leia cuidadosamente esta folha informativa antes de decidir participar. Desde já agradecemos a sua adesão, no entanto não existirá qualquer tipo de desvantagem se a sua decisão for contrária e agradecemos de qualquer modo, o facto de ter ponderado a sua participação. Em qualquer altura poderá abandonar este projecto sem qualquer desvantagem. Este projecto de estudo insere-se no âmbito das Ciências do Desporto e tem por objectivo verificar se diferentes programas de exercício físico moderado são capazes de modificar o "ambiente" hormonal em idosos e se se correlacionam com variáveis cognitivas, imunes e de stress, podendo o exercício funcionar como um factor protector contra as doenças crónicas próprias do envelhecimento.

Ao integrar este projecto, ser-lhe-á pedido que autorize a recolha de amostras de sangue venoso, saliva, medidas corporais, o preenchimento de vários questionários destinados a avaliar o seu nível de stress, a realização de vários testes de cognição, testes de avaliação funcional/condição física, recolha de sangue, saliva, utilização de suplementação alimentar específica (ver autorização corpo médico) e recolha dos dados biográficos. Todos os dados recolhidos serão confidenciais e só a equipa de avaliação terá acesso a eles. Os resultados deste projecto poderão ser publicados mas jamais permitirão a identificação de qualquer elemento. Se for o seu desejo os responsáveis pelo projecto prontificam-se a disponibilizar os dados individuais ao próprio. Os dados recolhidos serão armazenados em segurança e só os que foram mencionados poderão ter acesso a eles. No final todas as informações recolhidas serão destruídas, excepto aquelas que por política de investigação tenham implicações relativamente às conclusões deste projecto, que serão armazenadas em segurança. Se tiver dúvidas acerca do projecto agora ou no futuro não hesite em colocá-las aos responsáveis do projecto.

O investigador responsável: Doutora Ana Maria Teixeira
e-mail: ateixeira@fcdef.uc.pt

Termo de consentimento

Li a folha de informação relativa a este projecto e compreendi o seu âmbito e o que a participação nele envolve. Todas as minhas dúvidas foram esclarecidas. Compreendi que posso pedir informações adicionais em qualquer altura.

Sei que:

1. a participação é totalmente voluntária.
2. posso abandonar o projecto em qualquer altura sem qualquer desvantagem.
3. os dados recolhidos serão destruídos quando o projecto terminar, excluindo aqueles dados necessários para sustentar as conclusões do estudo que serão conservados em segurança.
4. sei os riscos que envolvem a recolha de dados prevista.
5. os resultados deste estudo poderão ser publicados mas o anonimato será preservado.

Concordo em participar neste estudo

....

(assinatura) (data)

SE NÃO FOR O PRÓPRIO A ASSINAR POR IDADE OU INCAPACIDADE

(se o participante tiver discernimento deve também assinar em cima, se consentir)

NOME: …

BI/CC N.º: .... DATA OU VALIDADE ….. /..… /…......

GRAU DE PARENTESCO OU TIPO DE REPRESENTAÇÃO: ....

ASSINATURA …

Este estudo foi previamente aprovado pelo Comitê Multidisciplinar de Ética da Faculdade de Ciências do Desporto e Educação Física da Universidade de Coimbra, integrado numa linha de pesquisa denominada PRO-HMECSI: Mediação hormonal do exercício no estresse, cognição e imunidade [FCT-PTDC/DTP-DES/0154/2012].

ANNEX II:

TEST BATTERIES

QUESTIONARIO BIOSSOCIAL — QBIOS

1	**Nome completo:**____
2	**Qual a sua idade?** _____
3	**Sexo** 1. Masculino 2. Feminino
4	**Estado civil:** 1.Solteiro 2. Casado/união de fato 3.Viúvo 4.Separado/divorciado
5	**Escolaridade:** 1.Nunca frequentou a escola 2.Não completou Primário 3.Primário 4.Preparatório 5.Secundário 6.Ensino profissional 7.Universitário
6	**Naturalidade (Concelho):** ______________________________
7	**Residência (Concelho):** ________________________________
8	**Onde vive atualmente?** 1.Casa própria 2.Lar 3.Casa dos filhos 4.Casa dos parentes
9	**Pratica exercício físico/ginástica de manutenção/ginásio?** 1. Sim 2.Não
10	**Qual a frequência semanal?** 1.Uma vez 2.Duas vezes 3.Três vezes 4.Quatro vezes ou mais

AVALIAÇÃO DA CONDIÇÃO GLOBAL DE SAÚDE

Índice de comorbilidade de Charlson — ICC-p

(Mourão, 2008; Charlson et al., 1987)

Instruções para preenchimento: Marcar com uma cruz caso seja acometido por uma ou mais destas doenças ou condições clínicas listadas em baixo:

☐	**1**	Enfarte do Miocárdio
☐	**2**	Insuficiência Cardíaca
☐	**3**	Doença Arterial Periférica
☐	**4**	Doença Cerebrovascular (AVC)
☐	**5**	Demência
☐	**6**	Doença Respiratória Crónica
☐	**7**	Doença do Tecido Conjuntivo
☐	**8**	Úlcera Gastroduodenal
☐	**9**	Hepatopatia Crónica Leve
☐	**10**	Diabetes
☐	**11**	Hemiplegia
☐	**12**	Insuficiência Renal Crónica Moderada/Severa
☐	**13**	Diabetes com Lesão em Órgãos Alvo
☐	**14**	Tumor ou Neoplasia Sólida
☐	**15**	Leucemia
☐	**16**	Linfoma
☐	**17**	Hepatopatia Cronica Moderada/Severa
☐	**18**	Tumor ou Neoplasia
☐	**19**	Sida definida
☐	**20**	___________________________________

Mini Avaliação do Estado Nutricional

(Loureiro, 2008; Guigoz et al., 1997)

MNA-p

I	**Avaliação antropométrica**
1	Índice de Massa Corporal (IMC)
	0 = IMC <19 · 1 = 19<IMC <21 · 2 = 21<IMC <23 · 3 = IMC> 23
2	Perímetro Médio Braquial (PMB em cm)
	0,0 = PMB <21 · 0,5 = 21<PMB <22 · 1,0 = IMC> 22
3	Circunferência da perna (CP em cm)
	0 = CP <31 · 1 = CP> 31
4	Perda ponderal (PP) nos últimos 3 meses
	0 = PP> 3 Kg · 1 = não sabe · 2 = PP entre 1 e 3 Kg · 3 = Sem PP
I	**Avaliação Global**
5	O doente vive independentemente (em contraponto de viver num lar)?
	0=Sim · 1=Não
6	O doente toma mais de 3 medicamentos prescritos (por dia)?
	0=Sim · 1=Não
7	Nos últimos dois meses o doente foi vítima de stresse psicológico ou doença aguda?
	0=Sim · 1=Não
8	Mobilidade
	0= Limitado a uma cadeira ou cama · 1= Consegue sair da cama/ cadeira, mas não sai à rua · 2=Sai à rua
9	Problemas neuropsicológicos?
	0=Demência severa ou depressão · 1=Demência ligeira · 2= Sem problemas psicológicos
10	Tem úlceras de pressão ou escaras?
	0=Sim · 1=Não
III	**Avaliação dietética**
11	Quantas refeições completas o utente come por dia?
	0= 1 Refeição · 1= 2 Refeições · 2=3 Refeições
12	O utente consome:
12.1	Pelo menos um porção de laticínios por dia? · 0=sim · 1=Não
12.2	Duas ou mais porções de feijão/grão, ovos por semana? · 0=sim · 1=Não
12.3	Carne, peixe ou aves diariamente? · 0=sim · 1=Não
	0,0= 0 ou 1 resposta for sim · 0,5= 2 Respostas sim · 1,0 3 respostas sim
13	Consome duas ou mais porções de fruta ou vegetais diariamente?
	0=Sim · 1=Não

14	A ingestão alimentar do utente foi reduzida nos últimos 3 meses devido anorexia, problemas digestivos ou dificuldades de deglutinação	
	0=Anorexia Severa 1=Anorexia Moderada 2= Sem anorexia	☐
15	Quantos copos/chávenas de bebida (água, sumo, café, chá, leite, cerveja, vinho) o utente consome por dia?	
	0,0=Menos de 3 copos 1=3 a 5 copos 2= Mais de 5 copos	☐
16	Modo de se alimentar	
	0=Alimenta só com ajuda 1=Alimenta-se sozinho mas com dificuldade 2=alimenta-se sozinho, sem problemas	☐
18	O doente considera ter algum problema nutricional?	
	0=malnutrição *major* 1=não sabe/malnutrição moderada 2= Sem problema nutricional	☐
18	Em comparação com pessoas da mesma idade, como é que o doente considera seu estado de saúde?	
	0,0= Não tão bom 1,0 = Tão bom 0,5 = Não sabe 2,0 = Melhor	☐

Questionário de sintomas do Trato Respiratório Superior **URTI-p**

Por favor indica a severidade dos teus sintomas nas últimas 24 horas, fazendo um círculo em cada sintoma

	Não tive este sintoma	Muito ligeiramente	Ligeiramente		Moderada		Severa	
	0	1	2	3	4	5	6	7
Corrimento nasal								
Nariz entupido								
Espirros								
Dor de garganta								
Garganta arranhada/ irritada								
Tosse								
Rouquidão								
Dor de cabeça								
Peito congestionado								
Sensação de cansaço								

Avaliação das Atividades Independentes da vida diária **ADL-p**

I	**Lavar-se**
	1. Toma banho sem necessitar de qualquer ajuda.
	2. Precisa apenas de ajuda para lavar uma parte do corpo.
	3. Precisa de ajuda para lavar mais do que uma parte do corpo, ou para entrar ou sair do banho.
II	**Vestir-se**
	1. Escolhe a roupa e veste-se por completo, sem necessitar de ajuda.
	2. Apenas necessita de ajuda para apertar os sapatos.
	3. Precisa de ajuda para escolher a roupa e não se veste por completo.
III	**Utilizar a sanita**
	1. Utiliza a sanita, limpa-se e veste a roupa, sem qualquer ajuda. Utiliza o bacio durante a noite e despeja-o de manhã, sem ajuda.
	2. Precisa de ajuda para ir à sanita, para se limpar, para vestir a roupa e para usar o bacio, de noite.
	3. Não consegue utilizar a sanita sozinho (a).
IV	**Mobilizar-se**
	1. Entra e sai da cama, senta-se e levanta-se sem ajuda.
	2. Entra e sai da cama e senta-se e levanta-se da cadeira, com ajuda.
	3. Não se levanta da cama.
V	**Ser continente**
	1. Controla completamente os esfíncteres anal e vesical, não tendo perdas.
	2. Tem incontinência ocasional.
	3. É incontinente ou usa sonda vesical necessitando de vigilância.
VI	**Alimentar-se**
	1. Come sem qualquer ajuda.
	2. Necessita de ajuda só para cortar os alimentos ou para barrar o pão.
	3. Necessita de ajuda para comer, ou é alimentado parcial ou totalmente, por sonda ou por via endovenosa

Avaliação das atividades Instrumentais da vida diária **IADL-p**

I	**Capacidade para usar o telefone:**
	1. Utiliza o telefone por iniciativa própria; procura e marca números, etc.
	2. Marca alguns números que conhecem bem.
	3. Atende o telefone mas não marca números.
	4. Não usa o telefone
II	**Fazer compras:**
	1. Consegue fazer as compras de que necessita sozinho
	2. Compra sozinho(a) pequenas coisas.
	3. Necessita de ser acompanhado para qualquer compra
	4. Incapaz de fazer compras.
III	**Preparar refeições:**
	1. Planeia, prepara e serve refeições adequadas, sozinho.
	2. Prepara refeições adequadas se possuir ingredientes necessários.
	3. Aquece, serve e prepara refeições mas não mantém uma dieta adequada.
	4. Necessita de refeições preparadas e servidas.
IV	**Cuidar da casa**
	1. Cuida da casa só ou com ajuda ocasional (exemplo: "trabalho doméstico pesado")
	2. Realiza tarefas diárias como lavar a louça ou fazer a cama
	3. Realiza tarefas domésticas diárias mas não mantém um nível aceitável de limpeza
	4. Necessita de ajuda em todas as tarefas domésticas
	5. Não participa em nenhuma tarefa doméstica
V	**Lavar a roupa:**
	1. Lava toda a sua roupa
	2. Lava pequenas peças de roupa
	3. É incapaz de lavar a sua roupa
VI	**Modo de transporte:**
	1. Desloca-se em transportes públicos ou viatura própria
	2. Não usa transportes públicos, exceto táxi
	3. Desloca-se em transportes públicos quando acompanhado
	4. Desloca-se utilizando táxi ou automóvel quando acompanhado por outro
	5. Incapaz de se deslocar
VII	**Responsabilidade pela própria medicação:**
	1. Toma a medicação nas doses e horas corretas
	2. Toma a medicação se preparada e separada por outros
	3. É incapaz de tomar a medicação
VIII	**Habilidade para lidar com o dinheiro:**
	1. Sozinho resolve problemas monetários como: passar cheques, pagar a renda
	2. Lida com compras do dia-a-dia mas necessita de ajuda para efetuar compras maiores
	3. Incapaz de lidar com o dinheiro

Avaliação do risco de quedas

FES-p

Abaixo estão indicadas várias tarefas. À frente delas encontra-se uma linha (0-10) que mede o grau de confiança, ou seja, o medo que você tem de cair na execução destas tarefas. Marque na linha com uma cruz o grau de confiança que sente ao executar esta tarefa.

1	**Vestir e despir-se**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
2	**Preparar uma refeição ligeira**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
3	**Tomar uma banho ou um duche**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
4	**Sentar/levantar da cadeira**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
5	**Deitar/ levantar da cama**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
6	**Atender a porta ou o telefone**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
7	**Andar dentro de casa**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
8	**Chegar aos armários**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
9	**Trabalho doméstico ligeiro (Limpar pó, fazer cama, lavar louça)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
10	**Pequenas compras**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

As próximas questões referem-se ao tempo em que esteve fisicamente activo/a nos **últimos 7 dias**. Pense nas actividades que desenvolve na sua actividade profissional, nas suas deslocações, nas actividades referentes aos trabalhos em casa, no jardim ou no quintal/campo e nas actividades que efectuou no seu tempo livre para recreação ou prática de Exercício Físico. As suas respostas são muito importantes! Por favor, responda a todas as questões, mesmo que não se considere uma pessoa fisicamente activa.

Ao responder às questões considere o seguinte:

- **Actividades Físicas Vigorosas** referem-se a actividades que requerem um esforço físico intenso e que fazem ficar com a respiração ofegante;
- **Actividades Físicas Moderadas** referem-se a actividades que requerem esforço físico moderado e tornam a respiração um pouco mais forte que o normal.

Ao responder às questões considere apenas as Actividades Físicas que realizou durante pelo menos **10 minutos seguidos.**

Q1 Nos últimos 7 dias, em quantos dias fez actividades físicas **VIGOROSAS**, pelo menos 10 minutos seguidos, como por exemplo, correr, fazer ginástica aeróbica, jogar futebol, andar de bicicleta a um ritmo rápido, transportar objectos pesados, fazer trabalhos pesados em casa, no jardim ou no quintal/campo, como cavar, ou qualquer outra actividade que fez aumentar **MUITO** a sua respiração ou batimentos do coração?

☐☐ Dias

Q2 Nos dias em que fez actividades físicas **VIGOROSAS**, durante quanto tempo, no total, realiza essas actividades?

☐☐ Horas ☐☐ Minutos

Q3 Nos últimos 7 dias, em quantos dias fez actividades físicas **MODERADAS,** pelo menos 10 minutos seguidos, como por exemplo, dançar, andar de bicicleta a um ritmo normal, transportar objectos leves, fazer trabalhos em casa, no jardim ou no quintal/campo, como aspirar, varrer, cuidar das plantas, ou qualquer outra actividade que fez aumentar **MODERADAMENTE** a sua respiração ou batimentos do coração? Por favor não inclua o "Caminhar".

☐☐ Dias

Q4 Nos dias em que faz actividades físicas **MODERADAS**, durante quanto tempo, no total, realiza essas actividades?

☐☐ Horas ☐☐ Minutos

Q5 Nos últimos 7 dias, em quantos dias **CAMINHOU** pelo menos 10 minutos seguidos**,** em casa, no trabalho, como forma de deslocação, por lazer, por prazer ou como forma de Exercício Físico?

☐☐ Dias

Q6 Nos dias em que **CAMINHOU**, quanto tempo, no total, costuma caminhar por dia?

☐☐ Horas ☐☐ Minutos

Q7 Num dia normal, dos últimos 7 dias, quanto tempo passa **SENTADO**? Isto pode incluir o tempo que passa sentado a uma secretária, a conversar com amigos, a ler, a estudar, a descansar ou a ver televisão.

☐☐ Horas ☐☐ Minutos

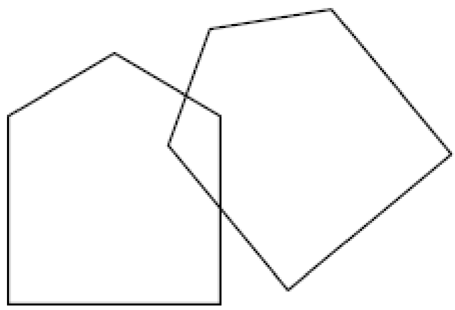
Avaliação da Fragilidade Física
(Furtado, Teixeira & Ferreira, 2014); Fried, 2001)

AFF-p

Instruções para preenchimento: um aplicador externo conduz os testes, respeitando a forma de avaliação de cada dimensão. Todavia, é valido recorrer aos arquivos médicos, caso alguma questão suscite dúvidas no seu preenchimento. Cada dimensão deverá passar pelo ajustamento estatístico para posterior cálculo do traço de fragilidade. Ver apêndice do estudo original	
1	**Lentidão da marcha:** Ao sinal o participante deve percorrer a distância de a distância de 4,6 metros em velocidade confortável num terreno plano, utilizando técnica de caminhada. Executar 3 tentativas para posterior cálculo da média dos valores, que deverão ser registrados em segundos: 1ª __________ 2ª __________ Média ____________
2	**Perda de peso não intencional:** perguntar ao participante a seguinte questão: Você perdeu 4 quilos ou mais de peso corporal de forma não intencional neste último ano? (ou valor acima de 5% do peso corporal, segundo registro médico). Duas opções de resposta: 1. Sim 2. Não
3	**Força muscular:** utilizando o teste de força de preensão manual, mensurar e registar a força no membro superior dominante. Executar 3 tentativas para posterior cálculo da média dos valores, que deverão ser registrados em quilos: Lado: Direito_____ Esquerdo_____ 1ª FPM_______ 2ª________ 3ª FPM_______ FPM (total)_______
4	**Exaustão (perceção subjetiva):** Fazer as 2 perguntas abaixo (7 e 20 CES-D) ao participante e verificar a concordância negativa ou positiva entre elas: a) Senti que tudo do que fazia era um esforço: Sim_______ Não_______ b) Senti falta de energia: Sim_______ Não_______
5	**Avaliação dos níveis de atividade física:** Aplicar o questionário IPAQ versão curta, que se encontra abaixo. Ler atentamente as questões antes de iniciar a aplicação.

	Mini Exame do Estado Mental	MMSE-p
I	**Orientação** (Um ponto por cada resposta certa)	
1	Em que ano estamos?___________	
2	Em que mês estamos?___________	
3	Em que dia do mês estamos?___________	
4	Em que dia da semana estamos?__________________________	
5	Em que estação do ano estamos?__________________________	
6	Em que país estamos?____________________	
7	Em que distrito vive?____________________________________	
8	Em que terra vive?______________________________________	
9	Em que casa estamos? ___________________________________	
10	Em que andar estamos? __________________________________	
		Pontos:___________
II	**Retenção** (contar um ponto por cada palavra corretamente repetida)	
11	"Vou dizer três palavras; queria que as repetisse, mas só depois que eu as dizer todas, procure sabê-las de cor":	
	(**PÊRA – GATO – BOLA)**	
		Pontos:___________
III	**Atenção e cálculo** (um ponto por cada resposta correta. Se der uma errada mas depois continuar a subtrair, consideram-se as seguintes como corretas. Pára ao fim de 5 respostas)	
12	"Agora peço-lhe que me diga quantos são 30 menos 3 e depois ao número encontrado voltar a tirar 3 e repete assim até eu dizer para parar" 30__27___24___21___18___15____	
		Pontos:___________
IV	**Evocação** (um ponto por cada resposta correta)	
13	"Veja se consegue dizer as 3 palavras que pedi há pouco para decorar" (Pêra – Gato – Bola)	
		Pontos:___________

V	**Linguagem** (um ponto por cada resposta correta)
14	"Como se chama isto?" Mostrar os objetos: **Relógio e lápis** **Pontos:**____________
15	"Repita a frase que eu vou dizer: "O RATO ROEU A ROLHA" **Pontos:**___________
16	"Quando eu lhe der esta folha, pegue nela com a mão direita, dobre-a ao meio e coloque-a sobre a mesa", (ou "sobre a cama", se for o caso); dar a folha, segurando com as duas mãos. **a) Pega com a mão direita; b) Dobra ao meio; c) Coloca onde deve** **Pontos**____________
17	"Leia o que está neste cartão e faça o que lá diz". Mostrar um cartão com a frase bem legível, **"FECHE OS OLHOS**"; sendo analfabeto lê-se a frase. *Fechou os olhos* **Pontos**____________
18	"Escreva uma frase inteira aqui". Deve ter sujeito e verbo e fazer sentido; os erros gramaticais não prejudicam a pontuação. **Frase:**____ **Pontos**____________
VI	**Habilidade construtiva** (um ponto pela cópia correta do desenho)
19	Deve copiar um desenho. Dois pentágonos parcialmente sobrepostos; cada um deve ficar com 5 lados, dois dos quais intersectados. Não valorizar tremor ou rotação.

Desenho	**Cópia**
	

Pontos____________

Atitudes Face ao Envelhecimento

AAQp-2

Este questionário se refere a forma como se sente em relação ao envelhecer. Por favor, responda todas as questões. Se não se sente seguro a respeito da resposta a uma questão, escolha aquela que lhe parece mais apropriada. Muitas vezes, esta pode ser a primeira ideia que lhe surge. Por favor, tenha em mente seus valores, esperanças, prazeres e preocupações. Pedimos que pense na sua vida em geral.

Por exemplo, pensando como seria de modo geral, uma pergunta poderia ser:

Eu não gosto de envelhecer

Nada verdadeiro	**Pouco verdadeiro**	**Mais ou menos verdadeiro**	**Extremamente verdadeiro**
1	**2**	**3**	**4**

Para responder, deve circular o número que melhor descreva o quanto concorda com esta afirmação. Por favor, leia atentamente todas as afirmações, reflita sobre o que sente e assinale na escala a sua resposta.

Agora responda as questões abaixo, assinalando o quanto você concorda com cada uma das afirmações. As questões referem-se às pessoas idosas de uma forma geral.

1 À medida que as pessoas envelhecem são mais capazes de lidar com a vida.

Nada verdadeiro	Pouco verdadeiro	Mais ou menos verdadeiro	Extremamente verdadeiro
1	2	3	4

2 É um privilégio envelhecer.

Nada verdadeiro	Pouco verdadeiro	Mais ou menos verdadeiro	Extremamente verdadeiro
1	2	3	4

3 A velhice é um tempo de solidão.

Nada verdadeiro	Pouco verdadeiro	Mais ou menos verdadeiro	Extremamente verdadeiro
1	2	3	4

4 A sabedoria vem com a idade.

Nada verdadeiro	Pouco verdadeiro	Mais ou menos verdadeiro	Extremamente verdadeiro
1	2	3	4

5 Há muitas coisas prazerosas no envelhecer.

Nada verdadeiro	Pouco verdadeiro	Mais ou menos verdadeiro	Extremamente verdadeiro
1	2	3	4

6	**A velhice é um período depressivo da vida.**			
	Nada verdadeiro 1	Pouco verdadeiro 2	Mais ou menos verdadeiro 3	Extremamente verdadeiro 4
7	É importante fazer exercício em qualquer idade.			
	Nada verdadeiro 1	Pouco verdadeiro 2	Mais ou menos verdadeiro 3	Extremamente verdadeiro 4
8	**Envelhecer tem sido mais fácil do que pensava.**			
	Nada verdadeiro 1	Pouco verdadeiro 2	Mais ou menos verdadeiro 3	Extremamente verdadeiro 4
9	**À medida que envelheço tenho mais dificuldade em falar sobre os meus sentimentos.**			
	Nada verdadeiro 1	Pouco verdadeiro 2	Mais ou menos verdadeiro 3	Extremamente verdadeiro 4
10	**À medida que envelheço aceito-me cada vez mais a mim próprio(a).**			
	Nada verdadeiro 1	Pouco verdadeiro 2	Mais ou menos verdadeiro 3	Extremamente verdadeiro 4
11	**Não me sinto velho(a).**			
	Nada verdadeiro 1	Pouco verdadeiro 2	Mais ou menos verdadeiro 3	Extremamente verdadeiro 4
12	**Vejo a velhice principalmente como um período de perda.**			
	Nada verdadeiro 1	Pouco verdadeiro 2	Mais ou menos verdadeiro 3	Extremamente verdadeiro 4
13	**A minha identidade não é definida pela minha idade.**			
	Nada verdadeiro 1	Pouco verdadeiro 2	Mais ou menos verdadeiro 3	Extremamente verdadeiro 4
14	**Tenho mais energia do que esperava ter na minha idade.**			
	Nada verdadeiro 1	Pouco verdadeiro 2	Mais ou menos verdadeiro 3	Extremamente verdadeiro 4
15	**Estou a perder a minha independência física à medida que fico mais velho(a).**			
	Nada verdadeiro 1	Pouco verdadeiro 2	Mais ou menos verdadeiro 3	Extremamente verdadeiro 4

16	**Problemas com a minha saúde física não me impedem de fazer o que quero.**			
	Nada verdadeiro 1	Pouco verdadeiro 2	Mais ou menos verdadeiro 3	Extremamente verdadeiro 4
17	**À medida que me torno mais velho(a) encontro maior dificuldade em fazer novos amigos.**			
	Nada verdadeiro 1	Pouco verdadeiro 2	Mais ou menos verdadeiro 3	Extremamente verdadeiro 4
18	**É muito importante transmitir a minha experiência aos mais jovens.**			
	Nada verdadeiro 1	Pouco verdadeiro 2	Mais ou menos verdadeiro 3	Extremamente verdadeiro 4
19	**Acredito que a minha vida foi relevante.**			
	Nada verdadeiro 1	Pouco verdadeiro 2	Mais ou menos verdadeiro 3	Extremamente verdadeiro 4
20	**Agora que estou mais velho(a), não me sinto envolvido(a) na sociedade.**			
	Nada verdadeiro 1	Pouco verdadeiro 2	Mais ou menos verdadeiro 3	Extremamente verdadeiro 4
21	**Quero ser um bom exemplo para os mais jovens.**			
	Nada verdadeiro 1	Pouco verdadeiro 2	Mais ou menos verdadeiro 3	Extremamente verdadeiro 4
22	**Sinto-me excluído(a) de algumas coisas, devido à minha idade.**			
	Nada verdadeiro 1	Pouco verdadeiro 2	Mais ou menos verdadeiro 3	Extremamente verdadeiro 4
23	**A minha saúde está melhor do que esperava para a minha idade.**			
	Nada verdadeiro 1	Pouco verdadeiro 2	Mais ou menos verdadeiro 3	Extremamente verdadeiro 4
24	**Procuro manter-me tão em forma e ativo(a) quanto possível, fazendo exercício.**			
	Nada verdadeiro 1	Pouco verdadeiro 2	Mais ou menos verdadeiro 3	Extremamente verdadeiro 4

Avaliação Autoestima Global

RGSE-p

	Para cada item faça uma cruz sobre o retângulo que corresponde à conceção de valor que tem por si próprio(a):	Concordo Plenamente	Concordo	Discordo	Discordo Plenamente
1	**No geral, estou satisfeito comigo mesmo.**				
2	**Por vezes penso que não sou nada bom (a).**				
3	**Sinto que tenho um bom número de qualidades.**				
4	**Estou apto(a) para fazer coisas tão bem como a maioria das pessoas.**				
5	**Sinto que não tenho muito de que me orgulhar.**				
6	**Sinto-me por vezes inútil.**				
7	**Sinto que sou uma pessoa de valor, pelo menos num plano de igualdade com os outros.**				
8	**Gostava de ter mais respeito por mim mesmo(a).**				
9	**Em termos gerais estou inclinado(a) a sentir que sou um(a) falhado(a).**				
10	**Eu tomo uma atitude positiva perante mim mesmo(a).**				

Avaliação Autoeficácia Geral percecionada **GSEE-p**

	Para cada item faça uma cruz sobre o retângulo que corresponde à conceção de valor que tem por si próprio(a):				
		De modo nenhum é verdade	Dificilmente é verdade	Moderadamente verdade	Exatamente Verdade
1	Eu consigo resolver sempre os problemas difíceis se eu tentar bastante.				
2	Se alguém se opuser, eu posso encontrar os meios e as formas de alcançar o que eu quero.				
3	É fácil para mim, agarrar-me às minhas intenções e atingir os meus objetivos.				
4	Eu estou confiante que poderia lidar, eficientemente, com acontecimentos inesperados.				
5	Graças ao meu desembaraço, eu sei como lidar com situações imprevistas.				
6	Eu posso resolver a maioria de problemas se eu investir o esforço necessário.				
7	Eu posso manter-me calmo ao enfrentar dificuldades porque eu posso confiar nas minhas capacidades para enfrentar as situações.				
8	Quando eu sou confrontado com um problema, geralmente eu consigo encontrar diversas soluções.				
9	Se eu estiver com problemas, geralmente consigo pensar em algo para fazer.				
10	Quando tenho um problema pela frente, geralmente ocorrem-me várias formas para resolvê-lo.				

Perceção face ao estresse

(Mota-Cardoso, 2002)

PSS-14

Para cada questão, pedimos que indique com que frequência se sentiu ou pensou de determinada maneira, **durante o último mês**. Apesar de algumas perguntas serem parecidas, existem diferenças entre elas e deve responder a cada uma como perguntas separadas. Responda de forma rápida e espontânea. Para cada questão, escolha a alternativa que melhor se ajusta à sua situação.

QN: Quase nunca	N: Nunca	PV: Por vezes	AF Com alguma frequência	MF: Muito frequente

1	Com que frequência tem ficado chateado pelo facto de ocorrer um acontecimento inesperado?					
2	Com que frequência tem sentido a sensação de ser incapaz de controlar as coisas importantes na sua vida?					
3	Com que frequência se tem sentido nervoso(a) ou stressado(a)?					
4	Com que frequência tem lidado com sucesso com os problemas e com as contrariedades do dia-a-dia?					
5	Com que frequência se tem sentido efetivamente envolvido(a) nas alterações importantes que ocorrem na sua vida?					
6	Com que frequência se tem sentido confiante acerca da sua capacidade de lidar com os seus problemas?					
7	Com que frequência tem sentido que as coisas lhe estão a correr como queria?					
8	Com que frequência tem sentido que é incapaz de dar resposta a tudo aquilo que tem para fazer?					
9	Com que frequência tem sido capaz de controlar situações irritantes na sua vida?					
10	Com que frequência tem sentido que tem as coisas sob controlo?					
11	Com que frequência se tem sentido irritado/ chateado por coisas que estão fora do seu controlo?					
12	Com que frequência tem dado consigo a pensar sobre as coisas que tem para fazer?					
13	Com que frequência tem sido capaz de controlar o modo como gasta o seu tempo?					
14	Com que frequência tem sentido que as dificuldade se estão a acumular tanto que será incapaz de as superar?					

Escala de avaliação da Depressão
(Gonçalves & Fagulha, 2003)

CES-Dp

Nesta página encontra uma lista das maneiras como se pode ter sentido ou reagido durante a última semana. Faça uma cruz no quadrado que se identifica com os seus sentimentos tendo em conta que as opções significam:

		Nunca ou muito raramente	Ocasional mente	Com alguma frequência	Com muita frequência ou sempre
Durante a semana passada…					
1	Fiquei aborrecido com coisas que habitualmente não me aborrecem.				
2	Não me apeteceu comer; estava sem apetite.				
3	Senti que não consegui livrar-me da neura ou da tristeza, mesmo com a ajuda dos amigos ou da família.				
4	Senti que valia tanto como os outros.				
5	Tive dificuldades em manter-me concentrado no que estava a fazer				
6	Senti-me deprimido.				
7	Senti que tudo do que fazia era um esforço.				
8	Senti-me confiante no futuro.				
9	Pensei que a minha vida tinha sido um fracasso.				
10	Senti-me com medo.				
11	Dormi mal.				

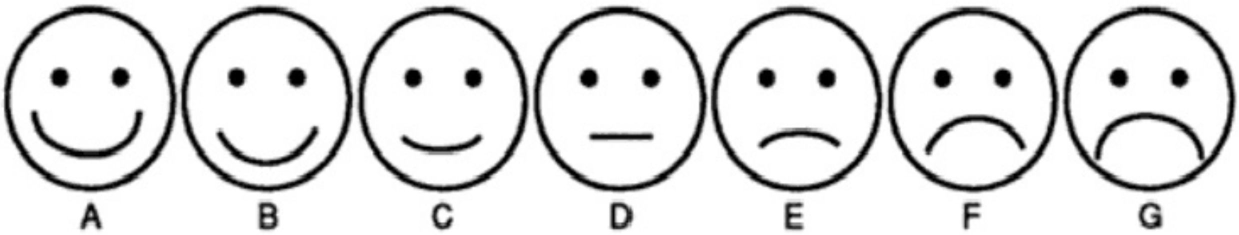
12	Senti-me feliz.				
13	Falei menos do que o costume.				
14	Senti-me sozinho.				
15	As pessoas foram desagradáveis ou pouco amigáveis comigo				
16	Senti prazer ou gosto na vida.				
17	Tive ataques de choro.				
18	Senti-me triste.				
19	Senti que as pessoas não gostavam de mim.				
20	Senti falta de energia.				

Escala das "caras" para avaliação da felicidade

FSHA-p

(Ribeiro & Matos, 2012)

Instruções: Aqui estão várias "caras" que representam alguns sentimentos. Por baixo de cada uma está uma letra. Qual das caras expressa melhor a forma como se sente (em relação à sua vida de modo geral)?



Avaliação da satisfação de vida — **SWL-p**

DT:	D:	DL:	N:	CL:	C:	CT:
Discordo Totalmente	Discordo	Discordo Ligeiramente	Nem Concordo nem Discordo	Concordo Ligeiramente	Concordo	Concordo Totalmente

		DT	D	DL	N	CL	C	CT
S1.	Na maioria dos aspetos a minha vida está próxima do ideal							
S2.	As condições em que decorre a minha vida são excelentes							
S3.	Estou satisfeito com a vida							
S4.	Até agora obtive a coisa mais importante que queria na vida							
S5.	Se pudesse viver de novo a minha vida, não mudaria quase nada							

ANNEX III:

PUBLISHED ARTICLES

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Physical frailty and cognitive status over-60 age populations: A systematic review with meta-analysis

Guilherme Eustáquio Furtado[a,g,*], Adriana Caldo[a,g], Taís Rieping[b,g], Edith Filaire[d,e,f,g], Eef Hogervorst[c,g], Ana Maria Botelho Teixeira[a,g], José Pedro Ferreira[a,g,*,1]

[a] Research Unit of Physical Activity and Sport at Faculty of Sport Sciences and Physical Education (CIDAF, UID/PDT/04213/2016) – University of Coimbra, Portugal
[b] Laboratory of Sport and Exercise Psychology of Faculty of Sport Sciences and Physical Education of University of Coimbra, Portugal
[c] School of Sport, Exercise and Health Sciences, Loughborough University, United Kingdom
[d] CIAMS, University Paris-Sud, Université, Paris-Saclay, 91405, Orsay Cedex, France
[e] CIAMS, Université d'Orléans, 45067, Orléans, France
[f] Research Team ECRIN, INRA, UMR 1019, Clermont-Ferrand, France
[g] Medical Psychology Unit, School of Medicine, Clinical Neuroscience and Mental Health, University of Porto, Al. Prof. Hernâni Monteiro, 4200-319, Porto, Portugal

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ABSTRACT

The aim of this meta-analysis was to analyse the magnitude of the effect-size of the cognitive status of populations over 60 years of age, when comparing nonfrail versus pre-frail and nonfrail versus frail subgroups. A systematic review of prospective studies published from 2000 to 2017 was completed in Medline, B-on, Ebsco, Ebsco Health, Scielo, ERIC, LILACS and Sport discus databases and observational, cohort and cross-sectional studies were selected. The Mini-Mental State Examination to screening cognitive status and the Fried phenotype for assess physical frailty state was used as clinical outcomes. After applying additional search criteria, 14 manuscripts (26,798 old participants) were selected from an initial universe of 1681 identified. When comparing the scores of cognitive status of the participants who were non-frail (n = 12,729, 47.4%) versus pre-frail (n = 11,559, 43.2%) and non-frail versus frail (n = 2452, 9.4%) subgroups, significant statistical differences were found for both comparisons (M ± SD = 0.60, 95%CI: 0.50-0.62, $p < 0.001$ and M ± SD = 3.43, 95%CI: 2.26–4.60, $p < 0.001$, respectively). It is clear that poor cognitive function is strongly closed associated with pre-frailty and frailty subgroups in older populations around the world.

1. Introduction

Increasing functional health status in older adults across the life has been given more attention in the last decade (WHO, 2012), including both cognitive and physical functioning. Cognitive status refers to all fundamental mental skills that regulate humans' lifestyles, such as instrumental daily life activities and complex behaviours (Carlson et al., 2009). An older age has been shown to be a risk factor for early dementia and age-related cognitive decline in specific areas, such as episodic memory (Misiak et al., 2013), with a third to half of the older adults in Europe complaining of cognitive impairment (CI), a possible precursor of early dementia (Verdelho et al., 2011). Recently, studies have found that older people with lower physical function, called the Physical Frailty syndrome (PFS), were more likely to develop CI (Buchman & Bennett, 2013; Gray et al., 2013). However, conversely, individuals with IC can also enter a spiral of early physical-functional decline, e.g. through engaging in less activity because they feel less secure and/or because a common co-factor (e.g. dementia pathology) driving both CI and apraxia (the inability to perform learned activities and routines) (Brigola et al., 2015; Panza et al., 2015; Ruan et al., 2015).

PFS is thought to be highly prevalent in old age, particularly in those with low education and those of low socioeconomic status (Guessous et al., 2014). According to Fried's model, the phenotype of clinical PFS is characterized by a critical mass of three or more "core frail components" which are: i) weight loss > 10 lbs in past year, ii) weak grip strength (lowest quintile), iii) exhaustion (by self-report), iv) slow gait speed (lowest quintile) and v) low physical activity (lowest quintile) (Fried et al., 2001). Likewise, Ensrud in 2007 identified the physical frailty phenotype as having the following components: i)

* Corresponding authors at: Research Unit of Physical activity and Sport at Faculty of Sport Sciences and Physical Education (CIDAF, UID/PDT/04213/2016), Estádio Universitário – Pavilhão III, Santa Clara, 3040-156, Coimbra, Portugal.
E-mail addresses: furts2001@yahoo.com.br (G.E. Furtado), jpferreira@fcdef.uc.pt (J.P. Ferreira).
[1] President of International Federation of European Adapted Physical Activity.

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diminished levels of physical activity ii) unintentional weight loss, iii) self-rated fatigue, as also identified by impaired hand grip strength and low performance in gait speed (Ensrud et al., 2007).

While these criteria have mainly physical components, Campbell and Buchner (1997) measured PFS by incorporating specific physical and cognitive tests, comprising i) grip strength, ii) chair stand, iii) submaximal treadmill performance, iv) 6 min walking test, v) static Balance Test, vi) body mass index (to assess weight loss), vii) arm muscle area (to assess sarcopenia, the muscle loss associated with frailty) but also viii) Mini-Mental State Examination (MMSE) to assess cognitive impairment (Campbell & Buchner, 1997; Folstein, Folstein, & McHugh, 1975). These multiple tests thus assess both physiological and psychological/cognitive functioning to allow for identification of specific areas of potential disability, which could perhaps be targeted by specific interventions (Brigola et al., 2015). However, because of its ease of application, the Fried model has been widely disseminated in several studies around the world (Theou et al., 2015).

Whether only one or several assessments are useful in the diagnoses of PFS is important for the complexity and cost of screening (Hamaker et al., 2012). For instance, according to some criteria, mental or cognitive impairment is a crucial factor for PFS and this would need to be assessed using objective instruments (Panza et al., 2015). On the other hand, PFS may also be an early indicator for possible later dementia (Gray et al., 2013). One study showed that at post-mortem, Alzheimer Disease brain pathology was associated with PFS both in people with and without dementia (Buchman et al., 2013).

Epidemiological studies demonstrate the interconnection between physical frailty and cognitive performance. However, longitudinal studies show this relationship and the emergence of cognitive changes, cognitive impairment and dementia to be associated with an increased risk of frailty status in older populations. Some systematic reviews have been carried out in order to clarify this association (Brigola et al., 2015; Panza et al., 2015; Ruan et al., 2015). However, a recent review of cross-sectional data used meta-analysis, comparing the means scores of MMSE among pre-frail and frail sub-groups, but omitted the non frail group data (Furtado, Teixeira, & Ferreira, 2017). The present paper, in order to complement this systematic review with metanalysis (SM) and to clarify the magnitude of effect size in mean cognitive status investigated frail, pre frail and non frail subgroups using the Fried of Physical Frailty Protocol.

2. Methods

2.1. Data sources

This work followed a pre-determined and published protocol available in PROSPERO 2017: number registration CRD42017057360 (Furtado, Caldo et al., 2017). The search was conducted in English language (published or in press) in the following databases: Medline, B-on, Ebsco, Ebsco Health, Scielo, ERIC, LILACS and Sportdiscus databases, with access made between December of 2016 and July of 2017, using the advanced meta-search option in which original articles of epidemiological studies of cross-sectional, observational, cohort and population-based published between 2000-2017. Key Medical Subject Headings (MeSH) and search indexed descriptors were used to refine the data search (Huang, Névéol, & Lu, 2011): (((“frail elderly” [MeSH Terms] OR “frail” [MeSH Terms]) AND “cognition” [MeSH Terms]) OR ([mild cognitive impairment]] AND “frail older adults” [MeSH Terms]) OR “frail older adults” [MeSH Terms] AND “[mini-mental State examination or MMSE]” AND “Fried criteria” AND “Frailty Phenotype AND “Phenotype of Fried. Studies done in the last 17 years, with samples of people over 60 years of age of both genders, who were not hospitalized samples were selected. The data source strategy included also additional terms related to indexed descriptors such as ‘Fried criteria’, ‘Fried Phenotype of Frailty’ and ‘Fried Phenotype’.

2.2. Central criteria of selected studies

The search was further limited by selecting articles including the Fried’s model to assess frailty status and Mini-Mental State Examination (MMSE) to assess cognitive status. The PFS Phenotype was developed by Linda Fried and collaborators (Fried et al., 2001). After consecutive studies on older adults samples, they identified five dimensions which translated into five criteria to operationalize PFS. Weight loss was assessed by self-reporting, targeting unintentional weight loss of four kilograms or more in the last six months or a loss of 5% of total body weight in the three months prior to the assessment date. Self report exhaustion was evaluated by negative concordance of questions number 7 and 20 of the Centre of Epidemiologic Studies in Depression scale. Weakness was analyzed using the handgrip strength test, adjusted for gender/body mass index. Slowness was measured using the 4.6 m walking test, which results are expressed in seconds and adjusted for gender/height. Low PA levels were assessed using the Minnesota Questionnaire - short version. The positive evaluation in one or two negative criteria classified the participants as pre-frail, in three or more as frail and as non-frail or robust, when the subject had none of the FS five criteria (Fried et al., 2001).

The MMSE is an instrument composed by 30 questions, and is able to assess the cognitive profile based on the evaluation of six areas of cognition: orientation, immediate recall, attention, calculation, delayed recall, and language (Han, Lee, & Kim, 2014; Mungas, 1991). It is a continuous score, ranging from 0 to 30 points (pts) and according to the criteria established in several studies, the following cut-off values that classify individuals (categorical scores) on cognitive profiles are: a) severe cognitive impairment (from 1 to 9 pts); b) moderate cognitive impairment (10 to 18 pts) mild cognitive impairment (19 to 24 pts), d) normal cognitive status (25 pts and above) (Folstein, Folstein, & McHugh, 1975).

2.3. Exclusion criteria

The exclusion criteria of the present study comprised the elimination of all articles that did not meet the initial selection criteria (include both MMSE and FPS), had poorly defined dimensions, did not report MSSE scores as mean and standard deviation, examination of middle-aged adults was omitted. Extended or congress abstracts, systematic reviews, book chapters, letters to editor, short surveys, study protocols, and interventional studies were also excluded.

2.4. Data extraction

The initial search to create the present study was carried out by two independent research assistants, who were trained in SM methods. Each research assistant performed the independent-blindly search and at the end of the work, the principal research was conducted a short briefing to assess the level of agreement of the search procedures. All titles and abstracts of identified articles were screened and the full-text articles were assessed for potential inclusion by the principal investigator and any conflicts that arose were reviewed until an agreement was reached. For the final selection of the articles we included all based-population studies, according to the FS subgroups non-frail, pre-frail and frail (as a categorical variable) as well as compare the mean scores of the MMSE results (as a continuous variable), according to the aforementioned subgroups.

2.5. Quality assessment (QA)

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement for the organization of this study was followed (Panic et al., 2013). PRISMA describes the four stages (identification, screening, eligibility, final selection) needed to perform the search and selection of manuscripts under a SM, and feature the graphic option to draw a flowchart (Liberati et al., 2009). At the same time, the PRISMA presents the PICOS acronym ('patient, problem or population', 'intervention', 'comparison, control or comparison', 'outcomes'), which directs the refinement of the systematic search, making the process more effective (Panic et al., 2013). In addition to this method, we chose to use the Strengthening Reporting of Observational studies in Epidemiology (STROBE) Positioning Statement, that the characterization of each assessed item has been described in detail elsewhere (Malta et al., 2010). This method consists of a checklist comprising 22 items, which characterizes a manuscript based on the quality assessment that it presents. In this study, we used a STROBE combined model of study designs, which is specifically assesses observational, epidemiological, population-based, cross-sectional or cohort studies (Abeysena, 2011). After applying the above criteria we attributed to the total score of the 22 items a value of 100%. The purpose of this procedure was not to use an established cut-off point to enter/or not enter the meta-analysis. Instead, the percentage value was used to identify studies in which low quality assessment could interfere with the results of the SM.

2.6. Statistical analysis

The results are expressed by calculating the values of the standardized mean and standard deviation (M ± SD) differences in MMSE scores when comparing the subgroups of NFvsPF and NFvsF, as well as their respective variance, confidence intervals (CI:95%), the magnitude of the effect size and levels of statistical significance, which was set at $p \leq 0.05$ (Batterham & Hopkins, 2006). The global M ± SD of the studies included in this review were calculated based on the random effects model, including the assumption of heterogeneity of the studies and their participants. The risk of publication bias was assessed by the method of visual inspection method of the scatter plot generated by the Egger's intercept test (Egger et al., 1997). This graphic assumes a format of an 'inverted funnel plot' inserted by a midline, with analogue display of points representing the studies included in the graphical analysis (Sterne, Egger, & Smith, 2001). Heterogeneity was measured using the Chi square, Cochran's Q, the Higgin I squared (I^2) and Tau square tests (T^2), assuming that a $T^2 > 1$ suggests presence of substantial statistical heterogeneity. In terms of I^2 test analysis, the percentage of the variance attributed to the heterogeneity of the study, ranges from low ($25\% < I^2 < 50\%$) to high ($I^2 > 75\%$) (Egger et al., 1997). If the Q test is statistically significant (set at $p < 0.05$) there is also evidence of heterogeneity. The SM was performed using the statistical program Comprehensive Meta-Analysis – Version 3.0 (Bax et al., 2007).

3. Results

3.1. Data search

Fig. 1 shows the paths covered for final studies selection that were later included in the meta-analysis. The initial search identified 1681 potentially eligible papers. After excluding articles following a review of titles and abstracts, replication and others reasons, such as systematic reviews and intervention studies, 149 full-text articles were examined in the screening stage. After applying the central criteria to the studies, 56 papers were advanced for the eligibility phase. From the eligibility stage, criteria such as presentation of MMSE scores as a categorical variable and treating the physical frailty as a continuous variable, as well as studies carried out with the same database, were the most common reason for papers exclusion. In total, 20 studies were included after quality analysis and six studies were excluded.

3.2. Characteristics of studies and participants

Table 1 shows the 14 epidemiological studies were included for data quantitative meta-analysis. The 14 studies included for final data analysis have a total sample of 26,798 participants which came from 11 different countries, with mean and their respective standard deviation of ages varying between 61.8 (1.4) to 87.5 (5.4) years old. Overall, the sample included 12,729 (47.4%) non-frail, 11,559 pre-frail (43.2%) and 2452 (9.4%) frail individuals. A total of 10 studies had samples from both genders (Abizanda et al., 2013; Al-Kuwaiti, Aziz, & Blair, 2015; Avila-Funes et al., 2009; Han et al., 2014; Kiely, Cupples, & Lipsitz, 2009; Macuco et al., 2012; Ottenbacher et al., 2009; Robertson et al., 2014; Tay et al., 2016; Yassuda et al., 2012), but only the study carried out by Sook-Han and colleagues presented a separate analysis performed by gender (Han et al., 2014). Three studies included female participants (Alencar et al., 2013; Furtado, Caldo et al., 2017; Samper-Ternent et al., 2008) and one study included only older men (Jacobs et al., 2011).

As we see in Table 2, four types of epidemiological studies were found: Three longitudinal (Avila-Funes et al., 2009; Ottenbacher et al., 2009; Samper-Ternent et al., 2008), four cohort (Abizanda et al., 2013; Alencar et al., 2013; Jacobs et al., 2011; Tay et al., 2016), six cross-sectional (Al-Kuwaiti et al., 2015; Furtado, Caldo et al., 2017; Han et al., 2014; Macuco et al., 2012; Robertson et al., 2014; Yassuda et al., 2012) and one observational study (Kiely et al., 2009). Study designs and full details are summarized in Table 1. The cognitive status measured by MMSE was assumed as the central outcome in 11 studies (Alencar et al., 2013; Al-Kuwaiti et al., 2015; Avila-Funes et al., 2009; Han et al., 2014; Jacobs et al., 2011; Kiely et al., 2009; Macuco et al., 2012; Ottenbacher et al., 2009; Robertson et al., 2014; Samper-Ternent et al., 2008; Yassuda et al., 2012) and as a co-variate in three studies (Abizanda et al., 2013; Furtado, Caldo et al., 2017; Tay et al., 2016). All of the included papers used a version of Fried's model and their respective five components were used to create frail sub-groups. However, the study conducted by Laura Tay and collaborators (Tay et al., 2016) did not have the three frailty subgroups and the main investigator decided to introduce it only in the statistical analyses that compared the non-frail versus frail individuals.

When looking to the mean scores of cognitive performance in the PFS subgroups and taking into account the cut-off values of the cognitive status by MMSE, In all studies the frail subgroup was classified as having cognitive impairment (MMSE lower 24 pts), expect for studies carried out in France (Avila-Funes et al., 2009), United States (Kiely et al., 2009) and Ireland (Robertson et al., 2014). In the pre-frail subgroup, a total of 7 studies (USA, South Korea, Brazil, Portugal, Mexico and United Arab Emirates) also presented the same cut-of values to classified participants as a cognitive impairment (Alencar et al., 2013; Al-Kuwaiti et al., 2015; Furtado, Patrício et al., 2017; Han et al., 2014; Macuco et al., 2012; Ottenbacher et al., 2009; Yassuda et al., 2012).

3.3. Magnitude of effect size

Regarding the central hypothesis of this SM, we attempted to assess whether the frailty subgroups, non-frail versus pre-frail (NFvsPF) and non-frail *versus* frail (NFvsF) differed in mean and standard deviation scores for cognitive performance. The results showed that the global effects of MMSE mean and standard deviation differences were statistically significant for both NFvsPF (M ± SD = 0.60, 95%CI: 0.50-0.62, $p < 0.001$) and NFvsF (M ± SD = 3.43, 95%CI: 2.26–4.60, $p < 0.001$) comparisons. The results of Z-values test scores showed that we may reject the null hypothesis as the frail subgroups-effect was not associated with cognitive performance) in both comparisons (NFvsPF, Z = 18.31 and NFvsF, Z = 5.73) (Fig. 2).

3.4. Homogeneity effects

To determine whether the observed variation fell within the interval assigned to the error of the studies sample and to test the null hypothesis according to which all the studies involved in this SM share a magnitude of common effects, the Cochran`s Q test (Q) was used. If all studies share the same magnitude of effects, the expected value of Q

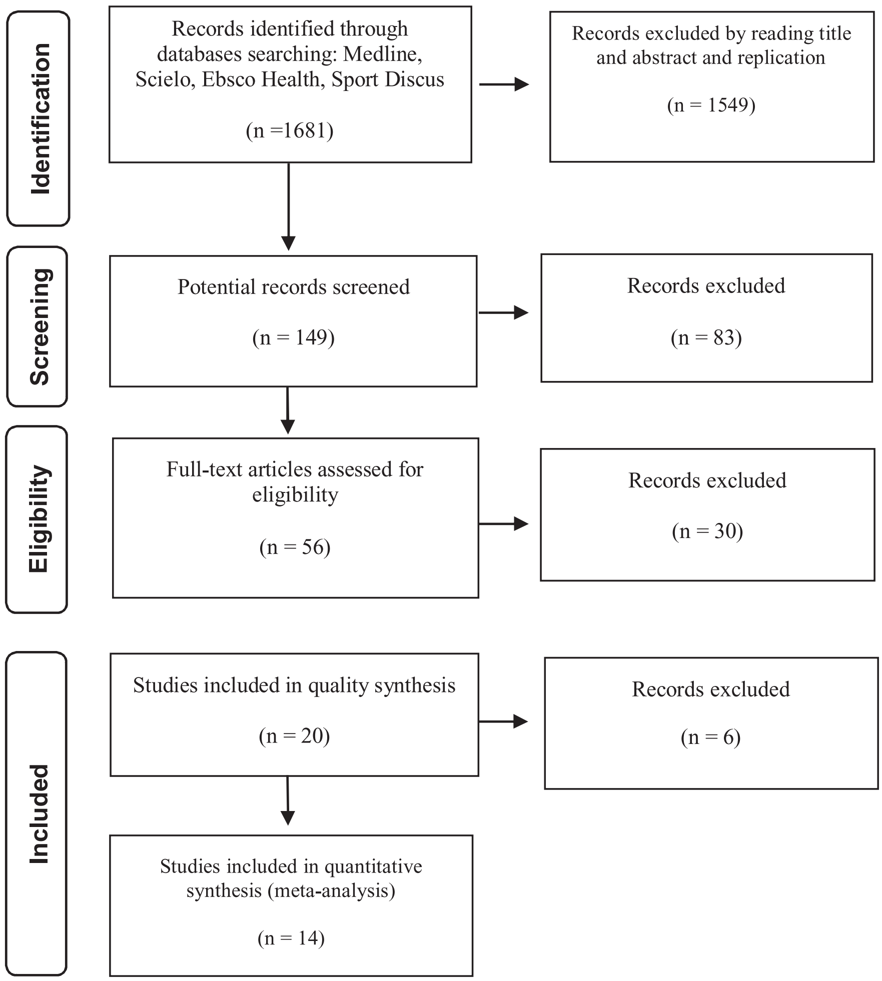


Fig. 1. Flow diagram of studies selection according PRISMA guidelines (Panic et al., 2013).

would be equal to the degrees of freedom, i.e., the number of studies minus 1. The value obtained from Q test for both comparisons were 857.820, with 14° of freedom (NFvsF) and 417.520, with 13° of freedom (NFvsPF). In both comparisons the values were statistical significant ($p < 0.001$) accepting the alternative hypothesis, i.e., the true magnitude of the effect varies from study to study.

The statistics of I^2 corresponded to the ratio of the real heterogeneity of the total variation of the observed effects, that is, it tells us what proportion (percentage) of the observed variance reflects the differences in the true magnitude of the effect rather than in the error of the sample(Dinnes et al., 2005). The obtained value of $I^2 = 98.368$ (NFvsF) and 96.886 (NFvsPF) which means that about 98.40% of the variance reflects the true effects. The Tau squared (T^2) values correspond to the variance of the true effect sizes among studies which were in the current SRM, 4.92 (NFvsF) and 0.54 (NFvsPF).

Table 1
Quality assessment scores of selected studies based on the STROBE check-list.

Items (paper sessions)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	100%	22
1. (Abizanda et al., 2013)	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	95%	21
2. (Alencar et al., 2013)	0	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	86%	19
3. (Avila-Funes et al., 2009)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	100%	22
4. (Furtado, Caldo et al., 2017; Furtado, Patrício et al., 2017; Furtado, Teixeira et al., 2017)	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	95%	21
5a. (Han et al., 2014)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	100%	22
5b. (Han et al., 2014)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	100%	22
6. (Jacobs et al., 2011)	0	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	91%	20
7. (Kiely et al., 2009)	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	95%	21
8. (Robertson et al., 2014)	0	1	1	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	1	1	1	86%	19
9. (Samper-Ternent et al., 2008)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	95%	21
11. (Al-Kuwaiti et al., 2015)	0	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	91%	20
12. (Macuco et al., 2012)	0	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	86%	19
13. (Ottenbacher et al., 2009)	0	1	1	1	1	1	1	0	0	1	1	1	0	1	1	1	1	1	1	1	1	1	82%	18
14. (Yassuda et al., 2012)	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	1	1	1	0	1	82%	18
15. (Tay et al., 2016)	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	1	91%	20
Median of total scores																							**92%**	**20**

Table 2
Characteristics of select studies following the PICOS statement (Panic et al., 2013).

Author's study	Country of Samples population	Sex	Age (M ± SD)	Study Method	Frailty Subgroups samples distribution (100%)			Mini-mental scores by Frailty subgroups (M ± SD)			Central outcomes	Main goal
					Non-frail n (%)	Pre-frail n (%)	Frail n (%)	Non-frail	Pre-frail	Frail		
1. Abizanda et al. (2013)	Albacete, Spain	M/F	79,4 ± 6,4	Cohort	n = 993 168 (16.9%)	482 (48.5%)	286 (22.8%)	26.61 (3.23)	24.92 (4.91)	22.31 (5.52)	Physical Frailty, morality, disability and activities of daily living	To analyse whether frailty implies increased risk of death and incident disability.
2. Alencar et al. (2013)	Belo Horizonte, Brazil	F	78,37 ± 7,2	Cohort	n = 160 47 (23.7)	112 (54.1)	48 (23.2)	24.02 (4.03)	21.11 (5.99)	17.02 (5.43)	Physical Frailty, cognitive status, hospitalization and death	Evaluate associations between frailty status and cognitive decline as well as the incidence of cognitive impairment over 12-month period.
3. Avila-Funes et al. (2009)	3 cities, France	M/F	74,1 ± 5,2	Longitudinal	n = 6030 2738 (45.4)	2871 (47.6)	421 (7)	27.51 (1.93)	27.42 (1.93)	26.91 (2.01)	Physical Frailty, mortality incidence, disability and cognitive profile	To determine whether adding cognitive impairment to frailty improves its predictive validity for adverse health outcomes.
4a. Han et al. (2014)	25 cities, South	M	68,1 ± 5,4	Cross-sectional	n = 4294 2200 (51.2)	1719 (40.3)	375 (8.7)	26.10 (2.93)	24.42 (3.21)	21.53 (5.11)	Physical Frailty and cognitive abilities	To analyse Association between frailty and cognitive disorder in community people.
4b. Han et al. (2014)	25 cities, South Korea	F	64,8 ± 3,72	Cross-sectional	n = 6094 2593 (42.5)	2894 (47.4)	607 (10.1)	23.81 (3.92)	21.73 (4.54)	18.61 (5.72)	Physical Frailty and cognitive abilities	To analyse association between frailty and cognitive disorder
5. Jacobs et al. (2011)	Jerusalem, Israel	M	87,5 ± 5,4	Cohort	n = 834 206 (24.5)	470 (56)	164 (19.5)	28.21 (2.34)	27.01 (2.72)	22.22 (6.12)	Physical Frailty and cognitive status	To examine the association between frailty and cognitive impairment and the impact on 5-years survival
6. Kiely et al. (2009)	Boston, United States	M/F	78,1 ± 5,4	Observational	n = 760 389 (51.2)	295 (38.8)	76 (10)	27.31 (2.53)	26.78 (2.72)	25.39 (3.21)	Physical Frailty, falls, disability and hospitalization.	To validate two established frailty indexes and compare their ability to predict adverse outcomes
7. Robertson et al. (2014)	Dublin, Ireland	M/F	61,8 ± 1,4	Cross-Sectional	n = 4349 3115 (71.6)	1144 (26.3)	90 (2.1)	28.88 (1.52)	28.41 (1.82)	27.63 (2.23)	Physical Frailty and cognitive abilities	To explore the relationship between cognitive function and physical frailty syndrome.
8. Samper-Ternent et al. (2008)	Texas, United States	F	75,2 ± 5,8	Longitudinal	n = 1370 684 (49.9)	626 (45.7)	60 (4.4)	26.11 (2.97)	25.41 (3.22)	24.81 (3.05)	Physical Frailty and cognitive profile	Examine the association between frailty status and change in cognitive function over time
9. Al-Kuwaiti et al. (2015)	United Arab Emirates, Abudabi	M/F	65,6 ± 6,2	Cross-Sectional	n = 151 75 (46.9)	53 (33.1)	23 (14.4)	24.72 (1.52)	23.71 (2.64)	19.73 (3.88)	Physical Frailty	To determine the prevalence and correlates of frailty
10. Macuco et al. (2012)	São Paulo, Brazil	M/F	72,3 ± 5,8	Cross-Sectional	n = 384 142 (36.9)	211 (54.9)	31 (8.2)	24.56 (2.77)	23.63 (3.72)	20.52 (5.54)	Physical Frailty and cognitive status	To examine the association between frailty and cognitive functioning
11. Ottenbacher et al. (2009)	Texas, United Status	M/F	74.03 ± 6.4	Longitudinal	n = 777 191 (24.5)	425 (54.6)	161 (20.9)	21.71 (3.88)	21.87 (41.10)	19.14 (5.63)	Physical Frailty and cognitive performance.	We examined the prevalence of frailty and explored the correlates associated with disability and morbidity
12. Yassuda et al. (2012)	Sao Paulo, Brazil	M/F	72.3 ± 5.8	Cross-Sectional	n = 384 142 (36.9)	211 (54.9)	31 (8.2)	24.66 (3.78)	23.68 (3.76)	20.50 (5.55)	Physical Frailty and cognitive function.	To explore the relationship between cognitive function and frailty.

(continued on next page)

Table 2 (*continued*)

Author's study	Country of Samples population	Sex	Age (M ± SD)	Study Method	Frailty Subgroups samples distribution (100%)			Mini-mental scores by Frailty subgroups (M ± SD)			Central outcomes	Main goal
					Non-frail n (%)	Pre-frail n (%)	Frail n (%)	Non-frail	Pre-frail	Frail		
13. Furtado, Teixeira et al., 2017; Furtado, Caldo et al., 2017; Furtado, Patrício et al., 2017)	Coimbra, Portugal	F	81.96 ± 7.9	Cross-Sectional	n = 119 19 (15.9)	n = 46 (38.7)	n = 54 (45.4)	23.75 (3.98)	21.58 (4.84)	18.11 (5.17)	Physical Frailty and physical fitness	To explore the relationship between physical frailty and physical fitness
14. Tay et al. (2016)	Singapore, Southeast Asia.	M/F	76.6 ± 6.7	Cohort	n = 99 20 (20.2)	–	79 (79.8)	16.72 (3.76)	–	19.03 (5.11)	Physical Frailty and cognitive status	To examine the independent and combined effects of inflammation and endocrine dysregulation on baseline frailty status and frailty progression at one year

3.5. Publication bias

To assess hypothetical publication bias, we initially performed the visual inspection of the funnel plot, suggesting low evidence for publication bias. However, we used Egger intercept test and standard deviation (SD), Confidence interval (CI): n95% and degree of freedom (df) to test the null hypothesis according to which the intercept is equal to zero (Fig. 3). The result for NFvsF intercept comparison was 5.05 (SE = 2.96, CI:95% = −1.27-11.38, t = 1.72, df = 13 and p = 0.10) and for NFvsPF comparison the intercept comparison was 3.34 (SE = 2.05, CI:95% = −1.12-7.81, t = 1.63, df = 12 and p = 0.12). In the both comparisons the p value was not significant, indicating no strong evidence for publication bias.

4. Discussion

4.1. Frailty, age and gender

Regarding PFS and sex differences, the older literature points to a similar association between physical frailty and cognitive decline in both male and female older adults (Han et al., 2014). It is perhaps for this reason that many authors did not present the statistical analyses stratified for sex. However, findings in recent studies that used other PFS screen tools are unanimous in revealing a higher incidence of PFS in older women when compared to older men (Chang & Lin, 2015; Theou et al., 2011, 2015). Older men (with or without cognitive decline) have physical frailty associated with a higher incidence of mortality when compared to older women and such results were corroborated in 3 studies selected for this SM (Abizanda et al., 2015; Avila-Funes et al., 2009; Jacobs et al., 2011). In the present study, similar to occurred in a previous study (Furtado, Teixeira et al., 2017), it was not possible to explore sex-differences, since only the study carried out in South Korea presented statistical analysis by gender (Han et al., 2014). In fact, sex is one of the variables which influence may help us to explain the high heterogeneity found in this meta-analyses (Egger et al., 1997; Sterne et al., 2001). Frailty linked to cognitive decline is identified in the literature as having a strong relationship with advanced age, although this phenotypes may be able to manifest itself early as well. In the present SM the results showed that only studies carried out in Portugal (Furtado, Patrício et al., 2017) (81.96 ± 7.91) and Singapore (Tay et al., 2016) (76.6 ± 7.03) with a higher mean age showed more cognitive decline and similar distribution in the PFS subgroups. Contrariwise, the studies conducted in South Korea (Han et al., 2014) and United Arab Emirates (Al-Kuwaiti et al., 2015) presented the same frailty and cognitive characteristics but had lower mean ages for cognitive scores. Factors such as education, public policies to adopt an active and healthy lifestyle during the course of life and different eating habits from country to country may interfere and could be identified in a more in depth meta-analysis.

4.2. Frailty, cognition performance and assessments

PFS assessment is used to identify older populations at risk for adverse aging-related health indicators (Mohler et al., 2014). Recent reviews recognized more than 25 types of frailty screening tools among which the Fried´s and colleagues set is the most widely used (de Vries et al., 2011; Schwenk et al., 2014; Sieliwonczyk, Perkisas, & Vandewoude, 2014). The PFS comprises five components and this screen tool has been confirmed associated with subsequent health outcomes in a succession of studies drawn from a range of diverse older populations (Bouillon et al., 2013; Brigola et al., 2015). However, Fried´s model, which comprises physical frailty, had a strong interrelationship with cognitive state as assessed by MMSE (Alencar et al., 2013; Han et al., 2014; Robertson et al., 2014; Yassuda et al., 2012). As the MMSE assesses several cognitive domains, it might be useful to determine which individual experienced cognitive deficits are most

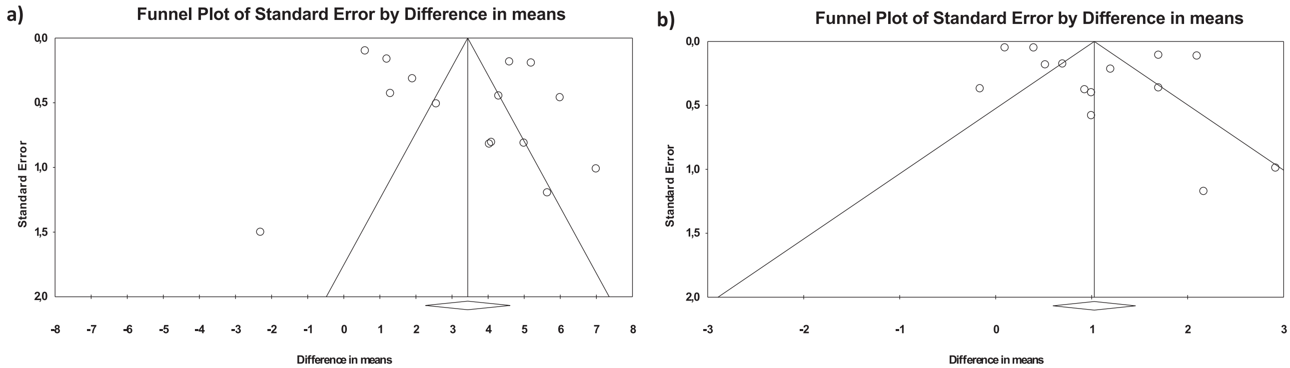
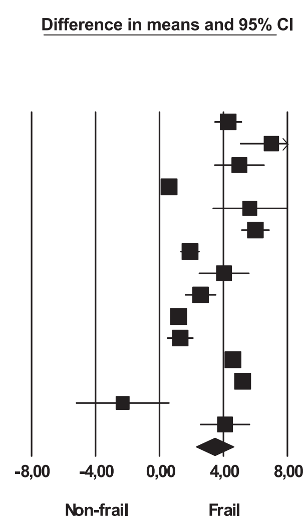


Fig. 2. Visual Funnel plot inspection associated to Egger's test. (a) Non-frail versus frail, (b) Non-frail versus pre-frail.

a)

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Abizanza et al. (2013)	4,300	0,448	0,201	3,421	5,179	9,593	0,000
Alencar et al. (2013)	7,000	1,012	1,024	5,016	8,984	6,916	0,000
Al-Kuwaiti et al. (2015)	5,000	0,813	0,662	3,406	6,594	6,147	0,000
Ávila-Funes et al. (2013)	0,600	0,100	0,010	0,404	0,796	5,989	0,000
Furtado et al. (2017)	5,650	1,198	1,434	3,303	7,997	4,718	0,000
Jacobs et al. (2011)	6,000	0,461	0,213	5,096	6,904	13,007	0,000
Kiely et al. (2008)	1,910	0,316	0,100	1,291	2,529	6,051	0,000
Macuco et al. (2012)	4,040	0,820	0,672	2,433	5,647	4,928	0,000
Ottenöacfter et al. (2009)	2,570	0,509	0,259	1,572	3,568	5,046	0,000
Robertson et al. (2014)	1,200	0,163	0,027	0,881	1,519	7,365	0,000
Samper et al. (2008)	1,300	0,429	0,184	0,460	2,140	3,032	0,002
Sook et al. (2014a)	4,600	0,185	0,034	4,237	4,963	24,862	0,000
Sook et al. (2014b)	5,200	0,194	0,038	4,820	5,580	26,824	0,000
Tay et al. (2016)	-2,300	1,502	2,256	-5,244	0,644	-1,531	0,126
Yassuda et al. (2012)	4,100	0,808	0,652	2,517	5,683	5,077	0,000
Global effect	3,435	0,599	0,359	2,262	4,609	5,737	0,000



b)

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Abizanza et al. (2013)	1,700	0,364	0,132	0,987	2,413	4,671	0,000
Alencar et al. (2013)	2,920	0,991	0,981	0,978	4,862	2,948	0,003
Al-Kuwaiti et al. (2015)	1,000	0,581	0,338	-0,139	2,139	1,720	0,085
Ávila-Funes et al. (2013)	0,100	0,051	0,003	0,001	0,199	1,970	0,049
Furtado et al. (2017)	2,170	1,174	1,378	-0,131	4,471	1,848	0,065
Jacobs et al. (2011)	1,200	0,217	0,047	0,774	1,626	5,525	0,000
Kiely et al. (2008)	0,520	0,184	0,034	0,160	0,880	2,832	0,005
Macuco et al. (2012)	0,930	0,378	0,143	0,188	1,672	2,458	0,014
Ottenöacfter et al. (2009)	-0,160	0,370	0,137	-0,886	0,566	-0,432	0,666
Robertson et al. (2014)	0,400	0,051	0,003	0,300	0,500	7,847	0,000
Samper et al. (2008)	0,700	0,177	0,031	0,353	1,047	3,955	0,000
Sook et al. (2014a)	1,700	0,108	0,012	1,488	1,912	15,697	0,000
Sook et al. (2014b)	2,100	0,114	0,013	1,876	2,324	18,372	0,000
Yassuda et al. (2012)	1,000	0,402	0,161	0,213	1,787	2,490	0,013
Global effect	0,565	0,031	0,001	0,505	0,626	18,313	0,000

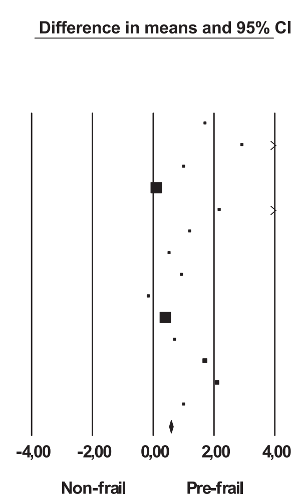


Fig. 3. Descriptive statistic of each study and global results of meta-analysis. (a) Non-frail versus frail, (b) Non-frail versus pre-frail.

significantly associated with frailty scores (Mungas, 1991). However, MMSE total score (rather than isolated cognitive ability screen tools) showed to be a better predictor of physical frailty scores (Abizanda et al., 2013; Avila-Funes et al., 2009). As the Fried construct seems to be the most used protocol for assessing the frailty phenotype, MMSE is the most widely used tool for assessing cognitive status, thus increasing the level of comparability with other studies (Vella Azzopardi et al., 2018).

4.3. Frailty subgroups and cognitive decline

The pattern of decreased cognitive performance in the comparisons of non-frail versus pre-frail and frail subgroups was found in all studies included in this meta-analysis, except in those carried out in Singapore (Tay et al., 2016), that showed higher MMSE values, i.e. better cognitive results in the frail subgroup. In the other comparisons, the mean differences in MMSE scores were always statistical significant. The results were recently confirmed when also comparing pre-frail and non-frail subgroups (Furtado, Teixeira et al., 2017). Various studies have confirmed the existence of cognitive decline in pre-frail and frail subgroups. However, according to our latest review of literature, this is the first study to statistically show the magnitude of the mean differences.

The strong evidence of communal physio-pathological chains is based on the occurrence of both physical frailty and decreased cognitive function involved in the same biopsychological systems (Gale et al., 2013). Recent findings suggest a severe loss of muscle (sarcopenia) and bone (osteopenia) mass as a common nutritional impairment in this population, causing cellular and molecular damage, reducing homeostatic reserves caused by mechanisms that are regulated by complex neuronal maintenance and repair networks (Chang et al., 2016). Cognitive Frailty, as it is known today, has become of major concern for public health, as a result of the increased incidence of many types of dementia (Panza et al., 2015), since it is characterized as a phenotype that represents large expenditures to health care systems (Macklai et al., 2013).

4.4. Study limitations

To the best of our comprehension this is the first analyses to systematically examine the interaction between physical frailty and cognition performance in the elderly population. Despite the high methodological quality of the studies included, this work has some limitations. It was not possible to perform a gender analysis, since only one of all the studies included presented the results according to the sex of the participants. The different criteria for the evaluation of frailty phenotype adopted by some researchers did not allow us to include more studies. Our results signify the importance of implementation of public policies to develop and improve non-pharmacological treatments (i.e. physical activity plus nutritional support) when evaluating physical impairments and their associations with cognitive decline to be used as a basis for health professionals decision-making.

5. Conclusion

Worse of physical frailty condition improves the predictive validity of the accepted currently definition of cognitive impairment, characterize as a low score of mini-mental cognitive test. The accuracy in the evaluation of cognitive functioning may help to well-define and characterize frailty associated to cognitive decline in older persons. This would be useful in expecting aging policies needs and to provide appropriate services to encouraged an active life style, aiming to large prevent the premature health decline effects in the old populations.

Conflicts of interest

The authors declare that they have no competing interests.

Contributors

Guilherme Furtado was a design and drafted the paper. Taís Rieping and Adriana Caldo helped with blinding data collection. José Pedro help analyzed, interpreted data and revised critically the manuscript. Eef Hogervorst did a critical revision of manuscript. Ana Teixeira and José Ferreira coordinated the research group. All the authors approved the final version of the manuscript.

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Physical Fitness and Frailty Syndrome in Institutionalized Older Women

Guilherme Furtado[1], Miguel Patrício[2], Marisa Loureiro[2], Ana Maria Teixeira[1], and José Pedro Ferreira[1]

Abstract

Associations between frailty and physical-functional fitness (PFF) indicators in frail women over 65 years of age remain largely unexplored. This study analyzed the relationship between frailty syndrome (FS) and PFF indicators and assessed how the latter might predict the former. Participants were 119 elderly women (81.96 ± 7.89 years) recruited from four social and healthcare centers. PFF was assessed through muscle strength tests of upper and lower limbs, endurance, agility-dynamic balance, flexibility, and body composition. The following FS indicators were assessed: weight loss, exhaustion, weakness, slowness, and low physical activity level. Significant correlations were found between FS and endurance, agility-dynamic balance, upper and lower limbs muscle strength tests. Comparitive analyses also revealed that, among FS groups, the frail subgroup performed significantly poorer on all PFF measures except body composition. Additionally, a receiving operating characteristics curve analysis revealed good diagnostic accuracy for predicting FS using the agility-dynamic balance test (Area Under Curve [AUC] = .82, 95% CI [0.74, 0.90]; sensitivity and specificity were 70.4% and 84.8% for the cutoff = 16.22 seconds). Accurately, the risk of frail condition (not pre-frail) increases about 2.12%

[1]Research Unit for Sport and Physical Activity (CIDAF) at Faculty of Sport Science and Physical Education (FCDEF), Coimbra, Portugal
[2]Laboratory of Biostatistics and Medical Informatics and IBILI, Faculty of Medicine, University of Coimbra, Coimbra, Portugal

Corresponding Author:
Guilherme Furtado, Faculty of Sports Science and Physical Education, University of Coimbra (FCDEF-UC), Estádio Universitário, Pavilhão III, Santa Clara 3040-156, Coimbra, Portugal.
Email: furts2001@yahoo.com.br

per second spent in this test. Thus, the agility-dynamic balance test is a promising tool for screening institutionalized older people for risk of FS.

Keywords
aging, development, physical development and measurement, motor skills, motor skills and ergonomics, balance, egonomics, frail older adults, physical fitness

Introduction

Frailty syndrome (FS) is a complex aging expression determined by ontogenetic and phylogenetic factors (Fried et al., 2001). Chronic stress has been shown to have immunosuppressive effects that accelerate aging and cause cumulative disorders in many physiological systems, resulting in a fragile state (Clegg & Trust, 2011). In FS, physiological reserve and defense functions decline (Fried et al., 2001), compromising the individual's capacity to withstand chronic biological stress (Afilalo et al., 2014) and leading to institutionalization or hospitalization, often followed by premature death (Lally & Crome, 2007). According to geriatric specialists, FS is highly prevalent and associated with five identifying criteria: weakness, low resistance to effort, slowness, low physical activity levels, and unintentional weight loss (Abizanda et al., 2013; Rockwood, MacDonald, Sutton, Rockwood, & Baron, 2014).

Despite relationships between the decline in the physical functioning and FS, we cannot attribute to FS any central cause (Cho, Scarpace, & Alexander, 2004; Greene, Doheny, O'Halloran, & Anne Kenny, 2014; Kim et al., 2010). Progressive muscle damage related to the deleterious effects of senescence seems to be at its pathophysiological core (Mohler, Fain, Wertheimer, Najafi, & Nikolich-Žugich, 2014). FS is associated with, but not a direct result of, aging (Romero-Ortuno, 2013). Currently, there are increasingly robust associations between FS and multiple comorbidities, that although less lethal, tend to accumulate with age (Robinson et al., 2009). Physical disability seems to be a primary pathway to FS (Macklai, Spagnoli, Junod, & Santos-Eggimann, 2013). Notwithstanding the high correlation between low levels of physical-functional health in frail populations (Peterson et al., 2009), some studies have recently discussed the potential attenuation and prevention effect that exercise may have on FS, through stimulating positive improvement in physical-functional fitness (PFF) indicators (Jeoung & Lee, 2015).

The American College of Sport Medicine describes PFF as multidimensional, including cardiorespiratory fitness, flexibility, body composition, muscular strength, and endurance (Garber et al., 2011). Despite the importance of all PFF dimensions, the scientific consensus considers cardiorespiratory fitness and muscle strength or resistance as most important epidemiologically from childhood (de Chaves et al., 2016) to old age (Nelson et al., 2007). In this sense, maintaining satisfactory levels of PFF through adherence to regular exercise appears highly beneficial in attenuating and preventing cardiometabolic diseases (Murphy, McNeilly, & Murtagh, 2010), osteoarticular disorders (Peterson et al., 2009), sarcopenia, and the frail condition (Mjm, van Uffelen, Riphagen, & van Mechelen, 2008; Park, Kwak, Harveson, Weavil, & Seo, 2015). Strong associations between health-related quality of life and PFF in populations over 60 years old have been reported (Takata et al., 2010).

Some researchers reported that the decline on PFF indicators associated with age is aggravated by a sedentary lifestyle (Kimura, Mizuta, Yamada, Okayama, & Nakamura, 2012). Women, aged over 60 years, have been found to be less physically active overall but more involved in household activities (Lee, 2008) than older men. On the other hand, the results of a recent and stronger epidemiologic study carried out in 11 countries revealed that women over 60 years of age in all these countries were more likely than men to have disabling, nonlethal conditions including physical disability (i.e., difficulties to perform general activities of daily life), osteoarticular diseases, depressive symptoms, and hypertension (Crimmins, Kim, & Solé-Auró, 2011). Many of these diseases are robustly related to sedentary behavior across life (Chastin, Fitzpatrick, Andrews, & DiCroce, 2014).

The study of associations between FS and some PFF indicators has recently gained the interest of the scientific community in its search for simple and effective means of preventing FS. Most of these studies have focused on people over 65 years of age living in the community (Drubbel et al., 2014). However, recent research showed a higher prevalence of various comorbidities, FS, and mortality among people living in centers for social and health care support (CSHS; Abizanda et al., 2014; Nóbrega, Maciel, de Almeida Holanda, Oliveira Guerra, & Araújo, 2014). This type of institution seems to exert a "protective effect" for many people, preventing other adverse clinical events mostly through improved nutrition (Abizanda et al., 2014). However, since a decrease in physical-motor proficiency, loss of functional autonomy (related to mental health), and absence of family are also psychosocial characteristics of this population (Abizanda et al., 2013), persons in these centers may be at particular risk for FS, and these centers may play a role in improving PFF.

Given an expected growth in the European adult population over 65 years of age and the fact that FS increases health costs and decreases health-related physical activity, it is essential to better understand the relationship between FS and PFF outcomes. Therefore, a set of objective and accurate assessment criteria appropriate for use among institutionalized older people an be valuable to both the recognition and amelioration of FS. This study explored the relationship between FS status and PFF indicators in institutionalized-dwelling older women and also explored the sensitivity, specificity, cutoff points, and predictive performance of specific senior PFF tests for identifying frailty status. We hypothesized that FS participants would be at higher risk of PFF decline, when compared with individuals identified as prefrail or not frail (robust), and we looked for independent associations between FS and PFF tests to better predict FS.

Method

Study Design and Participant Sample

This study was a prospective, cross-sectional, local, older population-based survey in which we collected information about FS incidence in older people living in centers for CSHS. The sample consisted of a subset of participants within the PRO-HMESCI study protocol (Teixeira et al., 2016), inserted in a PHALIF study: participative, health, and active lifestyle in frail institutionalized-dwelling individuals. Our initial sample consisted of 203 older participants aged over 60 years minus 84 participants who failed to meet exclusion criteria or dropped out as follows: Physical impairment associated with musculoskeletal disorders and joint or muscle pain in the performance of some specific movements or tests ($n = 34$), closed diagnosis of early-stage of dementia or mental disorder ($n = 9$); severe impairment of hearing or visual functions that made it impossible to perform all tests ($n = 7$); need of palliative health care or special nutritional support, with medical indications not to participate in the study ($n = 4$); participants who dropped out when applying the tests ($n = 10$); and male participants excluded for methodological reasons ($n = 20$). Participant inclusion criteria used were as follows: Women aged over 60 years and willing to assent to take part in the study spontaneously who were under control and updated with prescribed medications. The final number of participants was 119 older women. Needed statistical power was computed by considering the agility-dynamic balance test values in studies comparing frail and prefrail groups, using a Mann–Whitney U test, with a significance level of $p = 0.01$. The computations were performed on G*power 3.1.9.2, and the power was determined to be 0.99 (Faul, Erdfelder, Buchner, & Lang, 2009) with a sample of 119 and an effect size of 1.12.

Ethical Procedures

CSHS directors and elders who expressed interest in participating in the study signed an informed consent form, in which the privacy and anonymous identity of the data collected were guaranteed and any needed access to participants' medical records were given. The study protocol was approved by the Faculty of Sport Sciences and Physical Education Ethical Committee—University of Coimbra (reference code: CE/FCDEF-UC/000202013), in respect of Portuguese Resolution (Art.° 4st; Law n. 12/2005, 1st series) on ethics in research (Braga, 2013) and complied with the guidelines for research with human beings of the Helsinki Declaration (Petrini, 2014).

Outcome Measures

Data collection of sociodemographic and medical history status, FS, physical fitness, and anthropometric indicators was organized by the principal investigator and was performed by independent specialists (properly trained) of the research team. To minimize differences in data collection procedures, the same evaluator carried out data collection for all participants.

Sociodemographic status. Information on chronological age (continuous variable), marital state (assessed as a four categories variable: single, married, widowed, and divorced), and level of education (assessed as a continuous variable) was collected for each participant. The level of education was classified according to the Portuguese educational system and analyzed as a continuous variable (Fernandes, 2007).

Anthropometric measures. The standardized procedures described by Lohan et al. (Chumlea & Baumgartner, 1989) were followed for the collection of anthropometric data, including body mass weight determined using a portable scale (Seca®, model 770, Germany) with a precision of 0.1 kg, stature determined using a portable stadiometer (Seca Body meter®, model 208, Germany) with a precision of 0.1 cm, and body mass index (BMI), calculated according the formula ($BMI = weight/height^2$).

Comorbidities screening. The Charlson comorbidity index (CCI), used in this study, is a method of predicting mortality by classifying or weighting comorbid conditions. The CCI has been widely utilized by health researchers to measure burden of disease and has a weighted index based on 19 comorbid conditions. Its score can be combined or adjusted with age and gender to form a single index (continuous variable). Adding one point for each additional 10 years to the initial score has been shown to predict 1-year and 10-year mortality (Charlson, Szatrowski, Peterson, & Gold, 1994). Medical records provided by the medical and health professional team were used to verify information provided by study participants for use within the CCI.

Medication use assessment. Daily medication use by the participants was assessed through Question 6 of the Mini Nutritional Assessment (Guigoz, 2006), that asks the participant about prescription drugs taken per day. Additionally, the number of medications used was checked systematically through the institutional medical record of each participant, identifying and reporting polypharmacy (i.e., more than three prescription drugs per day) according to the Portuguese Classification System of Human Medicine (Santos & Almeida, 2010).

Cognitive status assessment. The Mini–Mental State Exam (MMSE) used in this study assesses five areas of cognition: orientation, immediate recall, attention and calculation, delayed recall, and language (Folstein, Folstein, & McHugh, 1975). The maximum MMSE score is 30 points, and a score below 24 points is considered abnormal and used for dementia and mild cognitive impairment (MCI) screening (Melo & Barbosa, 2015). The MMSE was used to classify participants by cognitive profile as a category variable, according to the following cutoff values: severe cognitive impairment: 1 to 9 points; moderate cognitive impairment: 10 to 18; MCI: 19 to 24 points; and normal cognitive status: 25 to 30 points (Mungas, 1991). Additionally, the MMSE can be analyzed as a continuous variable. Its purpose in this study was to help determine whether a low-cognition profile might have affected physical fitness trainability as has been shown by prior research (Uemura et al., 2013).

FS screening. Assessment of FS was evaluated according to Fried's five criteria of the frailty phenotype index (Fried et al., 2001): (i) Weight loss assessed by self-report of unintentional weight loss of four kg or more in the last six months; (ii) poor endurance and energy (self-reported exhaustion) evaluated by negative concordance of two questions, Number 7 and Number 20, of the questionnaire developed by the Center of Epidemiologic Studies for Depression, called the CES-D scale (Gonçalves, Fagulha, Ferreira, & Reis, 2014); (iii) weakness, analyzed using the handgrip strength test. This test uses a handheld dynamometer (Lafayette Dynamometer, model 78010, USA) and strength is measured in kilograms. The subject holds the dynamometer in the hand to be tested, with the elbow by the side of the body. When ready, the subject squeezes the dynamometer with maximum isometric effort, which is maintained for 5 seconds. The best result of the two trials was used for scoring purposes (Syddall, Cooper, Martin, Briggs, & Aihie Sayer, 2003). Participants who were unable to perform the handgrip strength test and those in the lowest 20% (adjusted for BMI and stratified by gender) were categorized as positive for the weakness criterion; (iv) slowness, as measured by the "15 feet walking test," consisting of an individual walk without assistance (4.6 m) where the time taken to complete it is measured and expressed in seconds, adjusted for gender and height. The best time of the two trials was used for final scoring (Newman, Haggerty, Kritchevsky, Nevitt, & Simonsick, 2003); and (v) low physical activity level, assessed by the International Physical Activity Questionnaire short form such that participants classified as having "low levels of PA" and "very low sedentary" on this instrument scored negatively in the FS criteria (Guessous et al., 2014; Pitanga, Pitanga, Beck, Gabriel, & Moreira, 2012). The prevalence of FS combined score was calculated, as well as the presence of each of the five items (0–5 points). According to the Fried protocol, a negative evaluation in one or two criteria classifies the participants as prefrail, in three or more as frail and as nonfrail or robust, when the subject has no score on any of the five criteria of FS (Fried et al., 2001).

Assessment of physical fitness indicators. The senior fitness test battery developed by Rikli and Jones (2013) was used to measure PFF. (i) The lower body strength is determined with the "30 seconds chair and stand test" (30 s-CS), measuring the number of total full chair stands that can be completed in 30 seconds with the arms folded across the chest; (ii) the upper body strength was assessed with the "30 seconds arm curl test" (30 s-AC) that measures the total number of bicep curls that can be completed in 30 seconds, seated in a chair and holding a hand weight of five lbs (2.27 kg) for women; (iii) for lower body flexibility, we used the "chair sit and reach test" from a sitting position at front of chair, with leg extended and hands reaching toward the toes, the number of inches (cm, + or −) between extended fingers and tip of toe were measured; (iv) the upper body flexibility (shoulder girdle) was measured using the "back stretch' test," that assesses the distance (cm, + or −) of approach between the middle fingers when one hand reaching over the shoulder and one up the middle of the back; (v) agility-dynamic balance was assessed using the 8 foot up and go test, that assesses the time in seconds required for the participant to get up from a chair (seated position), walk as quickly as possible around either side of a cone placed 2.44 m away from the chair, turn and sit back down in the seated position; and (vi) aerobic resistance was measured through the "2 minutes step test" (2 m-ST), that consisted of the number of full steps the subject completed in 2 minutes performing a stationary gait, with one hand resting on the wall and raising each knee to a midway point between the kneecap and iliac crest; the score is the number of times the right knee reaches the required height (Rikli & Jones, 2013). For all the PFF tests, the best score of the two trials performed was used for data analysis. When upper and lower members were tested on both sides (i.e., left and right), the best scoring side was the one considered for scoring purposes.

Statistical Analysis

The assumption of normality was checked by resorting to Shapiro–Wilk tests and by visual inspection of normality plots. When normally distributed, quantitative variables were described by their means and standard deviations. When not normally distributed, medians and the first and third quartiles were used instead. Nominal variables were described with absolute and relative frequencies. A comparison of quantitative variables between FS categories (no frail, prefrail, and frail) was performed using one-way analysis of variance test or Kruskal–Wallis test, as applicable. Associations between nominal variables were assessed using the chi-squared test and Monte Carlo simulations were performed when appropriate. Partial correlations between the FS combined score and PFF indicators were computed, together with partial correlations controlling for the cognitive status, comorbidities, and both factors at the same time. The magnitude of the associations was classified following recommendations: trivial ($r < .1$); small (r from .1 to .3); moderate (r from .3 to .5);

strong (r from .5 to .7); and robust (r from .7 to .9; Batterham & Hopkins, 2006). The variables expressing PFF results were analyzed regarding their predictive value to distinguish between frail and prefrail subgroups by performing a receiver operating characteristics curve analyses. A multivariate logistic regression was subsequently undertaken, considering all of the aforementioned PFF test performance variables as predictors of FS. IBM SPSS Statistics 21.0 and in R 3.3.1 software were used for all computations. The level of significance adopted was $p = .05$.

Results

Data from 119 participants were analyzed, and Table 1 presents descriptive characteristics of the participants for all variables. Analysis of the sociodemographic variables indicated that our participants were older women (81.96 ± 7.89), mostly without husbands (94.1%) and with low academic achievement levels according to the Portuguese education classification system (3rd grade). When the "no frail," "prefrail," and "frail" subgroups were compared, there were no statistical differences between these groups for chronological age, weight, and marital state. Statistical differences were found for height ($p < .05$). Concerning clinical status, the average scores of the total sample classified the sample as a whole as showing a cognitive status of MCI (MMSE, 20 points), a high incidence of multicormobidity and a high risk of mortality (CCI, 7 points), and a high incidence of polypharmacy. Differences between groups were found for MMSE scores that were lower ($p < .001$) and CCI scores that were higher ($p = .026$) in the frail group. There was also a clear tendency for increased polypharmacy in the frail subgroup.

Regarding FS assessment, 19 participants were classified as nonfrail (16%), 46 subjects as prefrail (38.7%), and 54 as frail (45.4%). Both for the prefrail and frail groups, as well as for the total sample, "weakness" was the dimension on which most participants obtained negative scores and "poor energy" was the dimension on which the fewest participants obtained negative scores.

Analyzing scores from the senior PFF tests battery and comparing the frailty subgroups, the frail group exhibited lower performance results on all PFF tests. A comparison between the three groups showed statistically significant differences attained for all PFF tests battery variables except for BMI, whose results indicated higher values in the direction of the frail group. In addition to the descriptive scores described in Table 1, a graphical representation (radar plot, Figure 1) also showed FS differences in PFF scores. In Figure 1, to ensure comparability and an easier visualization, the medians were computed for each of the three FS subgroups and then divided by the maximum of the three medians. It is worth mentioning that, for each FS component represented in the plot, higher results mean better performances. The frail group can be seen to have lower scores for all PFF variables except for body composition.

Table 1. Characterization of the Total Sample Study Population and Comparison by Frailty Phenotype Index for Sociodemographic, Clinical Status, Frailty, and Physical Fitness Indicators.

	Total sample ($n = 119$, 100%)	Nonfrail ($n = 19$, 16%)	Prefrail ($n = 46$, 38.7%)	Frail ($n = 54$, 45.4%)	p
Bio-sociodemographic					
Chronological age (years, A ± *SD*)	81.96 (±7,89)	81.68 (±6.72)	81.80 (±8.65)	82.19 (±7.72)	.959
Weight (kg, A ± *SD*)	65.45(±12.58)	66.22 (±11.33)	65.08 (±11.54)	65.49 (±13.98)	.946
Height (m, M1;3)	1.51 (1.47; 1.56)	1.56 (1.49; 1.62)	1.51 (1.47; 1.55)	1.50 (1.46; 1.52)	.008
Marital state (*n*, %)					
Single	31 (26.1)	6 (31.6)	12 (26.1)	13 (24.1)	.073
Married	7 (5.9)	4 (21.0)	1 (2.2)	2 (3.7)	
Widowed or divorced	81 (68.0)	9 (47.4)	33 (71.7)	39 (72.2)	
Level of education (degree; M1;3)	3 (3; 4)	4 (3; 6)	3 (3; 4)	3 (2; 4)	.063
Clinical status					
MMSE (score, M1;3)	20 (15; 25)	25 (21; 27)	21 (17; 25)	17 (13; 22)	<.001
CCI (score, M1;3)	7 (6; 9)	8 (6; 10)	7 (6; 8)	8 (7; 9)	.026
Medication use, per day (*n*, %)					
I use more than three	108 (91.5%)	17 (89.5%)	43 (95.6%)	48 (88.9%)	.465
I use three or less	10 (8.5%)	2 (10.5%)	2 (4.4%)	6 (11.1%)	
Frailty syndrome (*n*, %)					
Weakness (N:P)	85 (71,4): 34(28.6)	0 (0): 19 (100)	36 (78.3): 10 (21.7)	49 (90.7): 5 (9.3)	<.001
Slowness (N:P)	62 (52.1): 57(47.9)	0 (0): 19 (100)	14 (30.4): 32 (69.6)	48 (88.9): 6 (11.1)	<.001
Poor energy (N:P)	49 (41.2): 70 (58.8)	0 (0): 19 (100)	10 (21.7): 36 (78.3)	39 (72.2): 15 (27.8)	<.001
Weight loss (N:P)	19 (16): 100 (84)	0 (0): 19 (100)	3 (6.5): 43 (93.5)	16 (29.6): 38 (70.4)	.001
Low physical activity level (N:P)	55 (46.2): 64 (53.8)	0 (0): 19 (100)	13 (28.3): 33 (71.7)	42 (77.8): 12 (22.2)	<.001

(continued)

Table 1. Continued

	Total sample ($n = 119$, 100%)	Nonfrail ($n = 19$, 16%)	Prefrail ($n = 46$, 38.7%)	Frail ($n = 54$, 45.4%)	*p*
Physical fitness (M1;3)					
Back stretch test (centimetres)	43.00 (34; 56)	53.00 (39.00; 70.50)	44.00 (37.50; 60.50)	40.25 (31.00; 51.00)	.022
Agility-dynamic balance (seconds)	13.00 (10; 20.56)	9.75 (7.12; 10.58)	11.15 (9.20; 14.90)	20.14 (14.30; 25.97)	<.001
Chair sit and reach (centimetres)	36.00 (25.50; 42.50)	35.00 (23.00; 43.50)	38.75 (34.50; 43.50)	32.25 (22.50; 38.50)	.002
30 seconds chair and stand test (reps)	8.00 (6.00; 11.00)	11.00 (10.00; 12.00)	9.00 (7.00; 11.00)	6.00 (5.00; 8.00)	<.001
30 seconds arm curl test (reps)	10.60 (8.00; 12.00)	13.00 (11.00; 15.00)	11.00 (9.00; 14.00)	9.00 (7.00; 11.00)	<.001
2 minutes step test (reps)	37.00 (20.00; 44.00)	52.00 (44.00; 60.00)	39.50 (30.00; 45.00)	27.00 (16.00; 35.40)	<.001
BMI (A ± *SD*)	28.49 (±5.05)	26.95 (±3.78)	28.22 (±4.60)	29.27 (±5.69)	.205

Note. N = negative; P = positive; A ± *SD* = average ± standard deviation; M1;3 = median 1st quartile; 3rd quartile; *n*, % = number (percentage) of participants, where applicable.

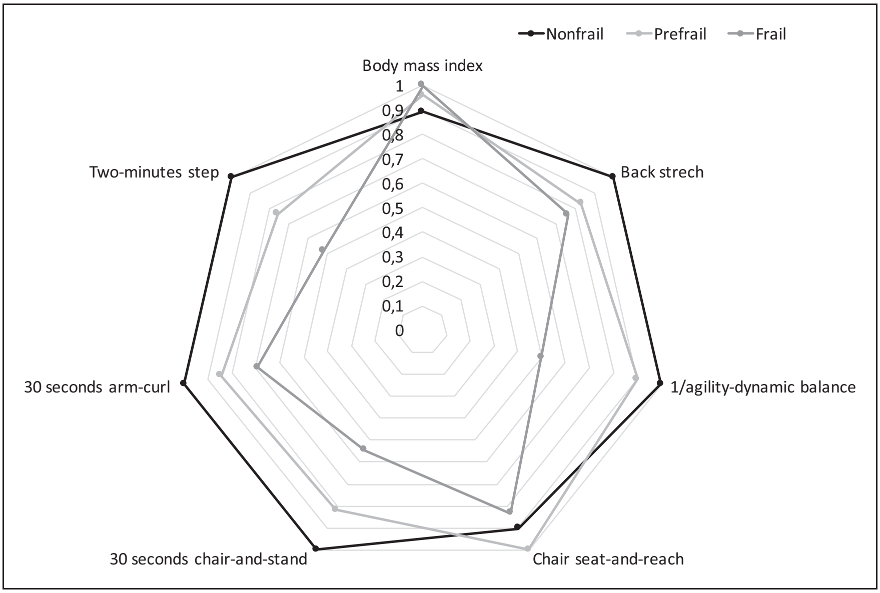

Figure 1. Radar plot of the variables of the physical fitness tests ($n = 119$).

Table 2. Spearman Total and Partial Correlations (Controlling for Cognitive, Comorbidity, and Both) Between Combined Score of FS and Indicators of Physical Fitness Tests ($n = 119$).

Control variables		Back stretch	Agility-dynamic balance	Chair sit and stand	30 seconds chair stand	30 seconds arm curl	2 minutes step	BMI
None	*r*	−.255	.662	−.289	−.555	−.456	−.617	.119
	p	.005	<.001	.001	<.001	<.001	<.001	.198
MMSE	*r*	−.212	.617	−.292	−.509	−.411	−.556	.157
	p	.021	<.001	.001	<.001	<.001	<.001	.090
CCI	*r*	−.231	.653	−.279	−.542	−.446	−.616	.096
	p	.012	<.001	.002	<.001	<.001	<.001	.303
MMSE and CCI	*r*	−.181	.604	−.280	−.489	−.398	−.552	.131
	p	.051	<.001	.002	<.001	<.001	<.001	.159

Note. BMI = body mass index; MMSE = Mini–Mental State Exam; CCI = Charlson comorbidity index.

Correlations between the combined score of FS and PFF indicators can be seen in Table 2. Additional partial correlation, controlling for cognitive state, comorbidity, and both variables were also included. Direct and strong correlations emerged from associations between FS combined score and agility-

Table 3. Predictive Performance of Physical Fitness Tests for Frailty Syndrome ($n = 119$).

Variables	Cutoff	Sensitivity (%)	Specificity (%)	AUC	AUC 95% CI
Back stretch	≤33.75	37.0	89.1	0.631	[0.522, 0.740]
Agility-dynamic balance	≥16.22	70.4	84.8	0.820	[0.739, 0.901]
Chair sit and stand	≤35.75	68.5	73.9	0.712	[0.609, 0.815]
30 seconds chair stand	≤6.50	51.9	89.1	0.754	[0.661, 0.847]
30 seconds arm curl	≤11.50	92.6	47.8	0.728	[0.626, 0.829]
2 minutes step	≤36.50	77.8	65.2	0.738	[0.640, 0.836]
BMI	≥29.89	53.7	63.0	0.550	[0.436, 0.664]

Note. BMI = body mass index; AUC = Area Under Curve; CI = Confidence Interval.

dynamic balance (ADB) test ($r = .662$; $p < .001$). An inverse and strong association emerged in 2 m-ST variables ($r = -.617$; $p < .001$). Inverse and moderate association appears in 30 s-CS ($r = -.555$; $p < .001$) and 30 s-AC ($r = -.456$; $p < .001$) tests; inverse and small associations values appear in BST and 30 s-CS tests ($r = -.$ 255 and $r = -.289$; $p < .001$, respectively). No statistical correlation between BMI and FS combined score was found. When the effects of cognitive profile, comorbidity, and interaction between both variables were removed, correlation scores decreased but did not change the magnitude of the correlations.

Subsequently, receiver operating characteristics analyses were performed to assess how PFF indicators may be used to predict FS status (see Table 3). The highest AUC value was attained for the ADB test, the 95% confidence interval being [0.739, 0.901]. The corresponding cutoff value, maximizing Youden's index, was seen to be 16.22 (seconds), with the sensitivity 70.4% and the specificity 84.8%.

Test performance indicators were used as predictors for FS in a logistic regression analysis aimed at distinguishing between prefrail and frail subgroups. Nonfrail participants were thus excluded from this analysis. Of the seven variables assessing test performance, only ADB test ($\beta = 0.198$; SE = 0.052; $p = .0000$; OR = 1.218; OR 95% CI [1.110, 1.349]) and 30 s-AC ($\beta = -0.213$; SE = 0.086; $p = .013$; OR = 0.808; OR 95% CI [0.683, 0.956]) were found to be statistically significant predictors. These two predictor variables were linearly related to the logit of the dependent variable using the Box-Tidwell procedure.

A multivariate outlier was identified using standardized residual and kept in the analysis. The model was seen to be statistically significant ($\chi^2[2] = 45.181$, $p < .001$) and to explain 48.6% (Nagelkerke R^2) of the variance in the outcome variable. It achieved a sensitivity and specificity of 70.4% and 84.8%, respectively, with AUC 0.848 with the corresponding 95% confidence interval being [0.773, 0.922]. Figure 2 shows only those significant variables in multivariate logistic regression analysis.

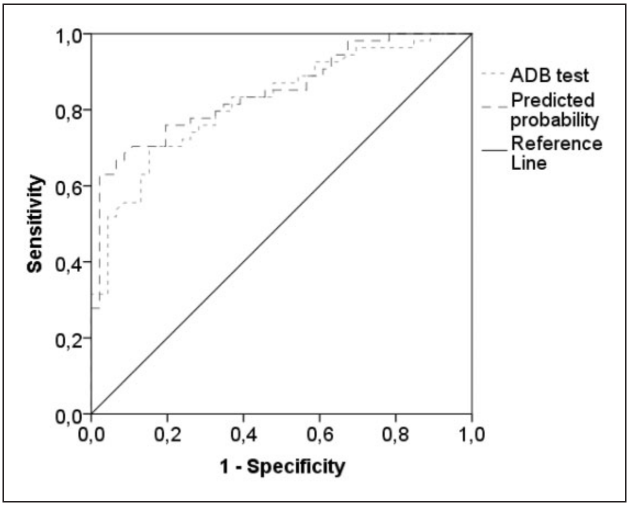

Figure 2. Receiver operating characteristic curve analysis for test performance ($n = 119$).

Discussion

The goals of this study were to explore associations between FS and PFF indicators and to analyze predictive performance of PFF tests among women living in centers for CSHS in the district of Coimbra, Portugal. To our knowledge, this study is the first scientific examination of the predictive performance of PFF indicators for evaluating FS in a Portuguese population over 65 years old. FS has similar prevalence (45.4% frail subgroup) when compared with other European countries that have studied samples living in CSHS (Abizanda et al., 2013).

According to other international studies, there is a clear trend toward an increasing prevalence of FS in samples of institutionalized individuals. Portuguese women over 65 years of age have distinct sociodemographic characteristics, when compared with South American (Yassuda et al., 2012), North American (Kiely, Cupples, & Lipsitz, 2009), and Asian populations (Han, Lee, & Kim, 2014). In agreement with other studies of participants with similar sample characteristics (González-Vaca et al., 2014), our bio-sociodemographic data revealed a trend toward lower levels of education in the prefrail and frail subgroups. Unlike other studies in which frail subjects were underweight (Donini et al., 2013), we found no statistical differences between groups in body weight and BMI. This fact may be explained by the nutritional support these individuals received from the care center in which they were living, consistent with a cross-sectional study conducted in Spain (González-Vaca et al., 2014). According to several researchers, in recent years, malnutrition is a frequent problem among people living in institutionalized context (Cereda, Valzolgher, & Pedrolli, 2008; De Luis et al., 2011; Donini et al., 2013). Our data highlight the importance of adequate nutritional balance, one of the variables at the core of the FS status. Especially for this study, it is important to note that body weight probably did not affect the assessment of PFF.

In terms of clinical history, cognitive impairment and incidence of comorbidities are the most explored dimensions in studies combining FS correlates (Brigola et al., 2015; Chang & Lin, 2015). Despite ICC scores, present data do not indicate an increase in the number of diseases in the direction of the frail subgroup. The prevalence of a high comorbidity index in our study sample was present in all the FS subgroups. The results of cognitive function assessed by the MMSE showed statistical differences between FS subgroups. The pattern of increased MCI occurrence among the prefrail and the frail people in this study was comparable to previous studies (Abizanda et al., 2013; Han et al., 2014). However, studies with similar samples with participants living in community-dwelling context have higher values in MMSE scores when compared with studies with institutionalized samples (Robertson, Savva, Coen, & Kenny, 2014).

Regarding differences in PFF indicators between FS subgroups, frail people exhibited smaller scores in the lower and upper body strength, lower and upper body flexibility, agility, dynamic balance, and aerobic resistance capacities compared with the nonfrail and prefrail subgroups. An improvement on PFF performance, through regular physical exercise practise, reportedly enhanced physiological parameters related to physical health, exerting therapeutic treatment effect for prevention and mitigation of specific outcomes of physical impairment and can also contribute to increasing physical activity and quality of life (Patel, Newstead, & Ferrer, 2012), even in people aged over 65 years old (Vrantsidis et al., 2014).

The scientific literature recognizes the importance of maintaining an active lifestyle across life to mitigate adverse and harmful negative effects on physical health. However, muscle strength and cardiorespiratory fitness are consensually the most encouraged PFF components to be predominantly trained because of the direct relationship between the human vital capacity and physiological reserve (Charansonney, 2011). A closer look at the FS subgroups, specifically the frail subjects, revealed that weakness (muscular strength), slowness (walking speed), and low physical activity levels were the three FS components on which a larger number of participants scored negatively. The results of partial correlation between FS combined score and PFF indicators (see Table 2) showed satisfactory correlations between these dimensions, even when controlling for the effects of comorbidities, cognition profile, or both. Some studies indicate that these clinical conditions exert influence on PFF variables, though this was not demonstrated in the present study. Generally, our results are consistent with other studies that explored associations among similar variables and dimensions (Chang et al., 2014; Jeoung & Lee, 2015).

A second central focus of the present study was an analysis of the potential performance of PFF tests for predicting the FS condition. We identified the 30s-AC and ADB test as two potential predictors of FS. The longer the ADB test took to be completed and the lower the number of repetitions in 30s-AC, the greater the risk of being frail. Notably, the ADB test was the best predictor. According to recent studies, this test seems to be an appropriate, independent, and predictive tool to detect frail subjects (Chang et al., 2014). Note that for the same sensitivity as the best univariate predictor (ADB test), the logistic regression model allows for a slightly higher specificity (89.1%, whereas it was 84.8%). In analytical terms, for this population or another with similar characteristics, taking longer than 16.22 seconds to complete this test predicts the existence of a frail condition. Accurately, the risk of frail condition (not prefrail) increases about 2.12% per second spent in the ADB test. Similar results were previously found in a similar study using an analogous test (the time up and go test) for predicting frail condition in community-dwelling subjects (Greene et al., 2014; Savva et al., 2013). However, in their sample, unlike the present study, the authors excluded individuals with MCI. As mentioned, the comparison of the ADB test values between frail and prefrail subgroups is of particular importance, since statistically significant differences were found between the ADB test values of the two groups ($U = 446$, $p < .01$).

The satisfactory execution of this test requires awareness, concentration on the information received (attention), and fast decision-making (reaction time) when the participant receives the signal to "raise from the chair" and walk as quickly as possible (Barry, Galvin, Keogh, Horgan, & Fahey, 2014); rising from a chair unassisted by upper limbs requires lower limbs muscle strength, and walking fast and turning around a cone placed at 2.44 m requires quickness, agility, dynamic balance, and body support (Cebolla, Rodacki, & Bento, 2015). Thus, this test requires the integration of physical capacities, highly dependent on a satisfactory neurocognitive functioning. Perhaps, this is the reason why the cutoff values for predicting risk of FS status in the present study were higher than previous studies in which the predictive cutoff value was $\geq$8.12 seconds (Chang et al., 2014) as our sample contained individuals whose MMSE test values were in the range of MCI.

The central findings of the present study support the power of the agility-dynamic balance test for predicting FS in institutionalized populations aged over 65 years, where application of Fried's criteria is not feasible. This study's limitations include a sample that was only representative of institutionalized women since randomly selected institutions in a "universe" of many others was the most feasible, fast, and economical method of data collection and the number of male participants motivated to participate was very low. However, comparing these data to similar results from previous research, we conclude that the agility-dynamic balance test is gaining clinical utility because of its accuracy in detecting physical frailty. It has potential for use as a reference measure in future exercise intervention studies.

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Authors Contributions

Guilherme Furtado drafted the paper and help in the acquisition data. Miguel Patrício and Marisa Loureiro performed the statistical analysis. José Ferreira and Ana Teixeira coordinated the research study protocol. All the authors have made a substantial contribution in their respective areas of expertise and approved the final version of the manuscript.

Declaration of Conflicting Interests

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Author Biographies

Guilherme Furtado has a degree in Sport Science and Physical Education (UNI-BH, Brazil), postgraduate in Functional Training (ULTH-FEDF, Portugal), and a master's degree in Exercise and Health in Special Groups (FCDEF-UC, Portugal). He has large professional experience in exercise programs. He is a doctoral fellow (CAPES Foundation—Ministry of Education, Brazil) in Physical activity and Health at University of Coimbra (FCDEF-UC). Research has focused on modulated effects of regular exercise on biopsychologies outcomes (hormonal, psychological, and physical fitness) in older adults with physical frailty condition.

Miguel Patrício has a degree in Mathematics (University of Coimbra) and a PhD also in Mathematics (Technical University of Eindhoven). He worked as an assistant professor at the Department of Mathematics of the School of Technology and Management of the Polytechnic Institute of Leiria between 2008 and 2012. Subsequently, he moved to the Faculty of Medicine of the University of Coimbra, where he now works as a researcher, focusing mostly on Applied Mathematics and Biostatistics.

Marisa Loureiro has a degree in Mathematics (since 2006 by University of Coimbra—Department of Mathematics) and master's degree in Teaching Mathematics (since 2010 by University of Coimbra—Department of Mathematics). She is a PhD Student in Mathematics with a specialization in Statistics (since 2015 by University of Évora). Currently, she is a trainer of Mathematics and Statistics and a member of Laboratory of Biostatistics and Medical Informatics, Faculty of Medicine of the University of Coimbra.

Ana Maria Teixeira has a degree in Biochemistry (UC, Portugal), master's degre in imunology (UP, Portugal), and PhD in Hematology from the University of London, UK. Currently, she is an associated professor with aggregation (CIDAF/FCDEF-UC) and her research focus on the areas of medical sciences with an emphasis on health sciences. The most common themes in the context of her scientific production are exercise immunology, training load, salivary IgA, immunessenescence, and health promotion. Currently, she is dedicated to research on the effects of exercise on hormonal mediation of stress, cognition, and immunity in older persons.

José Pedro Ferreira has a degree in Physical Education (Special Education or Rehabilitation), master's degreee in Children Motor Behavior (FMH-UTL, Portugal), and PhD in (University of Bristol, UK). Currently, he is a professor associated and research interests focus on the study of psychological variables associated with the practice of sport and exercise in special groups (CIDAF/FCDEF-UC). It teaches European programs Erasmus Mundus Master in Adapted Physical Activity and European University Diploma in Adapted Physical Activity. Currently, he is president of the European Federation of Adapted Physical Activity.

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Effects of a chair-yoga exercises on stress hormone levels, daily life activities, falls and physical fitness in institutionalized older adults

G.E. Furtado [a, c, *], M. Uba-Chupel [a, c], H.M. Carvalho [b], N.R. Souza [a], J.P. Ferreira [a], A.M. Teixeira [a]

[a] Research Unit for Sport and Physical Activity (CIDAF), Faculty of Sport Science and Physical Education, University Coimbra (FCDEF-UC), Portugal
[b] Faculty of Physical Education, University of Campinas, UNICAMP, Brazil
[c] CAPES Foundation, Ministry of Education, Brazil

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The aim of this study was to assess the changes mediated by exercise on activities of daily life and falls, physical fitness, salivary cortisol and alpha amylase in older adults living in social and health care givers centers.

Methods: Sample consisted in 35 women (83.81 ± 6.6 years old) were divided into two groups: chair-yoga exercises group (CY, n = 20) and control group (CG, n = 15). All subjects were evaluated before and after 14-weeks. CY was involved in exercise classes two times per week, while the GC did not participate in any exercise.

Results: Fear of falling decreased in both groups, cortisol increased and alpha-amylase decreased in the CG. No significant changes occurred in physical fitness outcomes. Conclusion: CY practice was able to maintain the physical fitness scores and stress hormone levels, but was not able to improve the subject's perception on the ability to perform the instrumental activities of daily life.

1. Introduction

Aging is characterized by deregulation of multiple physiological systems with deleterious effects on physical health and functional autonomy in older adults [1,2]. Biological chronic stress has been shown to have immuno-suppressive effects and to induce a physical-fragile state [3]. The gradual deterioration in the skeletal muscle system seems to be the central mechanism for decreased independency in activities of daily life (IADL) and physical fitness (PF) indicators [4].

The autonomy in the elderly can be characterized as the ability of the individual to perform IADL while demonstrating a satisfactory PF condition, without eminent risk of falling [5,6]. Functional impairment, especially when it is generated by the consequences of falls, increases public health spending to treat patients with later sequels [7]. For this reason, recent aging-autonomy models propose an integrated approach, whose major intervention mechanics are to assesses eminent risk of falls and improve PF over time [8].

Even non injurious falls are disabling with strong associations with activity constraint, isolation, deconditioning, increased fear of falling again and depression [7]. Associated with factors such as multi-comorbidity and polypharmacy, an increased risk of falls can further increase older adult's vulnerability [9]. In this sense, to check for possible associations between hormonal parameters related to stress and psychosocial and stressful constraints seems to be a prudent direction [10,11].

Cortisol (sCOR) is an essential hormone in the regulation of the biological stress response, but recently salivary alpha-amylase (sAA) has also emerged as a novel biomarker for evaluating stress [12]. These neuroendocrine markers play an important role in establishing the bodily reaction to stress and regulation of the autonomic function [13]. Stress responsiveness is primarily regulated by two neuroendocrine axes: the hypothalamic-pituitary-adrenocortical (HPA) and sympathetic adrenomedullary systems [14]. The HPA axis is a complex neuroendocrine stress system involved in bio-behavioral adjustments to confrontational stimuli and change [12]. Because saliva collection is a non-invasive method and for being accurate salivary biomarkers for detection of autonomic activity [15], sCOR and sAA received more attention lately in respect to their relationship with physical exercise [10]. However, results from

* Corresponding author. FCDEF-UC - Estádio Universitário, Pavilhão III, Santa Clara, 3040-156, Coimbra, Portugal.
E-mail address: furts2001@yahoo.com.br (G.E. Furtado).

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chronic exercise on neuroendocrine modulation in the older populations are scarce [11]. In the few studies that address exercise in the older person and biological stress, the use of diverse methodologies strip the accuracy of the inference of the results [16].

The premise that preserving an adequate state of physical independence in advanced age is related to satisfactory PF seems to be widely accepted [6,17,18]. For this reason, a physical exercise routine can be a complementary form of muscle damage prevention through the improvement of HrPf [19–21]. The American College of Sport Medicine (ACSM) makes it clear in their own guidelines when it refers that ten minutes of flexibility training a day, twice a week, will aid in the prevention of falls by improving balance [22]. But the recommendations on flexibility training are controversial since this type of training by itself does not seem to be enough to promote the functional benefits required by older people to maintain an adequate level of PF [23].

Among the various forms of exercise that could be practiced by older persons, yoga has been recommended as it could mitigate the deleterious effects of aging on flexibility [21,24]. According to the literature, the benefits of regular yoga practice include improvements in balance, coordination, strength and flexibility [19,25]. In older people with physical limitations to perform the full practice of yoga, adaptations may be made and an exercise program supported by a chair can be developed [21,24].

To date, few publications on the effect of yoga in olders have been published [23]. In a recent systematic review [19], the studies that tested the effects of yoga, mainly looked at variables such as strength, flexibility and cardiovascular resistance [25], psychosocial factors such as depression and anxiety [26], and biomarkers able to assess oxidative stress and lipid profile [27]. Studies involving athletes were also used to assess the acute effects of exercise on biological stress [28]. In a recent systematic review [19], Questions regarding whether biological levels of stress are associated with PF, fear of falling and psychosocial factors, as well as if the practice of yoga is able to change these parameters in the older person remain unanswered. Towards this purpose, the aim of this study was to evaluate the effects of a chair-based yoga exercise program on stress hormone levels, ADL, fear of falling and PF in institutionalized older women.

2. Methods

2.1. Initial procedures

Participants were older women living in social and health care support centres (SHC), located in the city of Coimbra, Portugal. All participants (or responsible) were required to give a full informed consent before beginning the research project. The study protocol was approved by Faculty of Sport Sciences and Physical Education Ethical Committee - University of Coimbra [Ref.: CE/FCDEF-UC/000202013]; it respects the Portuguese Resolution (Art.º 4th; Law n. 12/2005, 1st series) on ethics in research with humans [29], follows the guidelines for ethics in scientific experiments in exercise science research [30] andcomplies with the guidelines for research with human beings of the Helsinki Declaration [31].

2.2. Design of the study

This study was planned for approximately 20 weeks and was built in 3 different stages, as described below: First phase (2 weeks) consisted in the evaluation of the participants before chair-based yoga exercise program. Second phase 2 was an intervention study with implementation. Phase 3 (2 weeks) consisted in the evaluation of the participants after the 14 weeks of exercise. All the tests were applied before and after the exercise intervention in all groups (see Fig. 1). To minimize difference in procedures the same evaluators performed the data collection both at baseline and follow-up assessments.

2.3. Participants

According to a recent systematic review (sample average of 09 participants) previous studies on exercise interventions have shown small effect size in psychobiological outcomes in similar populations [16]. For this reason, a minimum sample of 15 participants per group was recruited, sufficient to identify possible beneficial effects taking into account the size of the effect size ($d = 0.40$, strong effect size, power = 0.80) established [32]. Additionally, another 7 participants were recruited (30% of 15 participants) in order to prevent dropout of the study sample [33].

In total, 58 participants from a center for social and health care support were selected from a convenience sample. After applying the inclusion and exclusion criteria and after dropout the final sample consisted of 35 female participants (age = 83.81 ± 6.6years old). The participants were allocated into two groups: chair-based yoga exercise group (CY, n = 20) and non-exercising control group, (CG, n = 15).

2.3.1. Sample selection criteria

Baseline assessment tasks included measures of biosocial and global health status, which associated with the medical staff report, formed the basis for determining the selections sample criteria's in the study. The inclusion conditions for the older participants stipulated in first order were: Being female participant aged over 60 years; drug therapy controlled and updated; If the participant present clinical condition or comorbidity, it must be stable and enable participation in yoga classes as decided by local medical staff. The exclusion criteria were: not completing or withdrawing from the '8-foot-up and go test' (FGT) in the maximum time of 50 s, since scores above this value indicate severe mobility dependence [34]; involvement in other structured exercise program; presence of severe cardiopathy, uncontrolled hypertension or asthmatic bronchitis, musculoskeletal dysfunctions that prevented the physical testes (i.e. osteoarthritis, recent fractures), mental disorder, hearing and vision impairment, morbid obesity or the use of

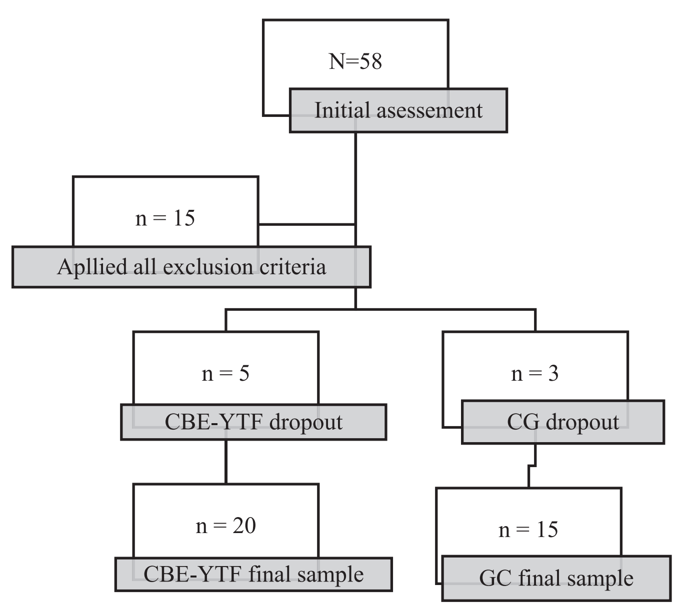

Fig. 1. Flowchart of the selection sample.

medications that significantly impair attention.

2.3.2. Masking

To minimize differences in assessment procedures the same evaluators performed the collection data at both baseline and follow-up measures. The psychometric scales were applied by independent assistant that establish contact with the participants without made references to the exercise program. The instructor of the exercise sessions did not took part in the data collection procedures. Precaution was taken to avoid interaction of CY exercises between individuals of the two groups by staggering the classes schedule.

2.4. Assessments

Measures of global health, biosocial status, psychometric (Portuguese version), physical-fitness and anthropometric were done by expert technicians.

2.4.1. Activities of daily life

The Lawton Instrumental Activities of Daily Living (IADL) questionnaire was used. The questionnaire is used for identifying how a person is carrying out daily activities at the present time and for identifying improvement or deterioration over time in 8 domains [35]. A summary score ranges from 9 (low function, dependent) to 20 points, for 'high function' independent [36].

2.4.2. Subjective fear of falling (risk of fall)

Tinetti Falls Efficacy Scale (FES) was used. The FES contains questions concerning the possibility of falling during the performance of 10 activities [37]. FES is represented on a 10-item analog scale and accordingly, the lower the score the greater the confidence, resulting in a high self-efficacy and reduced fear of falling when performing the 10 activities described in the questionnaire [38].

2.4.3. Physical tests assessment

The Senior Fitness Test battery [39] was used to assess PF. The lower body strength was determined with the '30 s's chair-and-stand test' (30s-CS), measuring the number of total stands completed in 30 s. The upper body strength was determined with the '30 s arm-curl test' (30s-AC) that measures the total number of arm curls executed in that time. To assess lower-body flexibility the 'chair sit-and-reach test' (CSR) was used measuring the distance in centimeters, (cm) of overlap or between the tips of the middle fingers when the arms are reaching up in the middle of the back as far as possible. To assess agility and dynamic balance the FGT was used, assessing the time needed for the participant to get up from the chair, walk as quickly as possible around either side of a cone placed 2.44 cm away and to sit back down in the chair. Each physical test has its respective cutoff value, however, the final scores were used as a continuous variable form.

2.4.4. Biochemical markers

Saliva will be collected by passive drool (method for collecting whole saliva), which provides the purest sample and making possible future testing. The individuals will salivate without any orofacial movement into high quality polypropylene vials to avoid problems with analyte retention or the introduction of contaminants that can interfere with the immunoassays. Collection was always at the same time of the morning in order to minimize the circadian effect of the markers used. After collection, the saliva containing tubes were store at $-20\,^{\circ}C$ until analysis, then defrosted and centrifuged in order to collect the saliva sample [40]. The determination of the sAA was done by kinetic assay (Salimetrics, UK) and concentration of sCOR was determinate by competitive ELISA (Salimetrics, UK), according to the manufacturer instructions [41].

2.5. CY exercise program

The creation of the chair based CY was based on the essential philosophy of Hatha Yoga and its āsanas, focusing on the flexibility benefits provided by them [19]. Music was not used during the sessions, since it could exert influence on neurocognitive aspects [42,43]. Exercise intensity was controlled using heart rate monitors (Polar, RCX5) randomly distributed between participants during the exercise program and monitored a low to moderate intensity effort, reaching intensities around 50–75% of maximum heart-rate values as recommended by the ACSM [22]. For safety reasons, exercise intensity was indirectly calculated using the Karvonen's formula to predict target heart rate (HR), but with maximal (max) HR being calculated using [$HR_{max} = 207$ (beats per minute) - $0.7 \times$ chronological age] for older people [44]. For this study, the sequences of exercises were prepared cautiously and reviewed according to the participants evolution [45], aiming to achieve moderate intensities in classes.

2.5.1. Exercise adherence

Classes were offered 2–3 times/week, during 14 weeks, in a total of 32 sessions. The percentage of exercise adherence to group classes was calculated individually through the total sum of participation. Entries were recorded in a checklist. When a participant had two consecutive absences, she was contacted to return to the group classes. An adherence to the exercise program between of 65%–75% [46], was established as minimum for each participant to be included in the study.

3. Data analysis

The Kolmogorov-Smirnov and visual inspection was done to check the distribution of data. For an elderly population, it should be noted that the intra-individual variability of the data becomes a major research challenge, with regard to homogeneity. Thus dependent variables were log-transformed before analysis to reduce non-uniformity of error as a recurring feature on data from biological nature (Feng et al., 2014), except FES and IADL which were based on Likert scales [47]. Descriptive statistics were summarized as average, standard deviation, range and association between variables was done using the Spearman correlations rank test. The magnitude of correlations was classified following the standards: trivial [$r \leq 0.1–0.3$]; moderate [$r < 0.3–0.5$]; strong [$r < 0.5–0.7$], robust [$r < 0.7–0.9$] [48]. Comparison between groups was accomplished using *t*-test for two independent samples. The *T*-paired test accessed differences between variables pre and post exercise and percent changes were calculated. The between-subject standard deviation for each dependent variable was used to convert the log-transformed changes of PF indicators into standardized [Cohen effect size (ES)] changes in the mean. The smallest standardized change was assumed to be 0.20 [49]. The statistical analysis was made with SPSS 20.0 (*Statistical Package for Social Sciences*, *IBM*), and $p \leq 0.05$ used as the level of significance.

4. Results

Table 1 shows the characterization of the sample. No statistically significant differences between the CG and CYG groups were found, in other words, they were homogeneous for all variables at the beginning of the study.

Associations between the variables studied at baseline were:

Table 1
Characteristics of experimental and control groups at baseline and comparison between groups by two-independent samples.

	Chair Yoga Exercises Group (n = 20)		Control group (n = 15)		*p*	*d*
	Average (SD)	Range	Average (SD)	Range		
Salivary Cortisol (ug/mL)[a]	00.57(00.23)	00.49–01.32	00.65(00.19)	00.26–01.12	0.488	0.09
Salivary Alpha Amylase (U/mL)	76.16(41.13)	05.24–180.07	67.98(54.60)	06.56–217.79	0.496	0.16
Chair sit-and-reach test (cm)	18.90(10.48)	02.00–32.00	16.90(10.72)	01.00–31.00	0.924	0.18
30s Arm-curl test (repetitions per time)[a]	11.45(04.10)	05.00–24.00	08.67(04.70)	02.00–19.00	0.091	0.63
30s chair-and-stand test (repetition per time)	09.20(03.75)	02.00–18.00	07.40(02.84)	03.00–13.00	0.590	0.48
8-foot up and-go test (seconds)	20.36(16.22)	08.04–60.00	17.10(11.90)	7.23–50.00	0.827	0.22
Falls Efficacy Scale (#)	27.85(21.63)	10.00–87.00	40.87 (22.76)	10.00–82.00	0.804	0.58
Instrumental activities Daily Living Scale (#)	20.15(04.13)	14.00–27.00	22.01(05.12)	12.00–30.00	0.601	0.11

$^{**}p \le 0.01$; $^{*}p \le 0.05$, comparisons between groups based on t-statistic.
[a] Logarithm transformed; SD: standard deviation.

IADL was inversely and moderately correlated with the FGT ($r = -0.347$, $p < 0.01$), 30s-AC ($r = -0.361$; $p < 0.01$), $p < 0.01$); FES moderately correlated with the 30s-CS ($r = 0.336$; $p < 0.01$) and sCOR showed a moderate and inverse correlation with CSR ($r = -0.431$; $p < 0.01$). There were no correlations between the levels of sAA and any of the other parameters assessed.

When comparing the results obtained before and after the 14 weeks CY exercise program (Table 2) FES values decreased in both groups. The percent change for the CY is dimmed to be possible beneficial (−36%; $p = 0.04$). However, the FES change in the CG was −45% ($p = 0.002$). In both groups a large magnitude of effect size ($d = 0.60$ and $d = 1.03$ respectively) was identified. A trend towards an increase in the values of the IADL scale in the CY group ($p = 0.055$) was also found with a magnitude of effect size considered as moderate ($d = 0.36$). No changes in the IADL score were detected for the GC.

Levels of sCOR increased significantly only in GC (+14%; $p = 0.050$) with a moderate magnitude of effect size ($d = 0.39$), whereas in the YG no significant changes in this hormone concentration occurred. The results also showed a significant decrease of sAA levels in the CG, with a substantial percentage of change and large magnitude of effect size (−47%, $p = 0.24$; $d = 0.78$). The HrPf indicators (FGT, 30s-AC and 30s-CS) did not change in both groups.

A new association between FES and the FGT test ($r = 0.49$, $p < 0.01$) - , $p < 0.01$) also emerged in the CY after the 14 weeks of the exercise program.

5. Discussion

The objectives of this study were to assess the effects of a structured program of CY in an older population on: physical fitness, which takes place as a set of global health-related measures [22]; on functional autonomy, which in this study was evaluated through subjective analysis instruments for activities of daily living, [36]; on the fear of falling [38]; and on biomarkers related to autonomic system function and biological stress, representing a promising line of studies in older populations [11].

5.1. CY intervention effects

The results of this study revealed significant changes or 'benefit possible' on FES when baseline values where compared to the ones after 14 weeks of exercise intervention with CY. However, this change could not be attributed to exercise only, since the CG also presented the same changes. It is possible that the change from winter to spring (the exercise program started in November and ended in March) might have also influenced the results obtained. However, two new correlations between FES and the FGT have emerged in the CY, together with the increase in the inverse correlation with the 30s-CS test ($r = -0.34$ versus $r = -0.57$) that are not present in the CG. Studies have linked PF and the risk of falls, but even when they found positive results, they recurred to other assessments, so it seems to be more important emphasizing the preventive character of the exercise (Gautam et al., 2011). This probably happened because a measure of subjective assessment, first of all, should be combined with studies that use direct measures related to falls, with the objective to explore the real sensitivity of exercise effects under these scales [19].

It would be important to check for the socially desirable answers; check if the initial values have been overestimated and finally, assess the relationship between the decreased FES with the improvement of the static and dynamic balance [50]. Improvements in such parameters were not found in our results (although a correlation between FES and the FGT, the test for static and dynamic balance, did appear), unlike other studies, which suggest that bodily practices like yoga or similar activity are more effective for the elderly

Table 2
Comparison between pre and post exercise intervention and control group (no exercise intervention) results by t-pairs and chances that the true difference in the changes is substantial.

	Chair Yoga Exercises Group (n = 20)					Control group (n = 15)				
	Pre	Post	*p*	Percent change	*d*	Pre	Post	*p*	Percent change	*d*
	Average (SD)	Average (SD)				Average (SD)	Average (SD)			
Salivary Cortisol (ug/mL)	00.57(00.23)	00.62(00.16)	0.158	+9	0.25	00.65(00.19)	00.73(00.22)	0.050	+14	0.39
Salivary Alpha Amylase (U/mL)	76.16(41.13)	70.54(43.46)	0.701	−7	0.13	67.98(54.60)	36.32(15.31)	0.024	−47	0.78
Chair sit-and-reach test (cm)	18.90(10.48)	21.01(13.02)	0.398	+11	0.17	16.90(10.72)	16.30(10.46)	0.883	−4	0.05
30s Arm-curl test (repetitions per time)	11.45(04.10)	10.95(03.33)	0.542	−4	0.13	08.67(04.70)	08.06(03.78)	0.929	−7	0.14
30s chair-and-stand test (repetition per time)	09.02(03.75)	09.30(04.24)	0.937	+1	0.06	07.40(02.84)	06.20(03.91)	0.128	−16	0.35
8-foot up and-go test (seconds)	20.36(16.22)	18.90(12.17)	0.989	−7	0.10	17.10(11.90)	14.02(05.75)	0.484	−18	0.32
Falls Efficacy Scale (#)	27.85(21.63)	17.90(08.08)	0.042*	−36	0.60	40.87 (22.76)	22.46(10.44)	0.002**	−45	1.03
Instrumental Activities Daily Living Scale (#)	20.15(04.13)	21.55(03.59)	0.055	+7	0.36	22.01(05.12)	22.33(04.28)	0.783	+2	0.06

$^{**}p \le 0.01$; $^{*}p \le 0.05$, comparisons based on t-paired test.

population when compared to other exercise programs [19,21,24,25,45]. The other PF tests results showed no improvements as no differences were found in the scores between the first assessment moment and 14 weeks after, at the end of the program.

Regarding the IADL our results show a tendency ($p < 0.055$, $d = 0.36$) for an increase in functional independency on these activities after the intervention program. Although this institutionalized groups do not have the opportunity and real need to perform independent activities since they live in a care giver center where most of those activities are provided for them, other activities like mobility, endurance to walk and other physical activities can assist to avoid accidents in those environments. (DeSure et al., 2013). In fact, our results did show a correlation between FES and IADL, that was reinforced after the exercise intervention in the CY. In our study both groups were classified as "severely dependent" (cut off > 20 points) at the beginning of the program and remained in that condition 14 weeks after. Studies with a similar methodological design and sample are scarce in the literature. Other studies used younger samples aged between 60 and 75 years old and that may justify the limited responses obtained with the chair based CY exercise program (Chou, Hwang, & Wu, 2012)[23].

A small and non-pathological increase of the sCOR levels in the CG was found in our study. A small rise in sCOR levels related to exercise practice was expected in the CY but not in the CG. Other factors may interact with sCOR levels such as psychosocial life stressful events with aging [51]. It is possible that the chair-based exercise could have helped protect against such stressors. The lack of studies involving similar samples makes it difficult to create a solid evidence of the role of exercise as modulator of HPA axis in this population [11].

At the same time, some studies involving analysis of the sAA reveal considerable variation in the activity of this enzyme across populations (Mandel et al., 2010). The patterns of between-population differences have been linked to the number of AMY1 copies, which is seen as an adaptive response to the intake of dietary starch (Perry et al., 2006). It can also reflect a decrease in mucosal immunity since sAA is also used as a first barrier to bacterial colonization in the mouth [40]. In this study there was a substantial decline in sAA values in the CG but not in the CY where the values remained stable.

The similarities of the PF parameters between the CG and CY suggest that this type of exercise does not promote significant changes (at physiological and PF levels) to justify its use in older subjects with these specific characteristics. Importantly, this age group is characterized as having a 'very poor physical condition', comparing our baseline results with the cutoff values of the original study realized in older American population [52], and with other studies using Portuguese samples living in the community [53].

In addition, factors such as volume, intensity and frequency of exercise (exposure over time) or even another type of exercise practice could be used to promote significant changes in these variables. For example, more intense and challenging yoga exercises maybe more effective as shown in other studies [19]. In our study, the average intensity based on heart rate monitoring varied between 50% and 57% of the theoretical HR_{max}. Such values are characterized as very low-intensity exercise [54], even for very old participants. However, the chair-based method adopted to perform the yoga exercises may have been a factor to the greater exercise adherence (average 69%) throughout the program compared to other studies.

The age group of the participants may be seen as limiting factor that attenuated the usual progression of the YG exercise program. It is expected that activities like yoga exercises move forward and challenge flexibility in the sitting and lying positions [25], or stay longer in standing position stimulating to improve the strength, resistance and static/dynamic balance [19].

6. Conclusion

The results suggest that the chair-based yoga exercises program was able to maintain the levels of sCOR and sAA protecting against stress and infection but was not able to promote substantial increments in the other variables analyzed. However, comparison between groups after the exercise program showed that there were statistically significant differences (results not shown) found mainly in the PF variables, which may reflect the maintenance of the PF capacities in the CY, corroborated by the increase seen in the IADL scores, as opposed to the CG that showed a trend towards a decline in the PF levels.

6.1. Limitations

The advanced average age of the participants in our study has led us to choose the chair-based exercise method, which limited the progression expected of many parameters of PF. It can also be hypothesized that the effect of motivation for the tasks, caused by emotional instability or acute manifestations of chronic diseases is a striking feature of these populations, and seemed to have also influenced the predisposition to complete the some activities inherent to the study [46].

6.2. Generalizability

This study provides scientific evidence that, apart from the adaptation of the chair-based exercise program, other variables must be controlled so that the practice becomes more effective for this age-group population. Thus, we recommend that social and health care centers incorporate these practices with the necessary adaptations from the traditional yoga, seen as a well-established practice with very positive benefits for older people.

6.3. Suggestions for the future research

We suggest the implementation of more studies using samples with low PF and more advanced age groups. Given the inter-person variability of some of the biochemical markers used, especially the sAA, increasing the sample size is also recommended. The progressive reduction of the time spent by the participants in the 'seated position in the chair' is also recommended. Such procedure would decrease the recovery interval to effort, increase intensity and add time to the exercise program. Thus, it would be expected that the participants perform more demanding routines from the physical point of view, which may raise the profile of the results and positively influence the subjective perception of functional autonomy related to activities of daily life and risk off falls.

Conflicts of interest

The authors declare that they have no competing interests.

Founding

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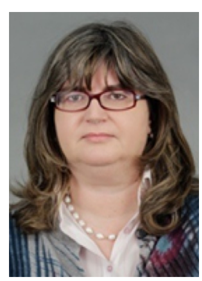
Guilherme Eustáquio Furtado (furts2001@yahoo.com.br) has a degree in Sport Science and Physical Education (UNI-BH, Brazil), post-graduate in Functional Training (ULTH-FEDF, Portugal) and a master's degree in Exercise and Health in Special Groups (FCDEF-UC, Portugal). He has large professional experience in exercise programs. He is a doctoral fellow (CAPES Foundation - Ministry of Education, Brazil) in Physical activity and Health at University of Coimbra (FCDEF-UC). Research has focused on modulated effects of crhonic exercise on biopsychological outcomes (hormonal, psychological and physical fintness) in older adults with frailty condition.

Mateus Uba Chupel (matheusuba@hotmail.com) has a degree in Sport Science and Physical Education (UnC, Brazil), a post-graduation in Exercise Physiology and master's degree in Biokinetics (FCDEF-UC). Actually he is professor on UnC (Brazil) and a PhD student in Physical Activity and Health at University of Coimbra (FCDEF-UC, Portugal). Actually, he is a financiated by CAPES Foundation, Ministry of Education, Brazil. His experience is focused on exercise physiology, biochemistry and supplementation, blood-brain barrier dysfunction and immunological parameters.

Humberto M. Carvalho (hmoreiracarvalho@gmail.com) has a degree in Sport Science and Physical Education, MSc in Sports Training for Children and Youth and PhD in Sport Science and Physical Education by the University of Coimbra. Currently is a post-doctoral fellow in Physical Education at the University of Campinas UNICAMP (Brazil). Has experience in multidimensional performance analysis in young athletes, particularly dealing with data analysis in longitudinal studies.

Nelba Reis Souza (nelbaef@yahoo.com.br) has a degree in Sport Science and Physical Education (UESB, Brazil) and a master's degree in Physical activity of Elderly (FDUP, Portugal). Currently, as a doctoral candidate in Physical activity and health at FCDEF-UC. She has research focus on the effects of exercise on physical fitness and psychossocial outcomes associated to body image and 'enpowerment' in older woman, with emphasis on qualitative research approachs.

José Pedro Leitão Ferreira (jpl.ferreira.2010@gmail.com) has a degree in Physical Education (Special Education /Rehabilitation), master's degreee in Children Motor Behavior (FMH-UTL, Portugal) and PhD in (University of Bristol, United Kingdom). Currently, he is a professor associated and research interests focus on the study of psychological variables associated with the practice of sport and exercise in special groups (CIDAF/FCDEF-UC). It teaches European programs Erasmus Mundus Master in Adapted Physical Activity and European University Diploma in Adapted Physical Activity. Currently he is president of the European Federation of Adapted Physical Activity.



Ana Maria Botelho Teixeira (ateixeira@fcdef.uc.pt) has a degree in Biochemistry (UC, Portugal), master's degreee in imunology (UP, Portugal) and PhD in Hematology from the University of London, United Kingdom. Currently she is an associated professor with aggregation (CIDAF/FCDEF-UC) and her research focus on the areas of medical sciences with an emphasis on health sciences. The most common themes in the context of her scientific production are exercise immunology, training load, salivary IgA, immunessenescence and health promotion. Currently, she is dedicated to research on the effects of exercise on hormonal mediation of stress, cognition and immunity in older persons.

ANNEX IV:

PUBLISHED ARTICLES RELATED TO THESIS

frontiers in Public Health

PROTOCOLS
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CrossMark

Study Protocol on Hormonal Mediation of Exercise on Cognition, Stress and Immunity (PRO-HMECSI): Effects of Different Exercise Programmes in Institutionalized Elders

Ana Maria Teixeira[1], José Pedro Ferreira[1], Eef Hogervorst[2], Margarida Ferreira Braga[3], Stephan Bandelow[2], Luís Rama[1], António Figueiredo[1], Maria João Campos[1], Guilherme Eustáquio Furtado[1,4], Matheus Uba Chupel[1,4] and Filipa Martins Pedrosa[1]*

[1] Faculty of Sport Sciences and Physical Education, University of Coimbra, Coimbra, Portugal, [2] National Centre for Sports and Exercise Medicine, Loughborough University, Loughborough, UK, [3] Medical Psychology Unit, Department of Clinical Neurosciences and Mental Health, Faculty of Medicine, Porto University, Porto, Portugal, [4] CAPES Foundation, Ministry of Education, Brasilia, Brazil

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Vladeta Ajdacic-Gross, Psychiatric University Hospital Zurich, Switzerland

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Francesco Panza, University of Bari Aldo Moro, Italy
Andreas Hoell, Central Institute of Mental Health (CIMH), Germany

***Correspondence:**
Ana Maria Teixeira
ateixeira@fcdef.uc.pt

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Physical activity (PA) in elders has been shown to have positive effects on a plethora of chronic diseases and to improve immunity, mental health, and cognition. Chronic stress has also been shown to have immuno-suppressive effects and to accelerate immunosenescence. Exercise could be a significant factor in ameliorating the deleterious effects of chronic stress, but variables such as the type, intensity, and frequency of exercise that should be performed in order to effectively reduce the stress burden need to be defined clearly. PRO-HMECSI will allow us to investigate which hormonal and immunological parameters are able to mediate the effects of exercise on mucosal immunity, psychological/biological stress, and cognitive functioning in older people. Phase I consists of an observational cross-sectional study that compares elders groups (n = 223, >65 years) by functional fitness levels aiming to identify biomarkers involved in maintaining immune and mental health. Neuroendocrine and immune biomarkers of stress, psychological well-being related to mental health, neurocognitive function, functional fitness, and daily PA will be evaluated. Phase II consists of a 28-week intervention in elders with

Abbreviations: α-amy, salivary alpha amylase; 2ST, 2-minute step test; 8-UGT, 8-foot up-and-go test; ACSM, American College of Sport Medicine Science; ACT, 30 seconds arm-curl test; AD, Alzheimer disease; ADL, Katz index of independence in activities of daily living; BDNF, brain-derived neurotrophic factor; BST, back stretch test; CAW, chair aerobic to improve walking exercises; CCI, Charlson comorbidity index; CRP, C-reactive protein; CSE, chair elastic-band strength exercises; CSHS, Centers for Social and Health Care Support; CSR, chair sit-and-reach test; CST, 30 second chair-and-stand test; CYE, chair yoga type flexibility exercises; DHEA, dehydroepiandrosterone; DST, digital span test; ES, effect size; FES, falls efficacy scale; HADS, hospital anxiety and depression scale; HPA axis, hypothalamic–pituitary–adrenal axis; HR_{max}, maximal heart rate; HVLT, Hopkins verbal learning task; IADL, Lawton independence activities day living scale; IFN-γ, interferon gamma; IL-1β, interleukin-1 beta; IL-10, interleukin 10; IL-6, interleukin-6; K–S, Kolmogorov–Smirnov test with Lilliefors; MCI, mild cognitive impairment; MMSE, mini mental state examination; MOCI, moderate cognitive impairment; NCP, normal cognitive profile; PA, physical activity; PF, physical fitness; PRO-HMECSI, hormonal mediation of exercise on cognition, stress, and immunity project; PSS, perceived stress scale; RSES, Rosenberg self-esteem scale; SCI, severe cognitive impairment; sCoR, salivary cortisol; sIgA, salivary immunoglobulin-A; SMT, symbol modality test; SWLS, satisfaction with life scale; TNF-α, tumor necrosis factor alpha; VFT, verbal fluency.

mild cognitive impairment (MCI) profile (n = 149, >65 years, divided in three groups of exercise and one control group), aiming to investigate whether the positive effect of three different types of chair-based exercise programs on physical and psychological health is mediated by an optimal endocrine environment. Primary outcomes are measures of cognitive function and global health. Secondary outcomes include the evaluation the other dimensions such as immune function, psychological health, and depression. Few studies addressed the effects of different types of exercise interventions in older population samples with MCI. We will also be able to determine which type of exercise is more effective in the immune and hormonal function of this population.

Keywords: exercise, older women, cognition, immunity, mental health

INTRODUCTION

Mild cognitive impairment (MCI) refers to a stage in which a person experiences memory loss to a greater extent than one would expect for that age, but do not yet meets currently accepted criteria for clinically probable Alzheimer disease (AD) or other types of dementia (1, 2). The recently coined concept of frailty – decreased resistance to stressors and increased risk for adverse health outcomes (3), has been reported to modulate the risk of several types of dementias and cognitive impairment *tour court*. Cognitive and physical frailty may be divided in subtypes according to their reversibility and task forces are proposing refined criteria to detect frail older subjects (4). Vascular, inflammatory, nutritional, and metabolic factors appear to be involved in late life frailty and are targeted as preventive causes of dementia (5). Recently published longitudinal studies report that muscle mass and physical performance may constitute an independent frailty component, according to the type of dementia, pointing to the need of further research (6). In general, the relationship between general cognitive function and physical frailty has been well documented (7). Although less consistently with dementia (8), but some authors argue that a dynamic perspective conveyed by longitudinal approaches of frailty may contribute to better understand transitions in cognitive status (9).

Immunosenescence is also a part of the aging process and is associated with an increased risk for autoimmune disorders, tumors, or infectious disease and neurocognitive disorders (10). The mucosal immune system, including the upper respiratory tract, is considered a first barrier to the colonization by pathogenic agents, reducing the incidence of upper respiratory tract infections (URTI) in humans (11). During aging, there is a decrease on salivary immunoglobulin-A (sIgA) secretion which is also linked to higher URTI incidence (12). Engaging in regular sports, exercise or systematic physical activity (PA) is known to protect against many factors associated with poor physical and psychological health and improves life expectancy (13). Cognitive functions sensitive to early dementia and age-related cognitive decline, such as memory and executive functions and simple and complex information processing reaction times have been shown to respond and be sensitive to the effects of exercise in both young and old ages (14). Six months of moderate levels of aerobic activity were sufficient to produce significant improvements in cognitive function, with the most dramatic effects occurring on measures of episodic memory and executive control (15). Dementia and vascular disease are leading causes of mortality in women, but risk seems to be reduced with exercise (16). Depressive symptoms are present in 12–30% elders (17), frequently associated with cognitive impairment (18). Furthermore, the presence of immune system dysfunction and inflammation has been reported to predict depressive symptoms during aging and appears to be the link between depression and dementia (19). It is very important for public health to identify the main factors associated with cognitive decline in the elders, subsidizing the creation of new methods of therapy. Exercise may have the largest positive effects on older women who have low levels of sex steroids after menopause which at the same time increase the risk for cardiovascular disease and dementia (20). The type of exercise seems to be crucial on increasing the aerobic capacity, but the evidence to support the involvement of flexibility, aerobic, and strength resistance exercise in improving cognition and psychological well-being related to mental health are not clear (14), and their effectiveness should to be investigated. Promising results have been reported in the reduction of depressive symptoms with PA interventions when including flexibility/resistance and low intensity exercise (21). In the older persons, PA appears to be beneficial for those presenting clinical depression, although the effect of different programs is still unclear (22). A few studies have looked at the effect of regular moderate exercise on SIgA, and there is no sufficient evidence to support the effect of exercise on IFN-γ and C-reactive protein (CRP) levels in elders (10). Regular exercise has also been shown to diminish the level of stress and anxiety and the risk of psychological diseases and emotional decline in elders (23). The responses of saliva flow rate and their composition during exercise are influenced by sympathetic nervous system activity and the hypothalamic–pituitary–adrenal axis (HPA-axis), the salivary glands being enervated by both parasympathetic and sympathetic nerves (24). Recent studies have identified salivary α-amylase (α-Amy) as a potential marker of sympathetic activity, while salivary cortisol (sCor) seems to be a valid measure for the HPA-axis activity (25). α-Amy is an enzyme that catalyzes starch into maltose and can be important to host defense by inhibiting the adherence and growth of certain bacteria (26). Testosterone levels decline with aging as well as cognitive function, and their levels seems to be diminished in patients with AD and MCI (27). Dehydroepiandrosterone (DHEA) is another steroid hormone involved in metabolism, produced mainly in the adrenal cortex, its functions are linked with anti-glucocorticoid, anti-oxidant anti-inflammatory, and immunomodulatory effects (28). Recently, DHEA has been investigated for its relationship to mental and physical stress and also in psychological and behavioral disorders. The DHEA plasma concentration and the ratio SCor/DHEA have also been shown to increase with PA (29). Salivary markers may serve as potential non-invasive tools for evaluation of the relationship between the central nervous system and mucosal immunity following psychological and/or physical stress and how these may affect cognitive functions (24).

In addition to these measures in saliva, peripheral blood concentrations of inflammatory biomarkers, such as interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), and interleukin-6 (IL-6), have previously been found to be elevated in cases of MCI and depression in comparison to healthy age-matched controls (23, 24, 29). Evidence shows that immunological and hormonal parameters are able to mediate the effects of exercise on mucosal immunity, psychological stress, cognitive improvement, and risk of dementia in the elders who are regularly active (30) and that regular exercise may provide an effective strategy in the treatment and prevention of associated disorders by anti-inflammatory benefits. IL-1β, IL-6, IL-10, IFN-γ, TNF-α, and CRP are important immune markers that interact in anti- and proinflammatory processes triggered by aging, and affecting the cognitive profile of the elderly. Studies have implicated the inflammatory pathway on increased severity of white matter hyperintensities and brain atrophy as mechanisms to develop brain alterations and cognitive decline in older subjects (31, 32).

Highlighted as an important neuroendocrine marker, the brain-derived neurotrophic factor (BDNF), is involved in neuroplasticity, differentiation, neuronal growth, learning, and memory (33, 34). Its decrease is reported in individuals with Parkinson's, AD, depression, and MCI, this last one a clinical condition evidenced through cognitive testing (35). Differences in BDNF polymorphisms may have consequences on antidepressant efficacy (36), and the presence of depressive symptoms is associated with lower BDNF peripheral levels before antidepressant treatment (37). Exercise can act as a positive mediator of cognitive functioning in individuals suffering from early dementia and mental disorders, these responses being attributed to a possible role of BDNF (15, 38).

AIMS OF THE STUDY

(a) To examine the multivariate associations between physical fitness (PF), cognitive indexes, biomarkers of inflammation, stress, and neurotrophic factors, associated with psychological well-being and mental health, in a cross-sectional study in older women subjects;
(b) To verify the hypothetical effect of different types of regular exercise practice on PF, hormonal responses related to immunological and neurocognitive systems in healthy older participants and those with MCI after 14 and 28 weeks of regular practice;
(c) To explore the associations between changes in neurocognitive and immunological systems, functional fitness, psychological well-being, and mental health by different exercise programs after 14 and 28 weeks of regular practice.

INITIAL PROCEDURES

All CSHS and participants (or responsible) will be required to give a full informed consent before beginning the study. Individuals who express interest in participating in the program will sign a statement of responsibility, in which the privacy of identity and data collected will be guaranteed as well as the possibility of accessing the medical report of the subject. The contact with the medical center was established as one of the criteria to verify the eligibility of each subject to perform the exercise program (**Figure 1**). Once individuals were interviewed to participate in the study, they were informed of the procedures for data collection and of the class sessions that would occur in the pilot study. An information session about the study protocol was created for presentation to local organizations and to all the individuals that express interest in participating in the study. The study protocol has been approved by Faculty of Sport Sciences and Physical Education Ethical Committee – University of Coimbra (number reference: CE/FCDEF-UC/000202013), and it is integrated in the research project entitled "PRO-HMECSI: Hormonal mediation of exercise on cognition, stress and immunity"; respected the Portuguese Resolution (Art.° 4st; Law no. 12/2005, 1st series) on ethics in research with humans (39); follows the guidelines for ethics in scientific experiments in exercise science research (40)

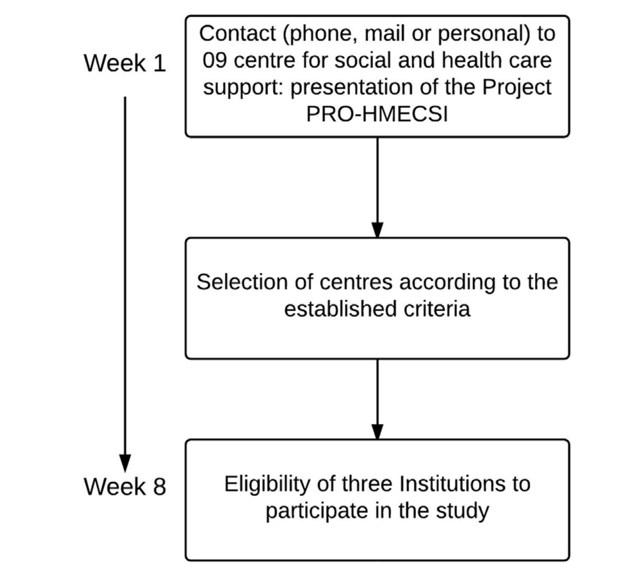

FIGURE 1 | **Flow chart of the PRO-MHESCI study design**.

and still, complied with the guidelines for research with human beings of the Helsinki Declaration (41).

CSHS Eligibility Criteria

CSHS eligibility criteria include (a) ability to participate in a study with total duration of 12 months and encompassing three phases: cross-sectional study, intervention, and detraining periods; (b) existence of an appropriate physical space to carry out the exercise sessions; and (c) required support of caregivers to assist with the elders displacement to the exercise classes.

Older Participant's Eligibility Criteria

The inclusion conditions for the older participants stipulated in order are being a female participant aged over 65 years; drug therapy controlled and updated; if the participant presents a clinical condition or comorbidity, it must be stable and enable participation in the exercise classes as decided by local medical staff. Specific criteria for participant exclusion are not completing or withdrawing from the "8-foot-up-and-go test" (8-UGT) in the maximum time of 50 s. According to previous studies with samples of institutionalized elderly, scores above this value indicate severe disability/mobility dependence (42); involvement in other structured exercise programs; the presence of any type of health condition that could prevent testing of functional autonomy, such as severe cardiopathy, hypertension, uncontrolled asthmatic bronchitis, and any musculoskeletal conditions that might prevent testing (i.e., osteoarthritis, recent fractures), mental disorder, hearing and vision impairment, morbid obesity, or the use of medications that could cause high attention impairment.

METHODS/DESIGN

This research is planned for ~16 months, and it is built in three different phases/studies as described below: the cross-sectional study 1 (4 weeks' duration) consists in the evaluation of older people (≥65 years old) aiming to investigate existing multivariate associations between PF, psychological well-being, cognitive, immunological, and neurotrophic factors in institutionalized elderly woman. Participants are older women living in CSHS. We will contact these subjects in CSHS located in the city of Coimbra, Portugal. Primary outcomes will be collected by a short test battery that measures biosocial, global health, cognitive, and PF indicators. PF battery, psychological well-being, multidimensional cognitive function profile, immunological, and neurotrophic factors are second outcomes and will also be collected. In addition, the secondary goals of this cross-sectional study 1 will be to identify the older women with MCI, for subsequent stratification and participation in the intervention study 2, described below.

The observational study 2 is an intervention study with three different chair-based exercise (CBE) programs for women aged ≥65 years. The study is designed to assess the effect of strength/elastic band, aerobic/walking, and yoga/flexibility exercise interventions on secondary outcomes of PF, immunological, and neurotrophic markers as well as cognitive function in older women with MCI, recruited in institutionalized context. It is assumed that the effect of the exercise programs is independent. Measurement of primary outcomes will take place 4 weeks prior to the beginning of the exercise programs, on the same variables of study 1. Participants in these groups will attend a 45-min exercise session, 2–3 times/week during 28 weeks. The exercise programs will be run in the care centers for safety, disability, and comfort reasons. An appropriate space will be prepared by our fitness instructor's team in each center to run the exercise sessions. Study 3 will involve analyzing the effect of 14 weeks detraining in all variables described in the observational study 2 above. Data regarding the assessment of psychological well-being related to mental health, cognitive function, PF, and biochemical markers will be collected (**Figure 2**).

SAMPLE SIZE

Sample size was estimated considering data of sample sizes described in a recent review (43) that obtained significant

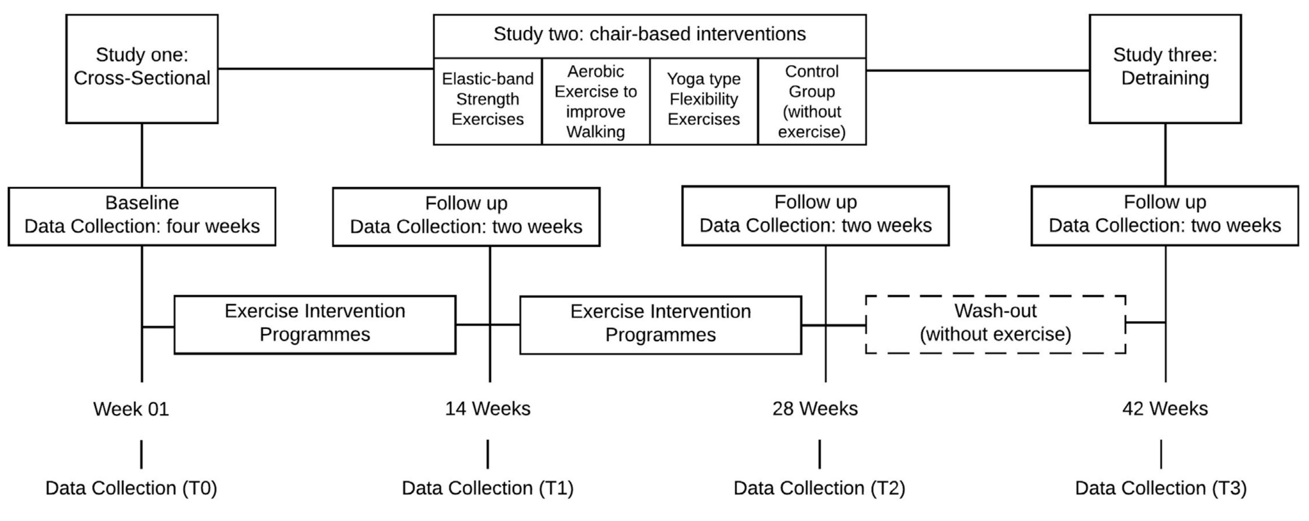

FIGURE 2 | **Timeline of the PRO-MHESCI: study 1 (cross-sectional), study 2 (Intervention), and study 3 (washout period)**.

results involving the effects of exercise on immunological and cognitive parameters of elderly samples with MCI. Estimating the incidence of MCI in institutionalized elders to be around 30 and 57% (44), a total of 223 participants will be recruited for study 1. The sample size for study 2 was estimated adjusting MANOVA for repeated measures effects, alpha (Type I error rate) at 0.05, and power (Type II error rate) at 0.85 were computed using G* Power Version 3.1.9.2 (45, 46). A total of 149 participants are estimated to provide enough information about the outcome variability in our study design. It is predicted that only 70% of the participants will complete the full program (47) justifying a minimum sample size of 25 individuals for both intervention and control group.

EXERCISE ADHERENCE

Exercise sessions will be offered 2–3 times/week, during 28 weeks, in a total of 78 sessions. The percentage of exercise adherence to group classes is calculated individually through the total sum of participation. Entries will be recorded in a database. When a participant has two consecutive absences, she will be contacted to return to the group classes. According to a recent systematic review, an adherence to the exercise program of 55% was established as minimum for each participant to be included in the study (47).

PILOT STUDY

A pilot study was conducted during 4 weeks with an exercise session per week. At the same time, interviews, psychometric scales, cognitive, and functional tests were applied to check the subject's conditions and evaluate the methods of application of the study. Classes with duration of 30 min were given during this period (pre-training, easy-level), to gain insight to the implementation of CBE programs, adequacy of the spaces and structures where the classes would take place, and test the rating of perceived exertion by the participants.

MASKING

The fitness instructor of the all CBE sessions will not take part in data collection procedures. Collection of saliva and blood samples as well as the global health assessment will be performed by a registered nurse. The assessment of psychometric, cognitive scales, and physical–functional fitness battery was organized by the principal investigators and will be applied by specialists and co-investigators of the research team. This assessment can be done in different days, respecting the motivation of the elders, interrupting the test, and continuing on another day if they feel tired or uncomfortable. To minimize differences in procedures the same evaluators that will perform the data collection will apply both baseline and follow-up questionnaires and physical–functional fitness battery tests. The specialists of PF, psychometric, and cognitive assessments will not make any reference to the exercise program and do not have access to the remaining data.

OUTCOME MEASURES

All outcome measures will be collected at baseline (study 1). After 14 and 28 weeks of exercise intervention (study 2) and after week 42 (washout period), biosocial and global health status will not be included. The primary outcomes are measures of cognitive function, biosocial, and global health status. One session will be used to administer a short test battery to measure biosocial, global health status, cognition (MCI screening), and PF (mobility screening) in this specific order. Secondary measures comprise psychological well-being, cognition, PF, anthropometric, immunological, and neurotrophic markers.

BIOSOCIAL STATUS

Information on sociodemographic characteristics such as chronological age (continuous and category form), gender (category), and education (continuous and category) will be collected and used for adjusting models.

NEUROCOGNITIVE PROFILE I: MEMORY COMPLAINTS AND MCI SCREEN

Participants included will be institutionalized older adults with memory complaints, i.e., those with possible MCI, who are at risk for developing dementia. For this purpose, the combination of two cognitive tests and respective cut-off values will be used.

MINI MENTAL STATE EXAMINATION

The mini mental state examination (MMSE) assesses five areas of cognition: orientation, immediate recall, attention and calculation, delayed recall, and language (48). The maximum score is 30 points and a score below 24 points is considered abnormal and used for dementia and MCI screening (49). The MMSE will be used to classify participants by cognitive profile as a category variable, following the criteria described by Mungas (1): (a) severe cognitive impairment (SCI, values between 01 and 09), (b) moderate cognitive impairment (MOCI, between 10 and 18); (c) MCI (values between 19 and 24); (d) normal cognitive profile (NCP, values between 25 and 30). The MSSE was included because it was shown to be sensitive to the effects of exercise in an older population (50).

HOPKINS VERBAL FLUENCY TEST

The Hopkins verbal learning task (HVLT) is one of the most commonly used memory tests in clinical neuropsychological evaluation of older adults and is used to assess verbal episodic memory, including immediate memory (48). It is a 4-min test, easy to administer, to score, and to well tolerate even by significantly impaired individuals. This test requires recall of a series of 12 words (nouns) from 3 semantic categories (precious stones, animals, and human dwellings) over 3 learning trials (35). Scores between 15.5 and 24.5 on this test indicate a risk of dementia or MCI (48). Recent studies indicate that this test has satisfactory construct and concurrent validity and good test–retest reliability, range 0.80 to 0.98 values (51, 52).

GLOBAL HEALTH STATUS EVALUATION

This evaluation includes the initial contact with the medical staff of the CSHS, in order to collect information on the medical history and current health of the participants that may condition their participation in the exercise programs. Additionally, comorbidity severity will be evaluated using the Charlson comorbidity index (CCI), in association with the medical drug record of the elders.

CHARLSON COMORBIDITY INDEX

The CCI is a method of predicting mortality by classifying or weighting comorbid conditions that has been widely utilized by health researchers to measure burden of disease. It has a weighted index based on 17 comorbid conditions that has been shown to predict 1- and 10-year mortality (53, 54). A recent studied aimed to update the index of 12 comorbidities showed adequate discrimination in predicting and classifying comorbidities, when analyzing data from six countries (55). In this study, the total score of the ICC is used as a continuous variable.

FUNCTIONAL FITNESS ASSESSMENT I: MOBILITY SCREEN

To assess quickness, agility, and dynamic balance, the "*8-foot up-and-go test*" (8-UGT) will be used. The time needed for the participant to get up from the chair, walk as quickly as possible around either side of the cone, and to sit back down in the chair is registered (56). According to recent research, the 8-UGT can be used to effectively screen older people at risk for low mobility (57, 58).

SECONDARY OUTCOMES

In total, three sessions will be used for collection of secondary outcomes. In the first session, cognitive and psychological tests will be applied. In the second day, blood and saliva samples will be collected. Anthropometric measures and PF tests will be applied in the third session.

NEUROCOGNITIVE PROFILE II: MULTIDIMENSIONAL COGNITIVE SCREEN

The cognitive profile assessment will be evaluated using the Portuguese version of the multidimensional evaluation cognitive battery developed by Hogervorst–Bandelow and used worldwide in many treatment and observational studies (13, 32). The cognitive testing requires <20 min, including MMSE and HVLT. These tests have in earlier interventions also shown to respond and be sensitive to the effects of exercise in the elders (59).

VERBAL FLUENCY TEST

Verbal fluency is a cognitive function that enables the retrieval of information from memory linked to executive and linguistic abilities (60). The verbal fluency test (VFT) evaluates an individual's ability to retrieve specific information within restricted search parameters, such as the semantic fluency, tested by asking the participant to generate a semantic category with names of animals (61). This test consists of giving the person 60 s to verbally list as many animals as possible.

DIGITAL SPAN TEST

The digital span test (DST) consists of two tests: in the first one, the examiner says a series of numbers and asks the participant to repeat them back in the same order. The test finishes when the subject fails two times in the same series or completes all the series (up to nine numbers). In the second one, the subject is asked to repeat a series of numbers in the inverse order. The first series begins with two numbers, and then continues in the same manner by increasing one number at each time. The test finishes when the subject fails two times in the same series or completes all the series (up to eight numbers). Administering the test forward assesses both attention and short-term memory. When the backwards version of the test is given, it also measures working memory (62).

SYMBOL MODALITY TEST

This is a measure of attention, perceptual speed, motor speed, visual scanning, and memory. A piece of paper with nine symbols corresponding to nine digits is given to the participants. On another sheet of paper, there are several rows of digits with empty spaces below them. The subjects are asked to fill in as many corresponding symbols as possible in 90 s (63).

PSYCHOLOGICAL WELL-BEING/MENTAL HEALTH

The test battery will be administrated by the same research team after a short briefing on the purpose of the study and requires <10 min. Standardized instructions will be given to all participants as well as encouragement to ask for help. Individual attention will be provided to participants with interpretation doubts, questions will be read to clarify the meaning assuring that no emphasis will be put on the question in order to avoid directing the answer. The test battery to be used in this study includes the Portuguese version of the tests describing below. All the tests scores will be analyzed as continuous variables.

ROSENBERG SELF-ESTEEM SCALE

A 10-item scale that measures global self-worth by measuring both positive and negative feelings about one self. The scale is believed to be unidimensional. All items are answered using a four-point Likert scale format ranging from "strongly agree" to "strongly disagree" (64). For items 1, 2, 4, 6, and 7, a reversal of the scores is done. The global self-esteem is represented by the sum of all scores and gives results between 10 and 40 points, where higher values represent higher levels of global self-esteem. Many studies have shown it to respond and be sensitive to the effects of exercise in the elders (65).

SATISFACTION WITH LIFE SCALE

The satisfaction with life scale (SWLS) is a short five-item instrument designed to measure global cognitive judgments of satisfaction with one's life. The scale usually requires only about 2 min of the participants' time (66). It uses a seven-point Likert scale, indicating your agreement with each item by placing the appropriate number on the line preceding that item. Results range between 1 and 35 points, with higher values representing higher levels of life's satisfaction (67).

PERCEIVED STRESS SCALE

The perceived stress scale (PSS) was originally developed as a 14-item scale that assesses the perception of stressful experiences by asking the participant to rate the frequency of his/her feelings and thoughts related to events and situations that occurred over the previous month. Seven out of the 14 items of PSS-14 are considered negative and the remaining 7 as positive, representing perceived helplessness and self-efficacy, respectively (68). For items 4, 5, 6, 7, 9, 10, and 13, a reversal of the scores is done. Final scores vary from 14 to 70 points. A higher score indicates greater stress (69).

HOSPITAL ANXIETY AND DEPRESSION SCALE

This questionnaire consists of two subscales, one measuring anxiety, with seven items, and one measuring depression, with seven items, which are scored separately. Each item is answered on a 4-point (0–3) response category, so that the possible scores range from 0 to 21 for anxiety and from 0 to 21 for depression. It takes 2–5 min to complete. The hospital anxiety and depression scale (HADS) manual indicates that a score between 0 and 7 is "normal," between 8 and 10 "mild," between 11 and 14 "moderate," and between 15 and 21 "severe" (70).

THE LAWTON INSTRUMENTAL ACTIVITIES OF DAILY LIVING SCALE

The Lawton scale is a suitable questionnaire to assess independent living skills. The instrument is most useful for identifying how a person is functioning at the present time and for identifying improvement or deterioration over time (71). There are eight domains of function measured with the Lawton independence activities day living (IADL) scale. Current recommendations are to assess all domains for both genders, although cultural differences with regard to the proposed tasks to be evaluated may exist. Participants are scored according to their highest level of functioning in that category (72). A summary score ranges from 0 (low function, dependent) to 8 (high function, independent).

KATZ INDEX OF INDEPENDENCE IN ACTIVITIES OF DAILY LIVING

The Katz index of independence in activities of daily living (ADL) is the most appropriate instrument to assess functional status as a measurement of the older person's ability to perform ADL independently (73). The index ranks adequacy of performance in the six functions of bathing, dressing, toileting, transferring, continence, and feeding. Participants are scored yes/no for independence in each of the six functions (74). A score of 6 indicates full function, 4 indicates moderate impairment, and 2 or less indicates severe functional impairment (75).

FALLS EFFICACY SCALE

The falls efficacy scale (FES) contains questions that assess the concern about the possibility of falling during the performance of 10 activities (76). The trust that the elders have to perform the activities without falling is represented on a 10 points analog scale ranging from "No confidence" (10 points) to "Completely confident" (1 score). The score of the FES is the sum of the scores obtained in each of the 10 items. The minimum score possible is 10 and the maximum is 100. Accordingly, the lower the score, the greater the confidence, resulting in a high self-efficacy (77).

BIOCHEMICAL ASSESSMENT I: COLLECTION OF SALIVA SAMPLE

Saliva will be collected by passive drool (the participant allows saliva to collect on the floor of the mouth, then leans forward and dribbles into a tube), for 3 min in high quality polypropylene vials to avoid problems with analyte retention or the introduction of contaminants that can interfere with the immunoassays. The collection times are always at the same time in the morning in order to minimize the circadian effect seen with some of the markers under study. Prior to the saliva collection subjects will be asked to rinse their mouth with water to remove food residues 10 min before sample collection and to avoid: alcohol for 12 h, dairy products for 20 min, a big meal for 60 min, foods with high sugar or acidity, or high caffeine content immediately before sample collection. The tubes containing the saliva will then be frozen, then defrosted and centrifuged in order to collect the saliva sample. The volumes measured, the flow rate calculated, and the samples will be store at −20°C until determination of the saliva markers proposed for this study. IgA, testosterone, cortisol, and DHEA will be analyzed by ELISA (Salimetrics, UK), and Alpha-Amylase by a kinetic-assay (Salimetrics, UK), according to standard procedures (78).

BIOCHEMICAL ASSESSMENT II: COLLECTION OF BLOOD SAMPLE

Blood will be collected by venopuncture, in a fasted state, by a registered nurse. Determination of blood counts done after the blood collection, and then the tubes will be centrifuged for the collection of plasma and serum and these stored in cryovials at −80°C until determination of the serum and plasma markers proposed for this study. The levels of the pro- and anti-inflammatory cytokines, such as IL-1β, IL-6, IL-10, IFN-γ, and TNF-α, the cardiovascular risk marker, such as CRP, and the neurotrophic factor, such as BDNF, will be analyzed by ELISA kits according to the manufacturers' instructions.

FUNCTIONAL FITNESS ASSESSMENT II: SENIOR FUNCTIONAL BATTERY

The functional fitness of every participant will be measured using the Senior Fitness Test battery developed and revised by Rikli and Jones (79). The lower body strength is determined with the "*30 second's chair-and-stand test*" (CST) that measures the total number of stands completed in 30 s. The upper-body strength is determined with the "*30 seconds Arm-curl test*" (ACT) that measures the total number of arm curls executed in the 30-s. The aerobic endurance is determined with the "*2-minute step test*" (2ST) that measures the number of full steps completed in 2 min, raising each knee to a point midway between the patella (kneecap) and iliac crest (top hip bone). Score is the number of times the right knee reaches the required height. To assess lower-body flexibility, the "*chair sit-and-reach test*" (CSR) measures the maximum reach as forward as possible toward or past the toes. The upper-body flexibility is determined with the "*back scratch test (BST)*" that measures the distance of overlap or between the tips of the middle fingers of the back. For the abovementioned each test, there is cut-off values adjusted for sex and age, which will be analyzed as continuous variables.

ANTHROPOMETRIC MEASURES ASSESSMENT

The anthropometric measurements will be applied in four different moments following standardized procedures (80): in the beginning of the project for the data collection of the cross-sectional study and at three time-points during the intervention study. Measurements will take place in a separate room in order to give some privacy to the participants. Body mass will be determined using a portable scale (Seca®, model 770, Germany) with a precision of 0.1 kg. Waist circumference will be measured using a retractable glass fiber tape measure (Hoechstmass-Rollfix®, Germany) with a precision of 0.1 cm. Stature will be determined using a portable stadiometer (Seca Bodymeter®, model 208, Germany) with a precision of 0.1 cm.

CHARACTERIZATION OF THE EXERCISE PROGRAMS

The development of the exercises programs will include the selection of intervention programs, defining the types of exercise, conducting literature review, consultation with specialists from each exercise program, presentation of the final version of the chair-based exercise program design, and beginning of implementation of the pilot study in care centers. All classes, of each exercise program, will be administered by two instructors. The main guidelines of exercise prescription recommended by the American College of Sport Medicine Science (ACSM) for older adults (81) will be followed. In addition, recent guidelines for exercise prescription in groups, with the support of a chair will be followed (82). The chair-based group exercise classes can vary in intensity from vigorous chair aerobics designed to provide muscle conditioning and aerobic benefits for healthy adults to movement that concentrates or maintaining a basic level function for older participants (82, 83). Music will not be used during the sessions, since the objective is to test the influence of exercise without music for some cognition parameters and therapy of music alone (84) or combined with physical exercise (85) can positively influence cognition. All exercise programs will have the same number of sessions. Detailed exercise description is presented in **Table 1**.

CHAIR ELASTIC-BAND STRENGTH EXERCISES

The chair elastic-band strength exercises (CSE) consist of an exercise class performing a determined number of sets, repetitions, cadence of execution, and rest between sets using a Thera-band® elastic bands exercise system (86), that takes into account the ACSM guidelines for muscle-strength exercises prescriptions for older populations (81). The session consist of six exercises for body mobilization and dynamic stretching (5 min warm-up); between 8 and 10 elastic-band exercises using the three first levels of elastic bands (yellow, red, and green), for the development of muscle-strengthening activity (20–30 min); five easy stretching exercises to promote cool down lasting 15 min. We will expect real effort to be 60–85% of maximum heart-rate values recommended by the ACSM as the work intensity for the older people submitted to exercise programs. This would allow the training stimulus dosage to be precisely controlled in both the session in progress and between different sessions (86).

CHAIR AEROBIC EXERCISES TO IMPROVE WALKING

The classes of chair aerobic to improve walking exercises (CAW) include activities that involve minutes of walking, chair-based sit, and reach exercises and activities for upper and lower body members. The walking time is expected to increase gradually during the program (81). The session has a maximum duration of 45 min divided into three parts with the following characteristics: warm-up (5–10 min) six exercises for body mobilization and dynamic stretching, 7–10 specific exercises to improve walking in a sitting and standing position, lasting 20–30 min, and cool-down easy stretching exercises to promote cool down lasting 15 min. Exercise intensity will be measured with heart rate (HR) monitors and real effort is expected to be 60–85% of maximum HR.

CHAIR YOGA TYPE FLEXIBILITY EXERCISES

The introduction of āsanas shall be made through a sequence of movements combined with breathing (87). This method allows

TABLE 1 | Overview of the two phases of chair-based exercise programs intervention and some specifics exercises.

Modality	Warm-up phase[a] (7 min.)	% HR / RPE	Main part of the workout/conditioning phase (30 min.)	% HR / RPE	Cool-down phase (7 min.)	% HR / RPE
Phase I – the first 14 weeks						
AEW	General body mobilization and dynamic stretching chair-based exercises	~50–60 1–3	Aerobic walking activity: divided in 7–10 sets. They will be held a series containing 4–8 chair-based aerobic exercises. After performing 2–3 sets, the participants will be encouraged to combine the walk around the gym-room during 2–3 min. Walking time may be increased gradually during the program. Example of exercises: (1) chair-based sit and reach, leg extension, and overhead reach and standing rear leg extension (2–3 sets × 10 reps); (2) 2-min walking; (3) arm rising, hip marching, chair stand, and upper-body twist; (4) 2-min walking	~60–70 3–4	General body mobilization and static stretching chair-based exercises	~50–55 1–2
EB-RT	Eight exercises performed in two sets of six repetitions (reps) for general body mobilization	~50–60 1–3	Muscle-strengthening activity: 8–10 exercises using the first level of elastic Thera-band. Will consisted in to pull-up the elastic-band for 10 reps × 2 sets, with the concentric phase for 1 s and eccentric phase for 2 s with 45 s rest between sets and exercises. Examples of exercises: (1) front squat, (2) unilateral hip flexion in the chair, (3) bench over row, (4) chest press, (5) standing reverse fly, (6) spine twist extension arm, (7) shoulder press/twist arm front position, (8) frontal total raiser, (9) biceps arm curl stand/chair, and (10) overhead triceps exertion	~60–70 3–4	General body mobilization and static stretching chair-based exercises	~50–55 1–2
YTF	Standing or sitting exercises of joint mobilization and exercises to promote respiratory body awareness	~40–50 1–2	Standing or sitting practice of *āsanas* and postures sequences. Ex: (1) "Seated Forward Bend" (*Paschimottanasana*), (2)"Butterfly" (*Baddha Konasana*), (3) "Seated Spinal Twist" (*Ardha Matsyendrasana*), (4) "Cow face pose" (*Gomukhasana*), (5) "Cat" (*Cakravakasana*), (6) "Child's Pose" (*Balasana*), (7) "Snake" (*Bhujangasana*), (8) "Child's Pose with arms extended" (*Utthita Balasana*), (9) "Side Bending Stretch" (*Tiryaka Tadasana*), (10) "Dorsal Torsion" (*Kati Chakrasana*), (11) "Triangle" (*Trikonasana*), and (12) "Eagle" or "Half eagle" (*Garudasana*)	~50–60 2–3	Sitting or lying respiratory body awareness exercises, located massages, exercises for muscle relief, and meditation and vocalization	~40–45 1–2
Phase II – the last 14 weeks						
AEW	General body mobilization, dynamic flexibility chair-based exercises, and 3 min of "easy walking"[b]	50–60 1–3	The progress of the program will be followed according to aerobic endurance activity guidelines, therefore basing on the inclusion of more difficult and complex chair-based aerobic exercises and challenges sequences. Additionally, it will be increased walking time and placed obstacles during the walking route (cones, floor markers, arcs) to work handedness, changes in direction and coordination	60–70 3–4	1–2 min easy walking, general body mobilization, and static stretching stand exercises	50–55 1–2
EB-RT	Six exercises (3 sets × 6 reps) for general body mobilization and dynamic stretching	50–60 1–3	The progress of the program will be grounded on the muscle-strengthening activity guidelines, therefore basing on the inclusion of more exercises sets. Also, the same exercises in the Phase I will be used, but with more complex progressions. Example: 2–3 sets × 10 reps of front Squat in the chair + frontal raiser	60–70 3–4	General body mobilization and static stretching chair-based exercises	50–55 1–2
YTF	Standing or sitting exercises of joint mobilization and exercises to promote respiratory body awareness	~40–50 1–2	The progress of the program will be grounded on the Hatha Yoga philosophy, therefore basing on the inclusion of more difficult and complex āsanas and challenging sequences. Postures will be modified or added, sequences should have more postures with more difficult transitions, and the goal range of each posture will be increased	~50–60 2–3	Sitting or lying respiratory body awareness exercises, located massages, exercises for muscle relief, and meditation and vocalization	~40–45 1–2

CBE, chair-based exercises; RPE, rated perceived exertion; % HR, percentage of the estimated maximal heart rate; Reps, number of repetitions; Rest, interval recovery.
[a]Specific exercises for different body segments, i.e., neck and shoulders, back and chest, waist and legs.
[b]Easy walking, 2–3 min of walking around the fitness room.

the modification of postures itself and of how to "enter" and "leave" the postures, which simplifies working with limiting conditions in group classes with various levels of physical ability and can be reviewed according to the participants evolution (88). Additionally, the methods of design of the exercise programs include the ACSM guidelines for stretching exercises prescriptions for older populations (81). The global exercise intensity will be measured with HR monitors, and it is expected that the real effort will be 50–75% of maximum HR, the values recommended by the ACSM.

EXERCISE INTENSITY CONTROL

Heart rate monitors will randomly be used in five participants, during the exercise sessions in all exercise programs, as aid adjustment and control of training loads. For safety reasons, exercise intensity is indirectly predicted using the Karvonen's formula to predict target HR but with maximal heart rate (HR_{max}) being calculated using Franklin, Whaley, and Howley formula's for older people (HR_{max} = 207 beat per minute − 0.7 × chronological age) (89).

EXERCISE ADHERENCE TO THE INTERVENTION PROTOCOL

The instructors will document attendance to each class and the levels of exercise adherence will be calculated using the number of sessions attended as a covariable in secondary analysis of the exercise results. Intervention groups are asked to attend at least 70% of the classes. The instructors and research team staff will be asked to motivate the participants every time an absence to two consecutive classes occurs (47).

DATA ANALYSIS

The assumption of normality will be checked by the Kolmogorov–Smirnov test with Lilliefors' (K–S) significance correction and by visual inspection of normality plots. In study 2, comparison between groups will be accomplished using Univariate Statistics, in particular the independent *T*-test for 2 paired samples, and one-way analysis of variance (ANOVA) for *K*-independent samples. To elucidate which pathways (as biological, psychological, and behavioral parameters) will play a significant role in the effects of exercise on cognitive function in the participants, we will conduct mediation analysis. In this case, hormonal mediation will be analyzed by including hormone levels as covariates in the models with cognitive and immunological outcomes, to see if they partially or fully explain the exercise effects (make exercise effects less or non-significant), where there are exercise effects. These analyses will be conducted using SPSS and R (www.r-project.org) at a significance threshold of alpha = 0.05, adjusted for multiple comparisons where relevant. Data analysis will include repeated measures ANOVA models for block designs of different exercise conditions (SPPS and R), and mixed effects models to include graded dose-dependent exercise effects whilst also allowing for repeated measures data (using R). ANOVA models require principally that variance between cells does not differ too strongly (not more than factor 2), which will be checked in the assumptions checking stage. Mixed effects models allow very flexibly for non-normal outcome data distributions, for example, binomial for accuracy data (e.g., correct/wrong answers on cognitive tests) or Poisson for count data. Biological and psychological data are also often log-normally distributed (e.g., hormone levels, reaction times), variables where this is applicable will be log-transformed if the resulting distribution shows a better match with a normal distribution. Model residuals will also be checked for deviations from normality. Because a large number of outcome variables will be collected in this study, variable grouping and compound score selection will be based initially on theoretical domains (90, 91). The between-subject SD for each dependent variable was used to convert the changes in all variables into standardized [Cohen effect size (ES)] changes in the mean. Using Hopkins as guide (92), ESs were considered as trivial ($d \leq 0.2$), small ($0.2 < d < 0.6$), moderate ($0.6 < d < 1.2$), large ($1.2 < d < 2.0$), very large ($2.0 < d < 4.0$), and nearly perfect ($d > 4.0$). This will be confirmed by correlation matrices (all variables in a group should correlate with at least 50%) and principal component analyses where the first component should carry at least 70% of the variance.

DISCUSSION

This study will allow us to investigate which hormonal parameters are able to mediate the effects of exercise on immunity, psychological stress, and cognitive improvement and dementia risk in older people who are regularly active and which type of exercise is more effective in promoting immune and psychological health and cognitive improvement. The final goal is to develop exercise protocols that may lead to prevention of disease and a better quality of life. This study also sustains the hypothetical premise that exercise improves neurocognitive functions, following a current trend study in the field of aging (23, 59, 93). However, to the best of our knowledge, no large intervention study has yet been conducted on the effect of these exercise interventions on cognitive decline in subjects with MCI. The pilot study for this type of population is essential as it will reveal to what extent adherence to exercise suffers influence of psychosocial factors in chronic diseases (94, 95). It is important to monitor the effectiveness of the program, as evidence shows that a low cognitive profile may compromise the trainability of the participants (96). This study also shows a strong multidisciplinary approach, since it is prudent to investigate the combined effects of some independent variables. In addition, we will also look at the hypothetical premise that some objective measures have strong associations with subjective perception measures.

AUTHOR CONTRIBUTIONS

AT and JF designed and coordinated the research project. GF and MC drafted the paper. All the authors have made a substantial contribution in their respective areas of expertise, critically revised the work, approved the final version, and agreed to be accountable for all aspects of the work.

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Predicting Frail Syndrome using adverse geriatric health outcomes: comparison of different statistical classifiers

Furtado, Guilherme†; Loureiro, Marisa†; Ferreira, José; Teixeira, Ana; Patrício, Miguel

Abstract— **The present work seeks to evaluate the role of statistical classifiers based on sociodemographic data, anthropometric measurements and adverse health outcomes for identifying frail individuals. Three classifiers were considered: Logistic Regression, Random Forest and Support Vector Machines. The best results were obtained with Logistic Regression models based solely on 3 predictors, which reached an area under the curve [0.80, 0.85], specificity [75%, 81%] and sensitivity [80%, 86%]. These models display a promising role as a brief and easy screening tool for Frail Syndrome and should be further assessed, notably by external validation.**

I. Introduction

Detecting frail syndrome (FS) in older populations using brief and easy screening tools is highly sought, as it may reduce costs and unnecessary complex health assessments, [1]. In a classical approach, Fried and colleagues have developed a construct, called "Frailty Cycle" [2]. They identified five components in the FS, that can classify the older population in frail, pre-frail and nonfrail subgroups [3]. Several authors report having sought or assessed psychosocial, clinical or physiologically relevant variables for their association with FS or evaluated how putative predictors of FS may serve as screening tools. In particular, [4] showed how motor performance tests such as a "chair stand" test may be used as screening instruments for FS in older adults. In [5], the Short Physical Performance Battery is studied in community-dwellers. Both gait and balance assessments with wearable sensor technology were evaluated in a small number of patients with peripheral artery disease in terms of their roles as early indicators of FS [6]. Timed up-and-go (TUG) test results in a large sample of the older Irish population were reported in [7], with TUG seen to accurately identify frail elements of the population but being less able to discriminate nonfrail from the pre-frail or frail. In [8] the authors sought to identify kinematic variables suitable for screening for FS. These kinematic variables were measured using inertial sensors embedded in smartphones that the participants wore in a small sleeve fixed around the trunk while performing the expanded TUG test. The role of physical activity levels (LPA) in different domains (notably, work, transportation, housework and leisure) was assessed as a predictor of absence of FS in the elderly, [9]. Serum sirtuins were reported to be promising noninvasive protein markers for FS in [10], whereas an association was seen to exist between FS in the older institutionalized men and inflammatory markers, in particular serum levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF- α) and high sensitivity C-reactive protein (CRP).

Though machine learning procedures are known to be data hungry [11], they allow combining several potential predictors of FS to obtain potentially better screening tools. However, few authors have attempted to use these procedures. In particular, [12] aimed at distinguishing between pre-frail and frail individuals with artificial neural networks based on an automatic system to measure general clinical indicators. The predictors were measured using devices that can also be used as furniture (for example, a chair with a pressure sensor) and electronic questionnaires. The neural networks were trained with data gathered on 160 subjects and assessed over data collected on further 149 people. The sensitivity and specificity of this approach were reported to be 79.7% and 86.2%, respectively. In [13] the authors further improved the results of an earlier article using logistic regression models [14], by studying how three physical assessments (TUG, five times sit to stand and quiet standing balance) could be taken as predictors in support vector machines (SVM) to distinguish between two groups of community-dwelling older adults: non-frail and frail. The latter group comprised not only individuals who were classified as frail by the Fried FS criterion but also those classified as pre-frail. Separate classifier models were generated for males (17 of which in the non-frail group and 16 in the frail group) and for females (41 of which in the non-frail group and 50 in the frail group). Ten repetitions of 10-fold validation were used to assess the sensitivity and specificity of the models, which are reported to be 91.3% and 96.5% for males and 86.0% and 73.0% for females, respectively.

In this exploratory study, we aim to assess how different machine learning procedures may be applied to accurately predict FS in institutionalized older woman, using adverse health outcomes, notably functional fitness, cognition status, state of depression, physical functioning, body composition, comorbidity index, levels of cortisol and chronologic age.

II. Methods

A. Design and ethical aspects

The FS incidence was assessed in older people living in Centers for Social and Health Care Support situated in the

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Guilherme Furtado (grant CAPES/CNPQ – Ministry of Education, Brazil, BEX: 11929/13-8), José Ferreira and Ana Teixeira are registered at Research Unit of Sport and Physical Activity, Faculty of Sport Science and Physical Education, University of Coimbra, CIDAF [UID/PTD/04213/2016] (e-mails: furts2001@yahoo.com.br, jpferreira@fcdef.uc.pt, ateixeira@fcdef.uc.pt respectively).

Marisa Loureiro and Miguel Patrício are with the Laboratory of Biostatistics and Medical Informatics and IBILI, Faculty of Medicine, University of Coimbra (phone: 00351239480029; fax: 00351239480217; e-mails: mjpd@uc.pt and marisa.loureiro@uc.pt, respectively).

† Equally contributing first authors.

district of Coimbra, Portugal. All participants expressed interest in participating in the study and signed a statement of responsibility. This study has been approved by the Faculty of Sport Sciences and Physical Education Ethical Committee (Reference CE/FCDEF-UC/000202013) - University of Coimbra and respects the Portuguese Resolution (Art.º 4st; Law n. 12/2005, 1st series) and [15] and Helsinki Declaration [16].

B. Participants

A total of 203 individuals aged over 65 years expressed interest in participating in the study. After selecting only female participants, accounting for dropouts and excluding individuals with low clinical health condition, a total of 118 older women were included in the study.

C. Data collection

Sociodemographic data: chronological age was assessed through data of birth.

Anthropometric measurements: Body mass was determined using a portable scale (Seca®, model 770, Germany) with a precision of 0.1 kilograms. Stature was determined using a portable stadiometer (Seca Bodymeter®, model 208, Germany) with a precision of 0.1 centimetres (CR = 0.98). Body mass index (BMI) was calculated according to the usual formula: BMI = weight/height2 [17].

FS screening: The prevalence of FS was calculated according to the Fried FS protocol [2]. Participants were classified as frail when three or more of the following criteria were present: shrinking, which was evaluated by self-report about unintentional weight loss of four kilograms or more in the last six months; poor endurance and energy (self-reported exhaustion), which was analysed by negative concordance of two questions from the CES-D depression scale [18]; weakness, which was assessed by handgrip strength test [19]; slowness, which was evaluated by 4.6 meters walking test [20] and low LPA, which was analysed resorting to the International PA Questionnaire (IPAQ) [21]. A participant was classified as pre-frail when one or two criteria were present and non-frail when none of the criteria held.

Adverse health outcomes: Cognitive status was assessed through Mini Mental State Exam (MMSE), [22]. Comorbidity was assessed using The Charlson Comorbidity Index (CCI) that measures burden of disease and has a weighted index based on 19 comorbid conditions, [23]. Depressive state was assessed by CES-D scale [18]. For Physical Functioning, the Portuguese version of Katz Index of Independence in Activities of Daily Living (ADL) was used. The Index ranks adequacy of performance in the 6 psychobiological functions [24]. For functional fitness, the lower body strength was assessed with the '30 seconds chair stand' (30CST) that measures the total number of executed in this period of time, [25]. In terms of the biochemical marker, saliva samples of Cortisol (sCOR) were collected by passive drool and analyzed by ELISA according to the manufacturer instructions (Salimetrics, UK). The complete method for treatment of biochemical samples was described in a previously published study protocol, [26].

D. Statistical analysis

All predictors were assessed for normality resorting to Shapiro-Wilk tests, [27]. Normally distributed variables are described as mean±standard deviation, whilst non-normally distributed variables are described as median (25th percentile; 75th percentile). Comparisons between groups were performed resorting to t-Student tests or Mann-Whitney U tests, as applicable.

A logistic regression model was used with all 8 predictors, the dependent variable expressing whether each subject was frail. All assumptions were verified. Subsequently, a forward logistic regression was employed to assess the contribution of the different predictors. These computations were performed on IBM SPSS Statistics 24. All 8 variables were considered to build up classification models, implemented in R 3.3.2 using the "randomForest", "e1071" and the base packages with default parameters. Logistic regression (LR), support vector machines (SVM) and random forests (RF) models, each including the n most meaningful predictors (n ranging from 1 to 8) were assessed. For that purpose, Monte Carlo cross-validation was used [3], with 500 random splits of the data into training and test sets, with 70.3% of the data assigned to the training set. For each model, a 95% confidence interval from percentiles for the area under the curve (AUC) was determined using ROC analysis.

III. Results

Out of the 118 female participants, 64 were observed not to be frail (this "Not frail" group comprises 19 non-frail individuals and 45 pre-frail individuals) and 54 observed to be frail. The data collected for the two groups is illustrated in Figure 1 and further described in Table 1.

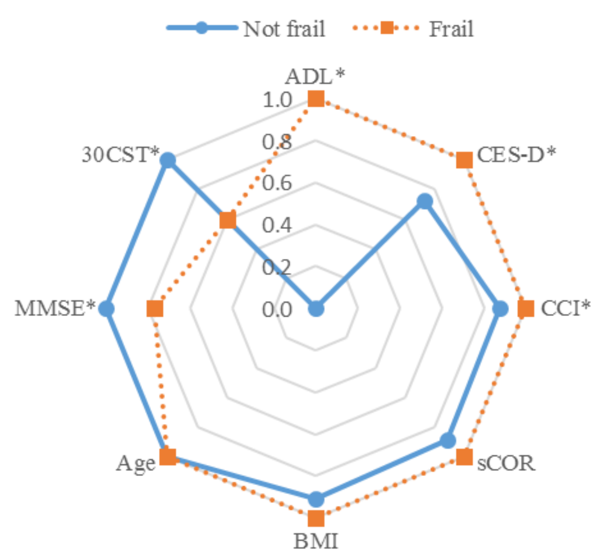

Figure 1. Radar chart illustrating the different profiles of the "Not frail" and "Frail" groups. For each predictor, its median value was computed for each group and normalised by dividing it with the largest of the two medians.

Table 1. Univariate comparisons of predictors between the "Not frail" and the "Frail" groups.

Variable	*Not frail (n=64)*	*Frail (n=54)*	*p-value*
ADL	0.0 (0.0; 1.0)	1.0 (1.0; 3.0)	<0.001
CES-D	17.5 (13.5; 25.5)	24.0 (20.0; 30.0)	<0.001
CCI	7.0 (6.0; 8.0)	8.0 (7.0; 9.0)	0.023
sCOR	0.24 (0.11; 0.30)	0.27 (0.16; 0.33)	0.182
BMI	27.8±4.4	29.3±5.7	0.126
Age	81.7±8.1	82.2±7.7	0.76
MMSE	22.0 (17.0; 26.0)	17.0 (13.0; 22.0)	<0.001
30CST	10.0 (7.0; 12.0)	6.0 (5.0; 8.0)	<0.001

Data is presented as mean±standard deviation or median (25^{th} percentile; 75^{th} percentile). The p-values were obtained with t-Student tests or Mann-Whitney tests, as applicable.

A statistically significant logistic regression model was obtained using all predictors, $\chi^2(8)=51.166$, $p<0.001$; Nagelkerke $R^2=0.470$, Hosmer and Lemeshow $\chi^2(8)=3.556$, $p=0.895$, see Table 2.

Table 2. Results of the logistic regression model obtained using all predictors as independent variables.

Predictor	*B*	*S.E.*	*p-value*	*95% CI for OR*
Age	-0.003	0.031	0.934	[0.939, 1.059]
BMI	0.059	0.050	0.240	[0.961, 1.170]
CCI	0.154	0.141	0.278	[0.884, 1.539]
MMSE	-0.122	0.048	0.011	[0.806, 0.972]
ADL	0.265	0.185	0.151	[0.907, 1.874]
CES-D	0.049	0.032	0.128	[0.986, 1.120]
30CST	-0.287	0.086	0.001	[0.634, 0.888]
sCOR	-0.211	0.805	0.794	[0.167, 3.927]
Constant	0.607	3.353	0.856	

B is the regression coefficient; S.E. is the standard error for B; 95% CI for OR is the 95% confidence interval for the adjusted odds ratio.

By decreasing order of importance, assessed by a forward logistic regression model with all predictors, the statistically meaningful predictors were: 30CST, MMSE and CES-D. Again by decreasing order of importance, this time assessed by a backward logistic model including all variables, the remaining predictors were: ADL, BMI, CCI, sCOR and Age.

The results obtained using the aforementioned classification models can be seen in Table 3.

Table 3. Area under the ROC curve, sensitivity and specificity obtained using three classification models and considering a varying number of predictors.

n	*Performance measure*	*LR*	*RF*	*SVM*
1	AUC	[0.76, 0.81]	[0.71, 0.76]	[0.74, 0.79]
	Sensitivity	[0.65, 0.72]	[0.64, 0.70]	[0.62, 0.69]
	Specificity	[0.78, 0.85]	[0.81, 0.86]	[0.80, 0.87]
2	AUC	[0.79, 0.83]	[0.71, 0.75]	[0.75, 0.80]
	Sensitivity	[0.71, 0.77]	[0.64, 0.71]	[0.67, 0.73]
	Specificity	[0.79, 0.85]	[0.75, 0.81]	[0.80, 0.86]
3	AUC	**[0.80, 0.85]**	[0.74, 0.79]	[0.79, 0.83]
	Sensitivity	**[0.75, 0.81]**	[0.68, 0.75]	[0.77, 0.83]
	Specificity	**[0.80, 0.86]**	[0.79, 0.86]	[0.79, 0.84]
4	AUC	[0.80, 0.84]	[0.76, 0.80]	[0.79, 0.83]
	Sensitivity	[0.74, 0.80]	[0.68, 0.74]	[0.74, 0.80]
	Specificity	[0.79, 0.85]	[0.82, 0.88]	[0.80, 0.86]
5	AUC	[0.80, 0.84]	[0.79, 0.84]	**[0.80, 0.84]**
	Sensitivity	[0.71, 0.77]	[0.72, 0.78]	**[0.75, 0.81]**
	Specificity	[0.81, 0.87]	[0.82, 0.87]	**[0.77, 0.84]**
6	AUC	[0.79, 0.84]	**[0.80, 0.84]**	[0.79, 0.84]
	Sensitivity	[0.70, 0.76]	**[0.73, 0.79]**	[0.72, 0.79]
	Specificity	[0.83, 0.89]	**[0.82, 0.88]**	[0.80, 0.86]
7	AUC	[0.78, 0.83]	[0.79, 0.83]	[0.78, 0.83]
	Sensitivity	[0.70, 0.76]	[0.70, 0.77]	[0.70, 0.77]
	Specificity	[0.81, 0.87]	[0.81, 0.87]	[0.80, 0.87]
8	AUC	[0.77, 0.82]	[0.77, 0.82]	[0.77, 0.81]
	Sensitivity	[0.70, 0.76]	[0.69, 0.76]	[0.68, 0.75]
	Specificity	[0.80, 0.86]	[0.80, 0.86]	[0.79, 0.85]

In the table, n is the number of predictors included in the classification models; LR is short for Logistic Regression; RF is short for Random Forest and SVM is short for Support Vector Machine. For each performance measure, 95% confidence intervals are presented.

The best AUC values for the LR models, [0.80, 0.85], were attained using solely 3 predictors. The corresponding 95% confidence intervals for the specificity and the sensitivity were [75%, 81%] and [80%, 86%], respectively. For the RF models, the best AUC values were [0.80, 0.84], with corresponding sensitivity [73%, 79%] and specificity [82%, 88%], attained using 6 predictors. As for SVM, the AUC reached [0.80, 0.84] when 5 predictors were used. The corresponding sensitivity and specificity were [75%, 81%] and [77%, 84%], respectively.

IV. Discussion

Other studies have reported using statistical classifiers to distinguish between FS status. In [12] the goal was to distinguish between pre-frail and frail individuals, while in [13] the distinction was made between a group of non-frail individuals and a group either pre-frail or frail. The present study focused on discriminating between frail and either non-frail or pre-frail instead. A direct comparison between the three studies is unfair, as the dependent variables were different, but it is noteworthy that there are no great differences in the sensitivities and specificities reached with the exception that, in [13], better results were obtained for models generated for male patients. The present work did not include male patients as the sample size for these patients would be quite small. Still, including 118 participants implied adopting a feature selection algorithm as models using statistical classifiers are known to require a large ratio of observation per variable for trustworthy results to be obtained, [11]. Performance measures obtained for models with fewer variables are, in this sense, more likely to be reliable. In particular, the LR models were able to attain high AUC values with solely three predictors. This is advantageous if one seeks to find brief and easy screening tools, as the practical application of the model would only require obtaining data on 30CST, MMSE and CES-D.

As usual, further validation should be undertaken to confirm the diagnostic value of the models, [28]. Moreover, it would be interesting and, to the best of our knowledge, novel, to propose models to distinguish between all three FS subgroups.

V. Conclusion

A logistic regression model with solely three predictors was sufficient to attain a 95% confidence interval for the AUC of [0.80, 0.85]. This is a promising result when seeking for a brief and easy screening tool for FS, which should be further assessed, notably by external validation.

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Dear Ms. Furtado:

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ANNEX V:

MAIN ACTIVITIES CARRIED OUT DURING THE COURSE

GENERAL INFORMATION AND BIOGRAPHY

Guilherme Eustáquio Furtado was born in October 219th, 1979 in the city of Belo Horizonte, State of Minas Gerais - Brazil. After finishing the secondary school in Belo Horizonte (1999), has a degree in Sport Science and Physical Education at *Centro Universitário de Belo Horizonte - UNI-BH* (2001-2005). During this period studied (1 one year) in the Faculty of Sport Science and Physical Education at University of Coimbra (FCDEF-UC), under the Socrates program (2003-2004). In the year of 2010, he concluded post-graduate course in Functional Training at Universidade Lusófona de Tecnologia e Humaidade, Portugal and in 2011 was finished master's degree in Exercise and Health in Special Groups at (FCDEF-UC,Portugal). During the period of 2013-2014 was a junior investigator in the project "Hormonal mediation of exercise on cognition, stress and immunity [PTDC/DES-DTP/0154/2012], with a research fellow from the Portuguese Foundation for Science and Technology – FCT. In the period of 2014–2018 he concluded a PhD student in Sport Sciences in the branch of Physical Activity and Health and had earned a grant from the CAPES Foundation – ministry od Education, Brazil. He has large professional experience in fitness exercise programs. Currently, research has focused on modulated effects of regular exercise on biopsychologies outcomes (hormonal, psychological and physical fintness) in older adults with physical frailty condition.

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- José Pedro FERREIRA[1]; **Guilherme FURTADO** [1,2]; Matheus UBA-CHUPEL[1,2]; Rafael CARVALHO1[1], Taís RIEPING[1]; Nelba SOUZA[1]; Fábio DIREITO[1]; Margarida FIGUEIREDO-BRAGA[3] and Ana TEIXEIRA[1.] Effects of an aerobic walking exercise program on salivary cortisol, cognition, depression and feelings of happiness of institutionalized elderly women. ***International Society for Exercise and Immunology (ISEI) – Wien, Austria* – 2015.** Oral Presentation.

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- Guilherme FURTADO[1,2]; Matheus Uba-Chupel [1,2]; José Pedro Ferreira[1] e Ana Teixeira[1]. Efeitos de um programa de treino de força nos marcadores salivares da imunidade, em mulheres idosas frágeis. ***1º Congresso Ibero-americano de Desporto, Educação, Atividade Física e Saúde, 2015 – Lisboa.*** Oral Presentation.

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ORAL COMMUNICATIONS IN THE COMMUNITY ACTIONS

- Furtado G., Ferreira; JPL; Teixeira AM. (2014) **Programa Ativa-Idade (PROJETO MESCHI): A importância da prática regular de exercício físico em idosos que frequentam lares e centros de dia.** Comunicação realizada na Cáritas Diocesanas de Coimbra: Lar e Centro de Dia para acolhimento de pessoas idosas. Coimbra, junho.

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- Furtado G.; Uba-Chupel, M.; Ferreira; JPL; Teixeira AM. (2014) **Programa Ativa-Idade (PROJETO MESCHI): Comunicação parcial dos resultados da intervenção.** Venerável Ordem Terceira Da Penitência De São Francisco: Lar e Centro de Dia para acolhimento de pessoas idosas. Coimbra, Dezembro.

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- Furtado, GF; Ferreira, JP (2014). **Planificação do Treino em Indivíduos com condições especiais.** Seminário apresentado aos alunos do curso do 2º ano licenciatura [UnC Desporto de opção] em Exercício e saúde em populações Especiais da Faculdade de Ciências do Desporto e Educação Física da Universidade de Coimbra, Maio.

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- Furtado, GF; Campos, MJ, Ferreira, JP e Teixeira, AM (2015). **Programa de exercícios para idosos frágeis II: Treino de combinado.** Seminário apresentado aos alunos do curso do 3º ano de licenciatura [UnC Desporto de opção] Faculdade de Ciências do Desporto e Educação Física da Universidade de Coimbra, fevereiro.

- Furtado, GF; Teixeira, AM (2015). **Prescrição do exercício físico baseada na evidência em idosos com condições clínicas.** Seminário apresentado aos alunos do curso de Mestrado em Exercício e saúde em populações Especiais da Faculdade de Ciências do Desporto e Educação Física da Universidade de Coimbra, Janeiro.

- Furtado, GF; Teixeira, AM (2015). **Eventos de meia distância: Implicações metabólicas.** Aula de substituição ministrada aos alunos do 2º ano licenciatura [UnC Bioquímica do Exercício] da Faculdade de Ciências do Desporto e Educação Física da Universidade de Coimbra, Maio.

- Furtado G.; Ulba-Chupel, M.; Carvalho, R.; AF Ferreira; JPL; Teixeira AM. (2015) **Programa Ativa-Idade: Prática regular de exercício físico em idosos que frequentam lares e centros de dia.** Comunicação realizada no Centro de Atendimento à Terceira Idade, SCM. Cantanhede, Janeiro.

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- Direito, F., Ulba-Chupel, M.; Ripieing, T. Furtado; AF Ferreira; JPL; Teixeira AM (2015). **Ação de mobilização para prevenção das quedas em idosos: Uma experiência de 'Flash mob dance' com idosos institucionalizados [vídeo]**. Parceria com Grupo *ProFouND: Prevention of Falls Network for Dissemination* – Cáritas Diocesana de Coimbra.

- Direito, F., Ulba-Chupel, M.; Ripieing, T. Furtado; AF Ferreira; JPL; Teixeira AM (2015). **Mobilização para prevenção das quedas em idosos: Uma experiência de 'Flash mob dance' com idosos institucionalizados [vídeo].** Parceria com Grupo *ProFouND: Prevention of Falls Network for Dissemination.* Acção realizada no Centro de Atendimento à Terceira Idade, Santa Casa de Misericórdia de Coimbra.

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PARTICIPATION IN SHORT COURSES, LECTURES AND SEMINARS (LISTENER)

- Ageing@Coimbra (2015). **3º Congresso Regional sobre o Envelhecimento Ativo e saudável.** Auditório Central da Universidade de Coimbra, Janeiro.

- Projeto *Do-Health* (2014). **Quedas em idosos: Sinais de Perigo. Previna-se!** Auditório Central dos Hospitais da Universidade de Coimbra, Setembro.

- Cavaglieri, C. (2014) ministrou também uma palestra intitulada **"*Anti-inflammatory effect of exercise in obesity*"** Comunição proferida no âmbito da disciplina de Doutorado Seminário II. Faculdade de Ciências do Desporto e Educação Física da Universidade de Coimbra. Fevereiro.

- *Carvalho, HM (2015).* ***Research Methods in Sport Science*****.** Curso de metodologia da pesquisa aplicado às Ciências do Desporto. Faculdade de Ciências do Desporto e Educação Física da Universidade de Coimbra. Fevereiro.

- Cursos Laboratório de Bioestatística e Informática Médica (2016): **Revisões sistemáticas e metanálise** [duração: 4 horas] anfiteatro da subunidade 1 da Faculdade de Medicina. 26/Fevereiro.

- Cursos Laboratório de Bioestatística e Informática Médica (2016): **Pensamento estatístico aplicável** [duração: 4 horas] anfiteatro da subunidade 1 da Faculdade de Medicina. 22/Fevereiro.

- Cursos Laboratório de Bioestatística e Informática Médica (2016): **Regressão Logística e Anáise de ROC** [duração: 8 horas] anfiteatro da subunidade 1 da Faculdade de Medicina. 22/Abril.

- Cursos Laboratório de Bioestatística e Informática Médica (2016): **Modelos de regressão** [duração: 8 horas] anfiteatro da subunidade 1 da Faculdade de Medicina. 20/Maio.

- Cursos Laboratório de Bioestatística e Informática Médica (2016): **Investigação replicável** [duração: 4 horas] anfiteatro da subunidade 1 da Faculdade de Medicina. 22/Setembro.

- Ageing@Coimbra: **4º Congresso Regional sobre Envelhecimento Ativo e Saudável** (2016). Auditório da Faculdade de Medicina da Universidade de Coimbra. Maio.

- **17º Fórum Internacional de Desporto** (2017): integrado na edição da semana cultural na Universidade de Coimbra, Coordenação do mestrado em Treino Desportivo para Crianças e Jovens, Faculdade de Ciências do Desporto e Educação Física da Universidade de Coimbra (Março/2017)

ELABORATION AND PARTICIPATION IN SCIENTIFIC ARTICLES

- Furtado G. ; SOUZA, N. R. ; Ferreira JP ; Letieri R ; Carvalho H ; DANTAS, E. ; **ROCHA, SV** . The effects of exercise on physical fitness in daily life activities, autonomy and satisfaction with life among the brazilian elderly (2015). Egitania Sciencia, v. 9, p. 52-63.

- Teixeira, AM. et al. (2016) Study protocol: Hormonal mediation of exercise on cognition, stress and immunity (PRO-HMECSI): effect of different exercise programmes in institutionalized elders. *Frontiers in Public Health* [**Aceite: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4921497/**]

- Marques, MC. et al. (2017) Influence of Yoga Practice on salivary anti-microbial proteins in an elderly population. *European Journal of Integrative Medicine*. [**https://ec.europa.eu/eip/ageing/sites/eipaha/files/results_attachments/influence_of_chair-based_yoga.pdf]**

- Furtado, G. et al. (2016) Effects of different types of chair based exercise programs on hormonal, functional autonomy and physical fitness in pre-frail elderly woman. **Complementary Therapies in Clinical Practice** [**Aceite: https://www.ncbi.nlm.nih.gov/pubmed/27502812**]

- Furtado, Guilherme*[1]; Loureiro, Marisa*[2]; Ferreira, José[1]; Teixeira, Ana[1]; Patrício, Miguel (2017) Predicting Frail Syndrome using adverse geriatric health outcomes: comparison of different statistical classifiers. IEEE Transactions on Biomedical Engineering Journal [https://ieeexplore.ieee.org/abstract/document/7889430/]

- Furtado, Guilherme*[1]; Loureiro, Marisa*[2]; Patrício, Miguel; Ferreira, José[1]; Teixeira, Ana[1] (2017) Examining relationship and potential predictive performance between physical fitness indicators and frailty syndrome outcomes in institutionalized woman over 60 years of age. **Perceptual and Motor Skills (Sage Journals)** [**http://journals.sagepub.com/doi/abs/10.1177/0031512517709915]**

- Furtado, Guilherme*[1]; Loureiro, Marisa*[2]; Patrício, Miguel; Hogervost, Eef; Bandelow, Sthepan; Ferreira, José[1]; Teixeira, Ana[1] (2017) Which physical functioning markers best correlate with the five components of Fried Frailty Criteria? **Jornal of Aging and Health** [**sob revisão]**

- Furtado, Guilherme*[1]; Ferreira, José[1]; Teixeira, Ana[1](2017) Frailty syndrome influence on cognition performance in populations over 60 years of age, part I: a systematic review with meta-analysis. **Revista Ciências e Saúde Coletiva** [**http://www.cienciaesaudecoletiva.com.br/artigos/fragilidade-e-desempenho-cognitivo-em-populacoes-idosas-parte-i-uma-revisao-sistematica-com-metanalise/16300?id=16300&id=16300&id=16300]**

- Uba Chupel, M. Furtado, G. Direito, F. Minuzzi, L. Colado, J. Ferreira, JP. Filaire, E. Teixeira, AM. (2017). Strength training improves the anti-inflammatory profile, cognition and physical fitness in older women with cognitive impairment. *Frontiers in Physiology* **https://www.ncbi.nlm.nih.gov/pubmed/28659812**

- Rieping, T.[1]; **Furtado, G.[1,2;]** Uba-Chupel, M.[1,2]; Ferreira, JP.[1]; Teixeira, AM.[1] (2018) Effect of different types of chair-based exercise programs on salivary biomarkers and functional autonomy in institutionalized older women. **Research Quartely of Physical Activity and Health** [**accepted article, final revision].**

- Uba-Chupel, M**, Minuzzi, L; Furtado, G.[1,2;]**.[1,2]; Filaire, E..[1]; Teixeira, AM.[1] (2018) Exercise and supplementation with taurine in the elderly: effects on immune and blood-brain barrier integrity markers. **Applied Physiology, Nutrition, and Metabolism https://www.ncbi.nlm.nih.gov/pubmed/29474803**

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- Furtado GE, Caldo A, Rieping T, Filaire E, Hogervorst E, Teixeira, AM, et al. Physical Frailty and cognitive status over-60 age populations: a systematic review with meta-analysis. Archives of Gerontology and Geriatrics [Internet]. 2018 Sep 1 [cited 2018 Jul 22];78:240–8. Available from: **https://www.sciencedirect.com/science/article/pii/S0167494318301377** ; **Impact fator: 2.241**

PARTICIPATION AS MEMBER OF A CO-ADVISOR OF MASTER'S THESIS

- Rieping, T. (2016) **Efeitos de diferentes tipos de programas de exercício físico no comportamento da alfa-amilase salivar e do cortisol e na autonomia funcional em idosas institucionalizadas.** Dissertação apresentada no Mestrado em Exercício e Saúde em Populações Especiais, FCDEF-UC, Portugal. Orientador: Prof. Doutor José Pedro Ferreira e Coorientador: Prof. Mestre Guilherme Furtado. Coimbra.

- Carvalho, Rafael (2016). **Efeitos de um programa de exercício físico aeróbio na mediação de indicadores biopsicológicos em idosas institucionalizadas.** Dissertação apresentada no Mestrado em Exercício e Saúde em Populações Especiais, FCDEF-UC, Portugal. Orientador: Prof. Doutor José Pedro Ferreira e Coorientador: Prof. Mestre Guilherme Furtado. Coimbra.

SCIENTIFIC PRIZES

- Furtado et al., (2016). Second prize of the best oral communication presented at the 3rd IPLeiria International Health Congress: Health, Demographic Changes & Well-being, organized by the Health Research Unit (UIS) of the IPL, Health Research Unit (UIS) of the IPLeiria School of Health Sciences - Leiria, Portugal (2016).

- Furtado, G. Ferreira, JP e Teixeira, A. Menção honrosa recebida através da Comissão de Coordenação e Desenvolvimento Regional do Centro e o consórcio Ageing@Coimbra. Concurso de Boas Práticas de Envelhecimento Ativo e Saudável (outubro, 2017).

REVIEWER OF ARTICLES IN NATIONAL AND INTERNATIONAL SCIENTIFIC JOURNALS

- Guilherme Eustáquio Furtado colaborador (Revisor) no Vol. 1, n.º 1 do ano 2015 da **Revista Portuguesa de_Investigação Comportamental e Social** – RPICS [**http://rpics.ismt.pt/index.php/ISMT**]

- "Exercise and Antioxidant Intake in Aging Normotensive and Hypertensive Individuals", for the upcoming issue of the **Journal Gerontology & Geriatric Medicine (**manuscript reference HGGM-16-004), August 04, 2016.

- Revisor do artigo "O apoio dos amigos na participação desportiva do atleta: uma revisão sistemática da literatura". ***Revista Iberoamericana de Psicología del Ejercicio y el Deporte***. *Abril de 2018.*

ACADEMIC-SCIENTIFIC MISSIONS

- **UNICAMP - Faculdade de Educação Física (2016).** Visita ao convite da professora Doutora Cláudia Cavalieri **(ver Anexo 3**) para acompanhado do trabalho relacionado a linha de investigação Exercício e Envelhecimento, intergrada ao meu período de férias no Brasil, outubro.

- **Faculdade de Psicologia, Ciências da Educação e Esportes - Blanquerna (University Ramon Llull).** Visita ao Convite da professora Doutora para acompanhamento do Projeto Europeu: Exercise Referral Schemes enhanced by Self-Management Strategies to battle sedentary behavior, which obtained a Horizon-2020 financial support from the European Commission (Project ID: 634270). The project's objective is to assess the long-term effectiveness (18 month follow-up) of a complex intervention on sedentary behavior and physical activity in a community dwelling older population based on existing exercise referral schemes enhanced by self-management-strategies.

- **Center of Sport Medicine and well being. Faculty of Sport Science, Loughborough University.** Visita ao abrigo do Programa Eramus+ (Mobilidade para estágio), sob a aceitação do Convite da professora Doutora Eef Hogervost para o desenvolvimento de atividades da linha de pesquisa: Study Protocol on Hormonal Mediation of Exercise on Cognition, Stress and Immunity (PRO-HMECSI): Effects of Different Exercise Programmes in Institutionalized Elders.