MEMO_MOVE
Effect of combined exercise and cognitive stimulation on fitness and cognitive function of individuals with mild cognitive impairment

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Tese para obtenção do Grau de Doutor em
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- Doutora Flávia Alexandra Borges Machado, investigadora auxiliar da Faculdade de Letras da Universidade de Coimbra.

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Declaração de Integridade

Eu, Catarina Alexandra de Melo Rondão, que abaixo assino, estudante com o número de inscrição D1932 de/o 3.º Ciclo/Doutoramento em Ciências do Desporto da Universidade da Beira Interior da Faculdade Ciências do Desporto, declaro ter desenvolvido o presente trabalho e elaborado o presente texto em total consonância com o **Código de Integridades da Universidade da Beira Interior**.

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Universidade da Beira Interior, Covilhã 30/03/2023

Academic thesis submitted with the purpose of obtaining a doctoral degree in Sport Sciences according to the provisions of Portuguese Decree-Law 107/2008 of 25 June.

Dedicatory

To my parents who are certainly proud of their daughter, for everything they taught me, for the values transmitted, for the opportunities they provided me, for encouraging me to fight for dreams and goals.

To my dear and friendly father, who despite not being physically here will always be in my heart accompanying me every step of the way. Today would be a day of pride, of great joy, of much happiness, of celebration for having reached one more achievement, this one of all the most important....

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“Life is not a straight and easy corridor

in which we can walk freely and without limitations,

but a labyrinth with many passages,

through which we have to search for our way,

lost and confused, where from time to time

we end up in a dead end.

But, if we have faith,

God will always open a door for us,

maybe not the one we have planned for ourselves,

but one that, in essence,

will prove to be good for us.”

J. Cronin“

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Oral Presentations

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Participation in scientific projects

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Abstract

After the sixth decade of life, the incidence and prevalence of dementia diseases doubles every five years. Portugal is an aging nation, therefore presents a high prevalence of Dementia or mild cognitive impairment (MCI).

Dementia is a condition in which there is progressive deterioration in cognition that affects day to day function and englobes numerous neuropathological conditions, such as Alzheimer disease, vascular dementia, multi-infarct dementia, Lewy body dementia or Parkinson's disease dementia. Physiologically, dementia is related with aberrant accumulation of damaged macromolecule caused by age-related oxidative stress increase, that can result in silent chronic inflammatory processes, reducing neurotrophines action and impairing the maintenance of cognitive performance. In this scenario, physical activity seems to help the reduction of chronic inflammation in the central nervous system, increasing neuroplasticity and promoting remodulation of neuronal circuits by increasing cerebral blood flow. MCI is a syndrome defined as cognitive decline greater than expected for an individual's age and education level but that does not interfere notably with activities of daily life and often is a precursor of Dementia.

Regular exercise has emerged as one of the most crucial lifestyle factors for improving both physical and cognitive performance among the elderly. However, although there are some indications of the benefits of aerobic exercise in reducing oxidative stress, little is known about (1) the evidence of the benefits of exercise on dementia; (2) the most adequate exercise plan to promote benefits on physical and cognitive function and (3) the benefits of multicomponent exercise (combination of exercise and cognitive stimulation) on physical fitness and cognitive function among people with Dementia or MCI. To address these questions several works were carried out:

(1) a critical review based on revision articles concerned the evidenced effects of physical exercise in people with MCI were made. Main conclusions enhance the benefits that patients with dementia have from various exercise programs to improve global cognition, especially in the early to moderate stage of the disease.

(2) In order to be more successful in the intervention, it was important to find out among the professionals working with these subjects which aspects they consider most relevant in the planning, and which are the main constraints. The main aspects mentioned were related with recommendations, such as the importance of including families and caregivers; the need to educate families and caregivers about the importance of physical exercise in

dementia; respect the patient's will to participate; promote the collaboration and involvement of the senior residence staff; ensure attentive, respectful, and friendly treatment; create a relationship of trust with the exercise professional; the appropriate design of physical exercise and cognitive stimulation; an appropriate schedule; and a safe environment. Additionally, the main concerns were related to dementia patients' resistance to participate in exercise programs, inappropriate activities or exercises; the risk of falls; the lack of exercises' adaptation; the difficulty in understanding instructions; the physical space for the implementation of programs not always being the most adequate; the lack of family support; the inadequate diagnosis of dementia; the danger of disorientation; episodes of violence; the willingness of people involved in the care of demented patients to collaborate; the lack of sensitivity in the treatment of people with MCI/Dementia; and the lack of adequate exercise equipment in nursing homes.

(3) The physical fitness level in older persons with mild cognitive impairment was assessed, evidencing that is very poor among this population, with severe consequences on their functional independence. Therefore, promoting an active lifestyle among this population should be a crucial concern, to maintain motor abilities to perform daily tasks.

(4) In order to establish the intervention characteristics, a literature review was conducted to collte and analyze previous work, which provided a summary the type of exercise that should be implemented among this population. The MEMO_MOVE program was structured and described, regarding (i) inclusion of a cognitive stimulation component; (ii) the kind of cognitive stimulation; and (iii) the type of exercise, duration, frequency, intensity, and program length.

(5) After the identification of the key aspects to include in the exercise program for subjects with MCI, and paying attention to the main recommendations and constrains identified by the professionals that take care of these people, a study to evaluate the effects of a multicomponent exercise program on cognitive function and physical fitness in elderly people with mild cognitive impairment and to identify the role of oxidative stress and brain derived neurotrophic factor (BDNF), had been carried out. At baseline, 37 elderly nursing home residents with mild cognitive impairment were divided into two groups: the control group (CG, n = 12, 81.8 years) and the experimental group (EG, n = 25, 83.2 years). These elderlies followed multicomponent exercise training with dual task for 24 weeks, with two sessions per week and 45–50 min per session. Exercises included strength training and aerobic exercises, taking into consideration functional movement and light to moderate intensity. Cognitive stimulation included computer exercises, balanced platform games, word games, puzzles, math calculations, progressive and regressive counting, and word

games. Physical assessments (weight, height, and body mass index), health and functional parameters (fitness tests: chair stand, arm curls, chair sit-and-reach, eight feet up-and-go, back scratch, 6-min walking, feet together, semi-tandem, and full tandem), lipid profile (total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides), measures of lipid peroxidation damage, thiobarbituric acid reactive substances (TBARS), total antioxidant capacity (TAC), and BDNF were measured in plasma, based on which analyses were performed before and after the 24 weeks of the multicomponent exercise intervention.

The main results showed an overall improvement in physical and functional performance. Regarding cognitive function, there were significant improvements in the cognitive performance, particularly in retention and recall capacity. Significant different variations between groups in Total Cholesterol between baseline and post intervention period, occurred. The plasma biochemical parameters of BDNF, decrease in both groups between baseline and post intervention. Total antioxidant capacity increased in both groups, however while CG increased lipid peroxidation, EG decreased it.

The results suggest that a multicomponent exercise training program (aerobic and strength exercises combined with cognitive stimulation) in institutionalized elderly with MCI is effective in improving physical fitness, memory and reducing oxidative stress-induced damage.

Keywords

Dementia, Mild Cognitive Impairment, Multicomponent Exercise, Cognitive Stimulation, Dual Task

Resumo

Após a sexta década de vida, a incidência e prevalência de doenças demenciais duplica a cada cinco anos. Portugal é uma nação envelhecida, pelo que apresenta uma elevada prevalência de Demência ou de deficit cognitivo ligeiro (MCI).

A demência é uma condição em que há uma deterioração progressiva da cognição que afecta o funcionamento diário e engloba numerosas condições neuropatológicas, tais como a doença de Alzheimer, demência vascular, demência multi-infarto, demência do corpo de Lewy ou demência da doença de Parkinson. Fisiologicamente, a demência está relacionada com uma acumulação aberrante de macromoléculas danificadas causada pelo aumento do stress oxidativo relacionado com a idade, que pode resultar em processos inflamatórios crónicos silenciosos, reduzindo a acção das neurotrofinas e prejudicando a manutenção do desempenho cognitivo. Neste cenário, a actividade física parece ajudar a reduzir a inflamação crónica no sistema nervoso central, aumentando a neuroplasticidade e promovendo a remodelação dos circuitos neuronais através do aumento do fluxo sanguíneo cerebral. O MCI é uma síndrome definida como um declínio cognitivo maior do que o esperado para a idade e nível de educação de um indivíduo, mas que não interfere notavelmente com as actividades da vida diária e é frequentemente um factor precursor da Demência.

O exercício regular é considerado um dos factores cruciais do estilo de vida para melhorar o desempenho físico e cognitivo dos idosos. No entanto, embora existam algumas indicações dos benefícios do exercício aeróbico na redução do stress oxidativo, pouco se sabe sobre (1) a evidência dos benefícios do exercício na demência; (2) as características do exercício mais adequadas para promover melhorias na aptidão física e desempenho cognitivo e (3) os benefícios do exercício de dupla tarefa (combinação de exercício e estimulação cognitiva) sobre a aptidão física e a função cognitiva entre as pessoas com demência ou MCI. Para responder a estas questões, foram realizados vários estudos:

(1) Foi feita uma revisão crítica considerando apenas artigos de revisão sobre os efeitos evidenciados do exercício físico nas pessoas com Demência/MCI. As principais conclusões são que há evidências de que o exercício pode potenciar a melhoria da condiçõa física e da cognição global, especialmente na fase inicial a moderada da doença.

(2) Para ter mais sucesso na intervenção, foi importante recolher informações dos profissionais que trabalham com esta patologia, sobre quais os aspectos que consideram mais relevantes no planeamento de um programa de exercícios, e quais são os principais constrangimentos na participação no programa. As principais recomendações recolhidas foram a importância de incluir famílias e cuidadores; a necessidade de educar as famílias e

cuidadores sobre a importância do exercício físico na demência; o respeito pela vontade de participação do paciente; a promoção da colaboração e envolvimento do pessoal da residência sénior; assegurar um tratamento atento, respeitoso e amigável; criar uma relação de confiança com o profissional de exercício; a concepção adequada do exercício físico e da estimulação cognitiva; um horário apropriado; e um ambiente seguro. Além disso, as principais preocupações estavam relacionadas com a resistência dos pacientes com demência em participar em programas de exercício, actividades ou exercícios inadequados; o risco de quedas; a falta de adaptação dos exercícios; a dificuldade em compreender as instruções; o espaço físico para a implementação de programas nem sempre sendo o mais adequado; a falta de apoio familiar; o diagnóstico inadequado da demência; o perigo de desorientação; episódios de violência; a vontade de colaboração das pessoas envolvidas no cuidado de pacientes dementes; a falta de sensibilidade no tratamento de pessoas com MCI/Demência; e a falta de equipamento de exercício adequado nos lares de idosos.

(3) Foi avaliado o nível de aptidão física em idosos com MCI/Demência, evidenciando que é muito baixo, com graves consequências na independência funcional. Portanto, promover um estilo de vida ativo nesta população deve ser uma preocupação crucial, para manter as habilidades motoras para realizar tarefas diárias.

(4) A fim de estabelecer as características da intervenção, foi realizada uma revisão bibliográfica para coligir e analisar trabalhos anteriores, que forneceu um resumo do tipo de exercício que deve ser implementado entre esta população. O programa MEMO_MOVE foi estruturado e descrito, relativamente a (i) inclusão de uma componente de estimulação cognitiva; (ii) o tipo de estimulação cognitiva; e (iii) o tipo de exercício, duração, frequência, intensidade, e duração do programa.

(5) Após a identificação dos aspectos chave a incluir no programa de exercícios para os indivíduos com ICM, e prestando atenção às principais recomendações e constrangimentos identificados pelos profissionais que cuidam destas pessoas, foi realizado um estudo para avaliar os efeitos de um programa de exercícios multicomponentes sobre a função cognitiva e a aptidão física em pessoas idosas com ligeira deficiência cognitiva e para identificar o papel do stress oxidativo e do factor neurotrófico derivado do cérebro (BDNF). Na linha de base, 37 idosos residentes em lares com ligeira deficiência cognitiva foram divididos em dois grupos: o grupo de controlo (GC, n = 12, 81,8 anos) e o grupo experimental (GE, n = 25, 83,2 anos). Estes idosos seguiram um treino de exercício multicomponente com dupla tarefa durante 24 semanas, com duas sessões por semana e 45-50 min por sessão. Os exercícios incluíram treino de força e exercícios aeróbicos, tendo em consideração o movimento funcional e a intensidade leve a moderada. A estimulação cognitiva incluiu exercícios de computador, jogos de plataforma equilibrados, jogos de palavras, puzzles, cálculos matemáticos, contagem progressiva e regressiva e jogos de palavras. Avaliações

físicas (peso, altura e índice de massa corporal), parâmetros de saúde e funcionais (testes de aptidão física: suporte de cadeira, caracóis de braços, sit-and-reach, oito pés para cima e para baixo, arranhão nas costas, caminhada de 6 minutos, pés juntos, semi-tandem, e tandem total), perfil lipídico (colesterol total, lipoproteína de alta densidade (HDL), lipoproteína de baixa densidade (LDL), e triglicéridos), medidas de danos de peroxidação lipídica, substâncias reativas ao ácido tiobarbitúrico (TBARS), capacidade antioxidante total (TAC), e BDNF foram medidas no plasma, com base nas quais foram realizadas análises antes e depois das 24 semanas da intervenção do exercício multicomponente.
Os principais resultados mostraram uma melhoria global no desempenho físico e funcional. No que respeita à função cognitiva, houve melhorias significativas na retenção e recordação, e no que respeita ao perfil lipídico, houve uma melhoria significativa no desempenho cognitivo.
Houve variações significativamente diferentes entre grupos no Colesterol Total entre o período de base e o período pós intervenção.
Os parâmetros bioquímicos plasmáticos de BDNF, houve uma diminuição significativa em ambos os grupos entre a linha de base e o período pós-intervenção. A capacidade antioxidante total aumentou em ambos os grupos. Em relação ao TBARS, pode notar-se que enquanto o CG aumentou a peroxidação lipídica, o EG diminuiu-a.
Os resultados sugerem que um programa de treino de exercício multicomponente (exercícios aeróbicos e de força combinados com estimulação cognitiva) em idosos institucionalizados com MCI é eficaz para melhorar a aptidão física, a memória e reduzir os danos induzidos pelo stress oxidativo.

Palavras-chave

Demência; Déficit Cognitivo Ligeiro; Exercício Multicomponente; Estimulação Cognitiva; Dupla Tarefa.

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List of Abbreviations

6SQuID	Six steps in quality intervention development
ABTS	Ethylbenzothiazoline-6-sulfonic acid
ACSM	American College Sport Medicine
AD	Alzheimer Disease
ATP	Adenosine triphosphate
BDNF	Brain Derived Neurotrophic Fac
CA	Cognitive Activity
CG	Control group
CR	Catarina Rondão
DC	Dulce Esteves
DNA	Deoxyribonucleic acid
EG	Experimental group
ETC	Electron transport chain
FITT	Frequency, intensity, type, and time
GLM	General Linear Model
JBI	Joanna Briggs Institute
MAPK	Mitogen-activated protein kinase
MCI	Mild cognitive impairment
MCI/D	Mild cognitive impairment or dementia
MDA	Malondialdehyde
MMSE	Mini Mental State Examination
MOCA	Montreal Cognitive Assessment
OS	Oxidative stress
PA	Physical activity
PM	Paula Mota
RCTs	Randomised control trials
ROS	Reactive oxygen species
SCD	Subjective Cognitive Decline
SD	Standard deviation
TAC	Total antioxidant capacity
TBA	Thiobarbituric acid
TBARS	Thiobarbituric acid reactive substances
TIDieR	Template for Intervention Description and Replication
TrkB	Tyrosine kinase receptor B
TUG	Timed Up and Go
WHO	World Report on Ageing and the Health of World Health Organization

Chapter 1. General Introduction

Physical fitness is closely related to quality of life in older people with dementia (Hesseberg et al., 2020), as it is essential to perform daily tasks, participate in social life, and live independently (Donnezan et al., 2018). Preventing decline in physical fitness is important as it is related to the independence and well-being of the older person. However, aging brings with it chronic illness, cognitive impairment/dementia, and hospitalization that have a direct impact on physical fitness and the ability to stay active (Hesseberg et al., 2020). Cognitive impairment/dementia can be associated with lower levels of physical fitness and become a serious threat to the independence and quality of life of older people (Bárrios et al., 2013; Hesseberg et al., 2020; Pettersson et al., 2005). Dementia is characterized by cognitive impairment that affects the ability to process thought, generating learning and memory problems. Dementia is usually a consequence of various cardiovascular and neurological diseases, such as Alzheimer's disease, a disease characterized by neurodegeneration caused by the accumulation of proteins such as Beta amyloid and tau proteins, which cause neuronal apoptosis, altering the synapse, as a result there are noticeable signs and symptoms, such as short and long-term memory loss, as well as other related behaviors, for example, changes in personality mood, which leads to isolation (Strøm et al., 2016).

According to statistics from the World Alzheimer Report 2018 "Alzheimer's. Realities and investigación en demencia" (World Health Organization, 2019) in the world, every 3 seconds a person is diagnosed with dementia. In 2018, 50 million people were diagnosed; a number that is expected to triple, meaning that by 2030, 82 million people will be diagnosed and by 2050, about 152 million people will have dementia.

Regarding the costs of these diseases, the "World Alzheimer Report 2018" stated that the annual cost for the management and treatment of dementia was $1 trillion, a figure that will double by 2030. In 2019, the annual global societal costs of dementia were estimated at US $1313.4 billion for 55.2 million people with dementia: US $213.2 billion (16%) were direct medical costs, US $448.7 billion (34%) direct social sector costs (including long-term care), and US $651.4 billion (50%) costs of informal care (Wimo et al., 2023).

As Dementia is a chronic neurodegenerative disease that results in a progressive loss of functional capacity and a gradual decline in autonomy and independence (Irazoki et al., 2017), it has a major emotional, social and economic impact for families/caregivers and society.

Considering that the cognitive decline characteristic of Dementia is directly related to loss of autonomy, need for institutionalization, and that there is no effective pharmacological treatment capable of treating dementia, the "Canadian Pharmacists Conference 2017 Sponsors" (2017), states that it is important to investigate non-pharmacological treatments aimed to slow cognitive decline.

Previous literature has found that physical activity interventions positively influence cognitive function in patients with dementia (Groot et al., 2016a). A preventive approach to balance, muscle strength, range of motion, gait, and cardiovascular capacity allows for maintenance and improvement of physical fitness in people with dementia (Rolland et al., 2007). Moreover, the potential of aerobic exercise at moderate intensities to improve cognitive function and fitness in patients with dementia must be emphasized (Yang et al., 2015).

Physical exercise increases cerebral blood circulation (Ogoh & Ainslie, 2009), stimulates the release of substances that aid central nervous system function, such as neurotrophines (Strutz et al., 2014), promotes neural growth, maintaining brain function and improving brain plasticity (Lin et al., 2018). In addition, physical activity can reduce oxidative stress and inflammation, contributing to reduce brain damage related with cognitive function loss (Llorens-Martín, 2018).

Physical activity interventions are, therefore, an attractive and effective alternative or complement to the current pharmacological treatment of cognitive symptoms in patients with dementia.

Thus, the major objective of this work was to design and implement an exercise program that includes cognitive stimulation targed to people with MCI/Dementia and evaluate the caused effects on fitness, cognitive function, including the role of oxidative stress and BDNF.

In order to acomplish this major objective, 5 specific objectives emerged:

1- Compile scientific evidence supporting the benefits of physical exercise in different valences of individuals with MCI/Dementia.

2- Compile the recommendations and concerns of a multidisciplinary team about the design and intervention of an exercise program for this population.

3- Characterize the physical fitness of the participants in order to design an individualized and specific intervention.

4- Carry out a literature review on the types of programs usually implemented in this population, as well as the characteristics of the exercises most used in the literature, with the aim of designing an intervention program and create a sustainable development structure for the evolution of the program.

5- Evaluate the effects of a dual-task, multicomponent exercise program on fitness and cognitive function of elderlies with mild cognitive impairment.

Accordingly, this thesis presents the following structure:

Chapter 2
scientific evidence supporting the benefits of physical exercise MCI/Dementia - critical review over revision articles.

Study 1 - Physical activity Interventions in Older Adults with a Cognitive Impairment: A Critical Review of Reviews

Chapter 3
The multifaceted nature of mental illness symptoms and the numerous effects of a patient's cognitive impairment necessitate the development of specialized interventions and treatment plans based on an interdisciplinary approach. This research sought to identify key recommendations, as well as the concerns of various experts, in order to gather the perspectives of an interdisciplinary team on the implementation of an exercise program for people with MCI or dementia.

Study 2 - Designing a combined exercise and cognitive stimulation intervention for people with mild cognitive impairment – Interdisciplinary and transdisciplinary perspectives.

Chapter 4
The main objective of this study was to examine the physical fitness of individuals with mild cognitive impairment, in order to assess the need for a specific physical activity program that improves their functional fitness status.
Study 3 - Physical fitness level of a population with mildcognitive impairment.

Chapter 5
Exercise is seen as a non-pharmacological treatment for dementia, with potential benefits of preventing cognitive decline and improving physical fitness. We aimed to describe the development phases of a program, which combines exercise with cognitive stimulation for a population with mild cognitive deficits, we called MEMO_MOVE.

Study 4 – *Development of a Combined Exercise and Cognitive Stimulation Intervention for People with Mild Cognitive Impairment—Designing the MEMO_MOVE Program.*

Chapter 6

The aim of this study was to determine the effects of a multi-component exercise program on cognitive function and physical fitness in elderly adults with mild cognitive impairment, including the involvement of oxidative stress and brain tissue-derived neurotrophic factor (BDNF).

Study 5- Multicomponent exercise program effects on fitness and cognitive function of elderlies with mild cognitive impairment: Involvement of oxidative stress and BDNF.

Chapter 7– General Discussion

In this chapter, the overall results of the investigation carried out will be discussed, based on the general objectives and the specific objectives established.

Chapter 8

This chapter summarizes the overall conclusions, limitations, practical implications and suggestions for future investigations.

Chapter 2. Literature Review

Study 1- Physical activity Interventions in Older Adults with a Cognitive Impairment: A Critical Review of Reviews

Physical activity Interventions in Older Adults with a Cognitive Impairment: A Critical Review of Reviews

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Abstract

Aim: This critical review explores the review material on physical activity combined with cognitive stimulation interventions in older adults with cognitive impairment and/or dementia.
Method: A critical, systematic, review of the review method was used, considering four electronic databases: WEB OF SCIENCE, SCOPUS, MEDLINE and the COCHRANE ELECTRONIC LIBRARY. The search terms “exercise”, “physical activity”, “cognitive impairment”, “dementia” and “systematic review” were used. All available reviews were marked against predetermined inclusion and exclusion criteria.
Results: There were 29 reviews that met the inclusion criteria. A combination of various types of training and aerobic exercises were the most frequently reported interventions; meanwhile, dual task training programs (combining physical exercise with cognitive stimulation), functional training programs along with exercises combination, aerobic exercise as well as strength, stretching or balance workouts were also reported.
Conclusion: The evidence is compelling; exercise can improve physical health by ensuring cognitive, psychological and behavioural benefits.
Overall, exercise can improve the physical and mental health of people living with dementia: there is sufficient evidence to recommend multimodal exercise.

Keywords: Mild cognitive impairment, dementia, physical activity interventions, review of reviews

Introduction

Aging is an irreversible process with biological, physiological and cognitive changes that are diverse and distinct (Clarke & Korotchenko, 2011; Cleeland et al., 2019). In fact, aging is related to a decrease in cognitive function and an increase in the prevalence of chronic pathologies such as dementia (Chapko et al., 2018). According to the World Report on Ageing and the World Health Organization (WHO), it is currently estimated that 35.6 million people worldwide live with dementia (World Health Organization, 2015) and this number is expected to reach 65 million cases in 2050 (*Risk reduction of cognitive decline and dementia: WHO guidelines*, sem data). The incidence and prevalence of dementia increases with age, almost doubling every five years after the sixth decade of life ((Cohen & Fülöp, 2021; *Risk reduction of cognitive decline and dementia: WHO guidelines*, sem data).

WHO, 2020, defines Dementia as *a syndrome – usually of a chrnic or progressive nature – in which there is deterioration in cognitive function (i.e. the ability to process thought) beyond what might be expected from normal ageing*.

In fact, dementia cannot be considered as a single disease: it has to be understood as a set of different pathologies that have a progressive neurological deterioration of brain cells in common and, therefore, a deficit in cognitive function (Lewis et al., 2020; Risk reduction of cognitive decline and dementia: WHO guidelines, sem data), which affects memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement, leading to the impairment of cognitive function beyond that expected with aging (Lewis et al., 2020; Wang et al., 2021).

Wang et al., (2021) present two types of dementia: (1) Degenerative Dementia, among which the most common are Alzheimer's disease, frontotemporal lobe degeneration and dementia with Lewy bodies; and (2) Vascular Dementia, originated from a stroke or chronic cerebrovascular lesions, resulting in poor blood circulation in the brain.

The weakening of cognitive function is commonly accompanied by deterioration in emotional control, social behaviour, disruptive behaviour, personality changes, delusions or motivation (*Risk reduction of cognitive decline and dementia: WHO guidelines*, sem data). These impairments cause dependency and can be overwhelming, not only for the people who have it, but also for their caregivers and family (Risk reduction of cognitive decline and dementia: WHO guidelines, sem data).

Cognitive ability can be impaired by a variety of neuropathological conditions, such as neurodegenerative diseases, in which the abnormal accumulation of certain proteins can cause silent chronic inflammatory processes. In this context, physical activity, by changing brain metabolism (Matura et al., 2017) and increasing aerobic fitness and cerebral blood flow (Lautenschlager et al., 2012), seems to contribute to the reduction of chronic inflammation in the central nervous system while increasing neuroplasticity (Erickson & Kramer, 2009; Haynes et al., 2017), promoting the reorganization of neural circuits (Bertelli et al., 2011; Nobili et al., 2018) and improving cognitive function (Groot et al., 2016b; McDonnell et al., 2011).

In fact, exercise in the elderly improves overall health status and prevents several negative aging outcomes, including coronary heart disease, stroke, type 2 diabetes, obesity, hypertension, certain cancers and osteoporosis (Galloza et al., 2017; Gomes-Osman et al., 2018; Vina et al., 2012). Exercise also contributes to the reduction of the risk of falls (Cadore et al., 2013) and mortality (Bauman et al., 2016).

Bauman et al. (2016) emphasize the importance of exercise in aging, recommending a shift in focus that gives priority to interventions that aim for the retention of muscle mass and balance, promoting motor function and autonomy.

Nuzum et al. (2020) refers to the fact that besides the benefits of exercise to overall health, better physical fitness also contributes to better cognitive functioning: individuals who are more physically active show better neurocognitive functioning compared to more sedentary individuals.

The study of the effect of exercise intervention on several physical and cognitive parameters has produced thousands of scientific papers. Considering the enormous amount of literature on this subject, numerous literature reviews were carried out.

Due to the number of reviews within this topic, an overall review of previously published reviews was justified as it provides a synopsis of the evidence in terms of the effects of exercise interventions in older adults with cognitive impairment on cognitive function and in physical fitness.

Consequently, the research question for this critical review is 'what are the findings of the reviews on exercise interventions for older adults with a cognitive impairment, concerning the type and characteristics of the exercise and effects on physical fitness and cognitive function?'

Therefore, this article aims to provide a theoretical framework to support a future exercise intervention for people with dementia/genitive impairment.

Methods

This critical literature review was based on the methodology presented by Booth et al. (2015) and Cammisuli et al. (2018). However, these authors specifically consider fall prevention interventions in older adults with cognitive impairment, whereas we aimed to evaluate the effect of exercise interventions in physical fitness and cognitive function, among the same population.

The primary purpose of this critical literature review was to gather and analyze previous literature reviews to investigate exercise interventions in adults with cognitive impairment, providing a clear summary of the evidence in this area to date and a set of data concerning the kind of exercise that should be recommended to improve both physical fitness and cognition among older adults.

A review of review method (Booth et al., 2015; Grant & Booth, 2009) was used to summarise the existent literature considering the number of reviews already published in this field. The types of reviews used in this article were: Systematic review, Review of studies (State of the Art Reviews), Meta-analysis, Narrative review, Umbrella review and Overview (Table 1).

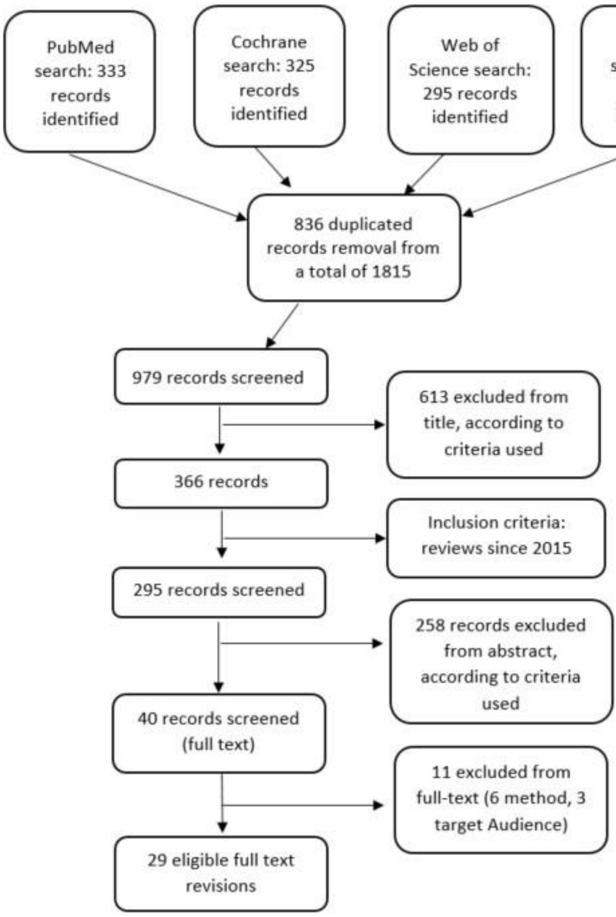

Figure 1.- Flowchart illustrating reviews identifie

Table 1. Revision types

Review type	Overarching goal	Search strategy	Appraisal of included studies	Analysis and synthesis	Key references
Systematic review	Aims to aggregate, critically appraise, and synthesize in a single source all empirical evidence that meet a set of pre-specified eligibility criteria in order to answer in depth a clearly formulated research question to support evidence-based decision-making.	Exhaustive literature search of multiple sources and databases using highly sensitive and structured strategies to identify all available studies (published and unpublished) within resource limits that are eligible for inclusion. Uses a priori inclusion and exclusion criteria.	Two different quality assessments must be addressed in systematic reviews: (a) risk of bias in included studies, and (b) quality of evidence by outcome of interest. Both assessments require the use of validated instruments (e.g., Cochrane criteria and GRADE system).	Two different types of analyses and syntheses methods can be used: 1. Meta-analysis (statistical pooling of study results), and 2. qualitative/ narrative: use of vote counting, content analysis, frameworks, classification schemes, and/or tabulations.	(Borenstein et al., 2009; Higgins & Green, 2008; Liberati et al., 2009)
Narrative review	Aims to summarize or synthesize what has been written on a particular topic but does not seek generalization or cumulative knowledge from what is reviewed.	Selective in nature. Authors usually select studies that support their own view.	No formal quality or risk of bias assessment of included primary studies is required.	Narrative using thematic analysis, chronological order, conceptual frameworks, content analysis or other classification criteria.	(Cronin et al., 2008; Green et al., 2006; Levy & Ellis, 2006; Webster & Watson, 2002)
Umbrella review	Tertiary type of evidence synthesis. Aims to compare and contrast findings from multiple systematic reviews in priority areas, at a variety of different levels, including different types of interventions for the same condition or alternatively, same interventions for different conditions, outcomes, problems, or populations and adverse effects.	Exhaustive literature search to identify all available systematic reviews (published and unpublished) within resource limits that are eligible for inclusion. No search for primary studies. Uses a priori inclusion and exclusion criteria.	Two different quality assessments must be addressed: (a) methodological quality assessment of the included systematic reviews, and (b) quality of evidence in included reviews. Both assessments require use of validated instruments (e.g., AMSTAR and GRADE system).	Many umbrella reviews will simply extract data from the underlying systematic reviews and summarize them in tables or figures. However, in some cases they may include indirect comparisons based on formal statistical analyses, especially if there is no evidence on direct comparisons.	(Becker & Oxman, 2008; Shea et al., 2009; Smith et al., 2011)

Met-analise	Meta-analysis is specifically designed to integrate the results of multiple studies on the same research question into a systematic review of the literature.	Note that meta-analysis should not be confused with systematic review of the literature itself, which is the systematic method used to find and critically evaluate all available scientific evidence on a research question.	The most commonly used method for assigning weight to each study is the inverse of the variance, i.e. the greater the variability, the smaller the study's share of the final conclusion.	The synthesis produced by the meta-analysis is weighted, with each study assigned a different weight, so that each contributes differently to the final conclusion. Because of increased sample sizes by combining studies, the synthesis produced by meta-analysis on a set of studies with good validity reduces our degree of uncertainty about the beneficial or undesirable effects of health interventions, for example. Systematic reviews with meta-analysis are the main guideline guiding evidence-based health care practices.	(Higgins et al., 2009)(Higgins et al., 2019)
Overview (Reviews os reviews)	Aim to provide "user-friendly" summaries of the breadth of research relevant to a decision without decision-makers needing to assimilate the results of multiple systematic reviews themselves. Often broader in scope than an individual systematic reviews , so that they can examine brode...options in ways that can be aligned with the choices thar decision-makers often make. In camparison to a synthesis of primary studies, overviews can be conducted more quikly.				Pollock et al.,(2016;2019)
State of the Art Reviews	Tends to address current matters in contrast to combined retrospective/current approaches. May offer new perspectives on issue or point out area for further research.				Grant &Booth (2009)

*"Synthesizing information systems knowledge: A typology of literature reviews," by G. Paré, M. C. Trudel, M. Jaana, and S. Kitsiou, 2015, *Information & Management, 52*(2), p. 187.

The electronic databases WEB OF SCIENCE, SCOPUS, PUBMED and the COCHRANE ELECTRONIC LIBRARY were systematically examined, using the following conjugation of terms: (1) ["exercise" OR "physical activity"], AND (2) ["cognitive impairment" OR "dementia"] AND (3) "systematic review" (4 combinations). The search was performed from March to May 2021.

The results from the literature search were selected from an initial search if they met the following criteria: (1) literature reviews (systematic, narrative, umbrella); (2) , included an adult population with a cognitive impairment recognised through cognitive testing (e.g. Mini Mental State Examination) or diagnosis (e.g. Dementia, Alzheimer's disease); (3) exercise based intervention; (4) results concerning physical fitness (fall prevention interventions were potentially eligible for inclusion as long as they included evaluation of physical parameters like strength, gait or equilibrium) or cognition (including better memory, mental abilities) if the revision considered any valid standardized neuropsychological test of cognition reported at baseline and follow-up; and (5) manuscripts written in English.

Exclusion criteria encompassed: (1) exercise interventions aimed at improvements in other factors including physical fitness or cognition, such as improvement of sleep patterns, general health, quality of life, pain management, mental health and improving psychological parameters such as mood or depression; (2) lifestyle interventions; (3) revision of exercise guidelines or recommendations; (4) the use of specific exercise programs such as tai-chi, yoga or dance; (5) patients that present psychiatric diseases and other comorbid medical conditions; and (6) manuscripts written in languages other than English.

Due to the number of reviews identified, 1815, a further exclusion criterion, namely reviews published before 2015, was introduced to ensure identification of recent evidence and recent evidence and the exclusion of material published prior to that year (as made by Booth et al., 2015). This screening finally yielded 29 studies to be evaluated (Figure 1), screened according to the PRISMA systematic review protocol (Liberati et al., 2009; Moher et al., 2010).

The search was performed by CR (first author). Two independent reviewers (DE and PM) assessed the included studies for their methodological quality (Table 2). Any discrepancies were discussed until a consensus was definitively reached.

Table 2. - Evaluation of the quality criteria fulfilment in RCTs examining the effects of exercise intervention on cognition.

Study	1	2	3	4
Brett et al., 2016	+	+	-	+
Bruderer-Hofstetter 2018	+	+	+	+
Cai et al., 2016	+	+	-	+
Cammisuli et al., 2017	+	+	-	+
Cammisuli et al., 2018	+	+	-	+
Chong et al., 2020	+	+/-	+	+
Gallou-Guyot et al., 2020	+	+	-	+
Gheysen et al., 2018	+	+	+	+
Gomes-Osman et al., 2018	+	+	+	+
Groot et al., 2016	+	+/-	-	+
Hernández et al., 2014	+/-	+	+	+
Demurtas., 2020	+	+	-	+
Lam et al., 2018	+	+	+	+
Chun-Kit et al., 2020	+	+	+	+
Learner et al., 2016	+	+	-	+
Lewis et al., 2020	+	+	-	+
Xudong Li et al., 2019	+	+/-	-	+
Loprinzi et al., 2018	+	+/-	-	+
Loprinzi et al., 2019	+	-	-	+
Park and Cohen 2019	+	+	-	+
Sandler et al., 2019	+	+	+	+
Biazus et al., 2020	+	+/-	+	+
Yeh et al., 2020	+	+	-	+
Song et al., 2018	+	+	-	+
Venegas-Sanabria 2020	+	+	-	+
Vseteckovaet al., 2020	+	+	-	+
Russ et al., 2021	+	+/-	-	+
Xiong et al., 2021	+	+	+	+
Zhang et al., 2019	-	+	+	+

Note: (1) The diagnosis of Alzheimer's Disease is based on validated criteria (NINCDS-ADRDA, 1984; APA, 2000; 2013); (2) Inclusion and exclusion criteria of the study are specifically described; (3) The study has sufficient statistical power (n ≥ 25 per group); (4) Intervention, measurements and outcome measurements are correctly described; legend: by + applicable; +/- superficially; not applicable.

The first author completed the search, and all included papers were reviewed for inclusion and the quality was independently evaluated by two reviewers (PM and DE; any discrepancies were discussed with the third reviewer). The included reviews were independently critiqued for their quality by two reviewers (DE and PM), using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Research Synthesis (Joanna Briggs Institute, 2014). This quality measure was used as recommended within the JBI: Methodology for Umbrella Reviews (2014) and rated the inclusion of topics such as review questions, inclusion criteria, search strategies, critical appraisals, and data extraction methods. Due to a variety of review methods (i.e., narrative, meta-analysis), a quality measure was indicated to provide clarity on how the reviews synthesized material and therefore achieved their results and recommendations. Data involving the details of participants, the number of studies included, the intervention types, the results and conclusions, and the effect sizes were extracted.

Results

The search process identified 29 reviews to be included. Figure 1 describes the reviews identified at each search stage. On occasion, the same study was identified from the different electronic databases and is identified as 'repeats'. Reasons for exclusion of reviews at the full-text stage are provided.

The populations studied, the outcomes, and the summaries from the included reviews are presented in Table 2. All selected papers studied adult populations with mild cognitive impairment or some type of dementia diagnosis.

According to the revision type, six different types were found, most of them being systematic revisions (n=23), as well as two meta-analyses (one with systematic review), one narrative revision, one umbrella revision, one review, and one over-review revision.

Review studies were divided according to the type of training (aerobic training, strength training, multicomponent training and Dual Task training) (Figure 2, Tables 3 - 6).

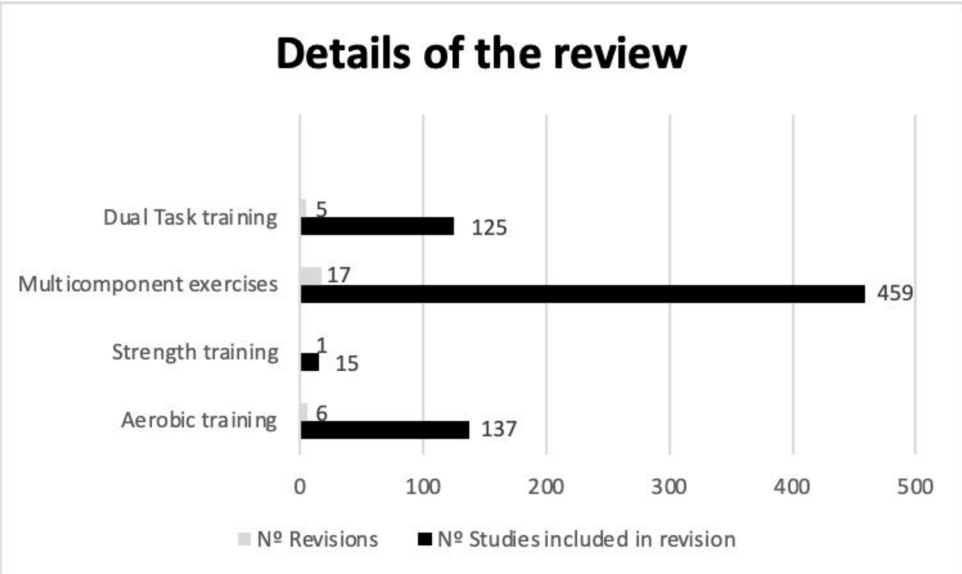

Figure 2 - Distribution of the review studies according to the type of training, and total studies.

Regarding the type of exercise program, six reviews focus on aerobic training benefits for individuals with MCI. These six reviews summarize the results of 137 intervention studies (Table 3).

3). **Table 3.-** Population, results and summaries of the reviews included for the aerobic training

Authors, year and review methodology	Number of included studies in review	Population, Prevalence of dementia and setting	Intervention: frequency, intensity, type, and time (FITT)	Outcomes Measured	Summary of findings	Exercise recommendations
Learner et al., 2016 Systematic review	6	Diagnosis of dementia and resident in a nursing home.	Different types of programs: walking, balance, and endurance for 1 hour, 3 times a week, for 15 weeks.	Improvement of cognition after exercise.	Longer duration aerobic exercise may be more effective in maintaining cognitive levels.	Aerobic exercise.
Cammisuli et al., 2017 Systematic review	9	Patients with MCI.	Aerobic training 50/60 minutes, 3 days a week.	Cognition.	MCI patients benefit from aerobic exercise, but it's not possible to conclude that aerobic exercise promotes a selective effect on cognition.	Aerobic training 50/60 minutes, 3 days a week.
Cammisuli et al., 2018 Narrative revision	8	Patients with probable AD.	Aerobic exercise.	Cognition.	AD patients can benefit from aerobic exercise intervention to improve global cognition	Aerobic exercise, 60 % of VO_2max, 30 min, 3 .days/week.
Gomes-Osman et al., 2018 Systematic review	98	Adults (age ≥60 years) with or without cognitive impairment.	Aerobic exercise.	Cognition.	There are cognitive improvements with exercise.	3 times a week for 60 hours spread over 25 weeks.
Vseteckova et al., 2020 Systematic review	10	Elderly people living with dementia in the community.	Walking exercise.	Physical, social, and mental improvement.	The benefits of walking as an activity that improves health and participants' well-being .	Outdoor walking.

Loprinzi et al., 2018 Systematic review	6	Patients with MCI.	Aerobic, resistance or combined exercise or exercise duration (less than or greater than a 6-month exercise program).	Cognition.	Exercises can have beneficial effects on memory function among people with MCI.	Aerobic exercise.

Only one review study was found regarding the effects of strength training in individuals with MCI, which included 15 intervention studies (Table 4).

Table 4- Population, results and summaries of the reviews included for the Strength training**.**

Authors, year and review methodology	Number of included studies in review	Population, Prevalence of dementia and setting	Intervention: frequency, intensity, type, and time (FITT)	Outcomes Measured	Summary of findings	Exercise recommendations
Lewis et al., 2020 Systematic review	15	Patients with MCI.	Strength, power and muscle flexibility.	Cognition physical condition.	General benefits for physical health, cognitive, psychological and behavioural aspects.	Muscle strength, balance and flexibility - an activity goal of 150 minutes per week of moderate-intensity aerobic exercise.

Considering the multicomponent exercise program, 17 reviews were found, summarizing 459 intervention studies (Table 5).

Table 5- Population, results and summaries of included reviews for multicomponent exercises

Authors, year and review methodology	Number of included studies in review	Population, Prevalence of dementia and setting	Intervention: frequency, intensity, type, and time (FITT)	Outcomes Measured	Summary of findings	Exercise recommendations
Hernández et al., 2015 Systematic review	14	People with mild cognitive impairment or dementia.	Physical activity and exertion (ie, multimodal, resistance training). Moderate intensity by in at least 30 minutes.	Strength exercises, stretching and aerobic capacity.	The practice of physical exercise helps to improve the performance of activities of daily living, improvement in neuropsychiatric disorders, improvement in depressive symptoms, improvement in cardiovascular and cardiorespiratory fitness, improvement in functional capacity components (flexibility, agility, balance, strength) and improvement in some of frontal cognitive function in patients with mild to severe AD	Multimodal, resistance training.
Brett et al., 2016 Systematic review	12	Diagnosis of dementia and being reside in a nursing home.	Exercise for 30 to 60 minutes per week. Different types of physical exercises aimed at strength, balance, flexibility, aerobic capacity, cognition, functional capacity and/or coordination.	Physical exercise has a positive effect on the health.	Exercise positively affects the health and well-being of people living with dementia in nursing homes.	30 minutes twice a week strength, balance, flexibility and endurance.

Cai Y, et al., 2016 Review of studies	13	Community-dwelling adults aged 60 years or older; participants had MCI.	Aerobic exercise, Tai Chi exercise, functional task exercise, resistance training and multicomponent physical training.	Improvement in the areas of global cognition, executive function, memory, attention, and processing speed.	More research will be needed to better understand the effect of physical exercise on cognitive function.	Durations of > 6 months aerobic exercise, Tai Chi exercise, functional task exercise, resistance training.
Groot *et al.*, 2016 Meta-analysis of RCTs	18	Patients with MCI.	Aerobic only, non-aerobic and combined.	Cognitive function, ADLs.	Cognitive function, ADLs.	Benefits of aerobic activity even at low frequency (40-45min week).
Lam et al., 2018 Systematic review	43	Patients with MCI.	Aerobic, balance, flexibility and functional training. 60 minutes a day, 2-3 days a week.	Cognition physical condition.	Physical training improves cognitive and physical function in healthy elderly adults, and it is viable and beneficial for people with cognitive problems.	Regular multimodal exercise with a combination of resistance, aerobic, balance, flexibility, and functional training for fence. 60 minutes a day, 2-3 days a week is effective for improving various aspects of physical functioning (strength of the lower limbs, mobility, balance, resistance to walking).

Song et al., 2018 Systematic review	11	Patients with MCI.	Aerobic exercise was of moderate intensity multimodal exercise program. Exercise programs included three or four types of exercise (aerobic, resistance training, stretching and balance, Tai Chi).	Physical condition.	Positive effects of physical exercise on improving global cognition.	Moderate-intensity aerobic exercise appears to have greater beneficial effects on executive function.
Xudong Li et al., 2019 Systematic review	20	Patients with MCI.	Combination of resistance, strength and balance interventions.	Cognition.	Exercise programs can play an important role in cognition and ADL.	Resistance, strength and balance interventions.
Loprinz et al., 2019 Systematic review	11	Patients with MCI.	Exercise protocols ranged from light stretching, basic exercise, aerobic walking, functional activities, and exercise combined with cognitive training.	Cognition.	exercise has many beneficial effects on brain function.	High intensity functional exercise is generally safe and viable for patients.
Park and Cohen et al,.2019 Systematic review	64	Older adults with various types of dementia.	Exercise (supportive exercise, aerobics, resistance exercise, stationary cycling, exercise, yoga, tai-chi, walking, dancing, multi-component exercise, mind-body exercise).	Functional ability, psychological/ behavioural or social factors.	Functional ability (beneficial), behavioural or social factors (mixed results), cognition (mild dementia) Individualised leisure and exercise activities that are simple, with structured one-on-one social interaction.	Not possible to retrieve.

Sandler et al., 2019 Systematic review	64	Patients with MCI.	Exercise, aerobics, resistance exercise, stationary cycling, exercise, yoga, taichi, walking, multi-component exercise, and body-mind exercise.	Cognition physical condition.	Exercise has a positive effect on physical health and psychosocial well-being.	Intensive exercise programs (aerobics, cycling, strength, flexibility, balance and endurance combined with walking) 2 to 3 times a week.
Biazus et al., 2020 Systematic review	27	Participants investigated (average age ≥60 years) with a diagnosis of MCI.	Kind of exercise [aerobic, endurance, multicomponent (ie, a type of physical training that combines different exercise regimens in the same exercise session, incorporating aerobic and/or resistance training and other forms of physical training.	Cognition.	Physical activity improves cognitive function in older people with MCI.	Perform at least 150 min/week of moderate-intense or 75 min/week of vigorous aerobic physical activity or an equivalent combination of both.
Chong et al., 2020 Narrative review	41	Older adults with MCI or SCD.	Aerobic physical activity, multimodal PA, balance. The intensity was moderate-vigorous in most studies and this was defined most often by target heart rate or maximal oxygen uptake (VO2 max). 60minutes a week 6 months.	Cognition physical condition.	PA can bring benefits to cognition and other health activities parameters in elderly people with MCI or SCD.	Aerobic exercise, progressive resistance training and balance exercises, all of which must be tailored to the individual.
Chun-Kit Law et al., 2020 Systematic review	50	People with mild cognitive impairment (MCI) or dementia.	Aerobic exercise, walking exercise and resistance exercise and combination with cognitive function was classified into global cognition, memory, executive function, reasoning, attention and language.	Cognition.	Exercise has been estimated as effective for global cognition, it can improve working memory.	Moderate to high intensity aerobic exercise 12 weeks.

Demurtas et al., 2020 Umbrella Review of Intervention and observational Studies	23	Patients with MCI.	Aerobic exercises, resistance exercises, balance and coordination exercises, motor-cognitive interventions (Virtual Reality, Exergaming).	Cognition.	Physical activity/exercise was able to improve cognitive and non-cognitive outcomes in RCTs.	Physical activity/exercise .
Venegas-Sanabria et al., 2020 Systematic review	11	Adults with dementia (of any type, including).	All exercise.	Cognition.	Benefit of global physical activity cognition, executive functions, memory, and processing speed among people with mild cognitive impairment and dementia.	Multicomponent exercises.
Yeh et al., 2020 Systematic review	15	Patients with MCI.	High intensity functional exercises.	Cognition physical condition.	High intensity functional training is beneficial for balance, walking speed.	High intensity functional exercise is generally safe and viable for patients with mild or moderate dementia. High intensity functional exercise is beneficial to the balance function and daily functioning among patients with insanity. High intensity functional exercise makes not improve cognition or depression based on current evidence.
Russ et al., 2021 Systematic review and metanalysis	7	Patients with MCI.	HIT program, High Intensity Functional Exercise (HIFE) program Duration 45-60 minutes, 12 weeks.	Cognition physical condition.	Present data support that HIT regimens have led to greater improvements in balance and ability to execute ADLs.	Physical training is recommended for Treating Dementia Symptoms Additional, Well-Designed Studies it would be helpful to identify more effective exercise factors for different. Types and stages of dementia.

Considering dual task training, 6 reviews were found, summarizing 125 intervention studies (Table 6).

Table 6-. Population, results and summaries of the reviews included for the Dual Task training**.**

Authors, year, and review methodology	Number of included studies in review	Population, Prevalence of dementia and setting	Intervention: frequency, intensity, type, and time (FITT)	Outcomes Measured	Summary of findings	Exercise recommendations
Bruderer-Hofstetter et al., 2018 Systematic review	17	Patients with MCI.	Dual task cognitive training exergames, dança ou TaiChi.	Cognition physical condition.	Improved specific aspects of physical ability and / or cognitive function.	The results of this systematic review confirmed that dual task intervention is more effective compared to active comparison interventions.
Gheysen et al., 2018 Systematic review	40	General mean age ≥ 65 years with or without mild cognitive impairments in the beginning.	Dual task, cognitive training and aerobic exercise or strength training.	Cognition physical condition.	Interventions combining physical and cognitive activity can improve cognitive level	Dual task cognitive training aerobic exercise or strength training
Zhang et al., 2019 Systematic review	34	Average age 65 years or older, participants had cognitive impairment or dementia.	Dual task, strength and balance training combined with, functional mobility and attention training and the training of executive functions.	Cognition.	There is evidence that anti-dementia drugs, exercise combined programs and exercises and cognitive interventions improve walking in people with MCI or dementia.	Physical training combined with cognitive training.

Gallou-Guyot at al., 2020 Overview	9	Participants with neurological diseases other than dementia or MCI.	Dual Task strength, march, mobility, balance and falls cognitive covered attention, memory and executive functions frequency (1-6 times a week), duration of sessions (30-180 min), and duration (4-52 weeks duration). Group gym sessions mind-body exercises such as tai-chi, dancing, music, or martial arts.	Cognition physical condition.	Dual-task training appears to be effective both cognitively and physically in adults with MCI or dementias.	Frequency: 1-6 times a week; duration of 30-180 min per session; and lasting between 4-52 weeks. Group gym sessions should include mind-body exercises such as tai-chi, dancing, music or martial arts.
Xiong et al., 2021 Systematic review and metanalysis	25	Healthy elderlies with no known cognitive impairment.	Aerobic, resistance or body-mind exercises. 3 weekly sessions ranged from 20 to 90 minutes in duration 1 to 12 months (VO2max).	Cognition.	Physical exercise results in significant improvement in working memory, inhibition, and cognitive flexibility in cognitively healthy older adults.	Aerobic exercises Body mind exercises.

Discussion

This study aimed to provide a theoretical framework to support future exercise interventions for people with dementia/genitive impairment. Twenty-nine review studies were analyzed, and although they were divided according to the type of physical training used as well as variables measured, all of them consistently reported benefits for the elderly with MCI.

From an initial search of 1815 reviews, only 41 met the defined criteria; however, only 29 presented sufficient methodological quality to be considered in this critical review. Many of the reviews were excluded due to a lack of either systematic research or analysis method, the heterogeneity of sample populations, as well as unclear interventions in the applied physical exercise programs. Moreover, only 8 of the 29 studies had higher values in terms of quality assessment (Bruderer-Hofstetter et al., 2018; Gheysen et al., 2018; Gomes-Osman et al., 2018; Lam et al., 2018; Law et al., 2014a; Sandler et al., 2019; Xiong et al., 2021; Zhang et al., 2019a). Although the 29 review studies included in this critical review concerned 721 interventions or review studies, it is likely that several studies had been repeatedly analyzed in several revision studies with the same aim. Consequently, the risk of analyzing the same intervention study several times exists, which may bias the results. It seems important to suggest that future revision studies take into consideration the period in which each revision performed its search process, avoiding the overlap of the same intervention studies.

Another concern is related to the revision types taken into account. In fact, six different revision types were included in this critical review (narrative, revision, over-review, systematic review, meta-analysis, and umbrella-review), which according to criteria such as the overarching goal, search strategy, appraisal of included studies, analysis and synthesis (Lau & Kuziemsky, 2017) make it difficult to achieve a concrete proposal of guidelines for the physical training of the elderly with MCI. Indeed, most of the review studies are too vague in what concerns exercise prescription, and those that were not vague were systematic reviews (Biazus-Sehn et al., 2020; Brett et al., 2016; Bruderer-Hofstetter et al., 2018; Cammisuli et al., 2018, 2017a; Gheysen et al., 2018; Gomes-Osman et al., 2018; Hernandez et al., 2015; Law et al., 2020; Learner & Williams, 2016; Lewis et al., 2020; X. Li et al., 2019; Loprinzi et al., 2019; Loprinzi et al., 2018; Park & Cohen, 2019; Russ et al., 2021; Sandler et al., 2019; Venegas-Sanabria et al., 2021; Vseteckova et al., 2020; Yeh et al., 2021), and meta-analysis (Groot et al., 2016b; Xiong et al., 2021). One narrative review has also been included (Chong et al., 2020); however, this could be could be seen as an actualization of a previous systematic review published a year before (Cammisuli et al., 2018, 2017a).

The main focus of this critical review was to evaluate the effects of physical exercise on the cognitive and physical fitness of elderlies with MCI. Based on the present findings, patients with dementia may benefit from various exercise programs, namely the improvement of global cognition, especially in the initial-to-moderate phase of the disease.

Regarding aerobic exercise intervention improving global cognition, especially in the moderate stage of the disease (Hernández et al., 2015), all studies referenced in this research show improvements (Cammisuli et al., 2018, 2017b; Gomes-Osman et al., 2018; Learner & Williams, 2016; Loprinzi et al., 2019; Xiong et al., 2021). Only two revisions distinguished between living in a community (Vseteckova et al., 2020) or nursing home(Learner & Williams, 2016). In nursing homes, programs tend to be more controlled and follow a predefined organization of the institution, which may contribute to the success of intervention programs. In contrast, programs for community-dwelling older adults with Subjective Cognitive Decline (SCD) depend on the involvement of family members and caregivers and their willingness to participate in the programs. Regardless of these constraints, the review of Vseteckova et al., (2020), which included 10 studies, found improvements in cognitive function in community-dwelling older adults with aerobic training.

Aerobic exercise is a low cost, low risk, and widely available strategy for counteracting the consequences of Dementia on the brain. Among the main methods used to perform aerobic exercise, walking (Learner & Williams, 2016; Vseteckova et al., 2020) has stood out as the foremost method to improve brain physiology (improving mitochondrial function, increasing antioxidant capacity, and reducing oxidative stress (Rondão et al., 2022), as well as reducing chronic inflammation in the central nervous system, increasing neuroplasticity, and promoting the reorganization of neural circuits (Erickson et al., 2011a). If performed outdoors, it may also stimulate attention, memory, executive function, orientation and, if accompanied, language. As exercise with the elderly who have MCI should also be supervised and accompanied, walking outdoors may also be advantageous to the caregiver. This could be an appropriate exercise proposal for those individuals who live in a community setting.

Only three revisions (Cammisuli et al., 2018, 2017b; Gomes-Osman et al., 2018) propose guidelines for aerobic exercise, while the remaining (Cammisuli et al., 2018, 2017a; Gomes-Osman et al., 2018) are too unspecific as they propose aerobic exercise three times per week. Only Cammisuli et al. (2018) suggest an intensity of 60% of maximal oxygen uptake (VO_2maximum). Although this is a very precise method to utilize when prescribing exercise intensity, it may be difficult for exercise professionals to do so based on maximal oxygen uptake, as most of them cannot afford it. We therefore suggest that future recommendations should use other physiological parameters, such as heart rate, which are more feasible and easier to use.

Considering the effect of strength training in the cognition of older adults with MCI, only one systematic review was included (Lewis et al., 2020). This revision summarizes 15 intervention studies and reports general benefits in cognitive function, psychological health, and behavioural aspects. As strength training sessions imply the existence of a clearly defined routine with sequential exercises and a set number of repetitions, it demands that the subject be alert when performing said tasks in order to stimulate cognitive function. Besides the effect of strength training on muscle strength (Lewis et al., 2020), which in turn reduces the risk of falls, it also promotes changes in self-image and self-esteem (Lewis et al., 2020) with consequences in general psychological well-being. Although several benefits have been identified, the training load recommendations proposed by this revision study are 150 minutes of exercise (strength, balance and flexibility) per week with moderate to vigorous intensity.

Multimodal exercise interventions are the most frequently reported in adults with and without cognitive impairment, both in community and residential settings. Twenty-three revision studies were found considering the elderly with MCI, which, due to the heterogeneity of the programs reviewed, makes it difficult to propose a model of intervention. In fact, five revision studies summarize the effects of multicomponent exercise training in more traditional and academic programs (Biazus-Sehn et al., 2020; Brett et al., 2016; Chong et al., 2020; Hernandez et al., 2015; Lam et al., 2018; Law et al., 2020; Li et al., 2019; Sandler et al., 2019; Song et al., 2018), including strength or resistance exercises, aerobic exercise, balance and flexibility, reflecting the guidelines proposed by the ACSM (American College Sport Medicine). All of these revision studies reported benefits in cognitive function, which may be explained as aforementioned by a combination of benefits due to aerobic, or strength training. The remaining multicomponent exercise programs include revisions of functional training (Lam et al., 2018; P. Loprinzi et al., 2019; Russ et al., 2021; Venegas-Sanabria et al., 2021; Yeh et al., 2021), and others which combine different types of exercise such as Tai-chi, virtual reality or exergames, yoga and mind body exercise (Cai & Abrahamson, 2016; Demurtas et al., 2020; Park & Cohen, 2019). Most of them report benefits in cognitive function; however, possibly due to a lack of criteria in the selected studies (Park & Cohen, 2019), recommendations could not be made. As should be expected, innumerous differences in exercise protocols make it difficult to prescribe general guidelines for multicomponent exercise intervention. Nevertheless, these types of interventions represent programs which are more dynamic, creative, and motivational for older adults with MCI, thus it could be a way to improve program attendance and success.

Regarding Dual Task training revision studies, five met the defined criteria (three systematic reviews, one meta-analysis and one over-review). For the purpose of this critical review, a study was included in terms of Dual Task training if during a motor task exercise the subject had to perform a cognitive task (e.g. calculation during walking, evocation and orientation during a trail, among others) (Gheysen et al., 2018)). Despite the diversity of intervention programs (aerobic + cognitive, strength + cognitive, coordination + cognitive, balance + cognitive, etc.), results consistently suggested benefits at both the physical and cognitive level in people with MCI (Bruderer-Hofstetter et al., 2018; Gallou-Guyot et al., 2020; Gheysen et al., 2018; Xiong et al., 2021; Zhang et al., 2019a). In fact, the effect of transferring cognitive function to physical ability has been shown through the effectiveness of cognitive dual task training on balance and postural control in older adults (Bruderer-Hofstetter et al., 2018; Li et al., 2010). Moreover, improvements in cognitive functioning tended to be greater for interventions consisting of PA + CA (Physical Activity + Cognitive Activity) combined simultaneously, in contrast to PA + CA interventions which were combined sequentially. Furthermore, results showed that improvements in cognition can be expected after combined PA + CA interventions for both cognitively healthy and moderately impaired older adults (Bruderer-Hofstetter et al., 2018; Gallou-Guyot et al., 2020; Gheysen et al., 2018; Zhang et al., 2019a).

Dual task training has some important benefits. Besides the fact that it performs two tasks simultaneously, motor and cognitive, it may be a form of cognitive distraction, allowing the exercises to be performed without focusing on the possible pain or discomfort caused by the exercise itself.

The results of these review studies improve the effectiveness of dual-task interventions (Bruderer-Hofstetter et al., 2018; Gallou-Guyot et al., 2020; Gheysen et al., 2018; Xiong et al., 2021; Zhang et al., 2019a). Summarizing the recommendations, the effectiveness of the interventions depends on the frequency (if possible, every day), and the duration (30-180 min per session). Also, it is suggested that each session should include mind-body exercises such as walking, strength exercise, functional mobility, exergames, dance, music, or martial arts, simultaneously with cognitive tasks (Bruderer-Hofstetter et al., 2018; Gallou-Guyot et al., 2020; Gheysen et al., 2018; Xiong et al., 2021; Zhang et al., 2019a).

Considering the effects of different methods of exercise on physical function, most of the results report improvements in variables specific to the type of exercise performed. Regarding this, those that performed aerobic exercise improved aerobic capacity (Cammisuli et al., 2018, 2017a; Gomes-Osman et al., 2018; Learner & Williams, 2016; P. D. Loprinzi et al., 2018; Vseteckova et al., 2020), and those that trained strength improved strength and overall functionality while reducing the risk of falling in daily living activities (Lewis et al., 2020). The remaining revisions presented different outcomes in functionality which vary according to the variables measured (Biazus-Sehn et al., 2020; Brett et al., 2016; Cai & Abrahamson, 2016; Chong et al., 2020; Demurtas et al., 2020; Hernandez et al., 2015; Lam et al., 2018; Law et al., 2020; Li et al., 2019; Loprinzi et al., 2019; Park & Cohen, 2019; Russ et al., 2021; Sandler et al., 2019; Song et al., 2018), including the risk of falling (Bruderer-Hofstetter et al., 2018; Gallou-Guyot et al., 2020; Gheysen et al., 2018; Xiong et al., 2021; Zhang et al., 2019a). Dual task interventions were mainly concerned with the improvement of cognitive function.

Despite the complexity in not only the selection process of the revision articles and the analyses of different methodological issues, but also the heterogeneity of the exercise interventions which were implemented, it is possible to recommend the practice of daily physical exercise combined with cognitive tasks, and other forms of stimulation (music, exergames, dance…) for individuals with MCI. In fact, the gains made in cognitive function seem to depend more on the frequency of the exercise sessions, while the gains made in terms of physical function depend on the duration of intensity of at least three times per week. Particularly in elderly individuals with MCI, we suggest that the frequency of the stimulation through exercise follow a daily routine to avoid the delay and onset of the impairment of cognitive function. Moreover, the planning of exercise sessions should include aerobic, strength, balance, flexibility and agility exercises combined with cognitive tasks. Combining strength and balance exercises with mobility training, which targets basic functions needed during daily living activities (functional mobility training) such as sit-to-stand, walking, wandering in spaces, and turning, may be effective for improving gait (Hausdorff et al., 2008; Yogev‐Seligmann et al., 2008). Since it is difficult to achieve a high attendance rate in such programs, we propose that a minimum of two-three sessions occur in the presence of an exercise professional, and the remaining sessions occur at the individual's residence with remote monitoring and/or the use of exergames. Regarding the low fitness capacity of most of these individuals, it may be advisable that, at the beginning of the program, exercise sessions be performed at home throughout the day, divided into 3 to 4 sessions lasting 10 minutes.

Limitations

Some of the main concerns of this critical revision is the low methodological quality of several of the included revision articles, which restricts the ability to objectively propose guidelines of physical exercise for people with MCI.

Another limitation is related to the process of the analyses of revision articles. In fact, although at first glance a critical revision seems to be an excellent opportunity to summarize the main findings of hundreds or thousands of intervention studies analyzed in each review article, a cautious reflection should be carried out because the same articles could have been cited in different revisions.

Future contributions

An important aspect to incorporate in future revision studies is the inter-individual variability in responses to exercise, and modifiable factors (e.g., diet) as well as non-modifiable factors (e.g., genetic), which could impact the effect of exercise (Müllers et al., 2019).
Another recommendation that is still required is the elaboration of a manual with a program including the advocacy of Dual task training in interventions for individuals with MCI.

Conclusion

Based on the present findings, patients with dementia may benefit from various exercise programs to improve global cognition, especially in the initial-to-moderate phase of the disease. In addition, exercise can improve the balance ability of MCI patients and reduce the risk of falls. Consequently, this allows preliminary counselling of patients with mild Dementia, particularly those who are sedentary, to begin with daily multicomponent exercise in conjugation with cognitive tasks, and other creative forms of brain stimulation.

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Chapter 3.

Study 2 - Designing a combined exercise and cognitive stimulation intervention for people with mild cognitive impairment – Interdisciplinary and transdisciplinary perspectives.

Combined exercise and cognitive stimulation for people with mild cognitive impairment – interdisciplinary perspectives

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Abstract

Introduction: Older adults with mild cognitive impairment or dementia (MCI/D) are at high risk for a decrease in both motor performance and cognitive abilities, leading to serious loss of autonomy. Physical exercise can not only counteract this tendency by improving physical fitness and the ability to perform everyday tasks but can also increase cognitive stimulation. However, the multi-faceted nature of dementia symptoms and the numerous consequences of a patient's cognitive impairment requires the development of tailored treatments and intervention programs based on an interdisciplinary approach. This investigation aimed to collect the perspectives of an interdisciplinary team on the implementation of an exercise programme for people with MCI/dementia; namely, to identify the main recommendations as well as concerns of different experts.

Methods:
Semi-structured interviews were conducted with a range of experts: (1) Medical Neurologists; (2) Exercise Physiologists; (3) Neuropsychologists; (4) Social Work Technicians; (5) Fitness instructors; (6) patients and caregivers/family. The interviews were based on three questions: (1) "What characteristics should be present in an exercise-based intervention for people with MCI?; (2) "What kind of cognitive stimulation should be utilized?"; and (3) "What are the main concerns about exercise in relation to this population?".

Results:
Each area of expertise identified major recommendations and concerns regarding the implementation of a combined exercise program for people with MCI/D.

The recommendations found include: the importance of engaging families and caregivers; the necessity of increasing families and caregivers' knowledge about the significance of exercise in dementia; respecting a patient´s and caregiver's willingness to participate; promoting the collaboration and involvement of the senior residence's staff; ensuring caring, respectful and friendly treatment; creating a relationship of trust with the exercise professional; the appropriate design of the exercise and cognitive stimulation; an appropriate schedule; and a safe environment.

Major concerns reported by all experts are related to the resistance of dementia patients and their caregivers in participating in programs, the inadequacy of activities or exercises, the risk of injury; the lack of the adaptation of exercises; the difficulty of patients to understand instructions; the physical space for the implementation of programs not always being the most adequate; and the lack of family support.

Conclusion:

The interdisciplinary approach revealed multiple barriers, but also the opportunity to design a more adequately structured intervention, which is tailored to and addresses the individual needs of older people with dementia in a community setting. The benefits of interdisciplinary collaboration are widely heralded by scientists in many fields, but the effectiveness of alternative strategies to promote such a collaboration is not well-understood. It is proposed that more research including interdisciplinary contributions be conducted on exercise programs for people with MCI/ Dementia in order to improve the quality of interventions and services.

Keywords
Multicomponent exercise in mild cognitive impairment, Interdisciplinary recommendations, Interdisciplinary concerns

Introduction

Dementia is a chronic and terminal condition with multi-factorial causes as well as numerous consequences on a patient's life (Rodriguez et al., 2020). It is defined as a neurodegenerative syndrome characterized by a decline in functional capacity and cognition (Haaksma et al., 2017) that consists of a global and irreversible loss of cognitive ability, accompanied by a range of neuropsychiatric symptoms and a reduced ability to perform everyday activities (Dening & Lloyd-Williams, 2020).

According to Alzheimer's Disease International (2021), there are over 10 million new cases of dementia worldwide each year, implying one new case every 3.2 seconds.

Physical activity (PA), by increasing aerobic fitness and cerebral blood flow, seems to contribute to the reduction of chronic inflammation in the central nervous system, increase neuroplasticity, and promote the reorganization of neural circuits (Erickson et al., 2011b). Huang et al., (2022) emphasize that exercise may exert protective effects on cognitive function by (1) raising the levels of growth factors such as brain-derived neurotrophic factor and insulin-like growth factor 1, (2) regulating inflammatory cytokines, (3) relieving oxidative stress, (4) increasing cerebral blood flow, (5) reducing Aβ concentration, and (6) inhibiting tau phosphorylation. In fact, PA has been associated with a lower incidence of MCI and dementia (Beckett et al., 2021; Blondell et al., 2014; Guure et al., 2017; Nuzum et al., 2020) as an increased amount of leisure-time spent on physical activities leads to a 64% reduction in the risk of developing dementia in individuals with MCI (Feter et al., 2021; Grande et al., 2014).

Therefore, PA is considered an effective non-pharmacological strategy to attenuate or delay the evolution of dementia-related degenerative diseases (Erickson et al., 2019; Maliszewska-Cyna et al., 2017; Paillard et al., 2015).

In recent years, a variety of programs have been developed to increase cognitive and motor functions in older adults with MCI (Brasure et al., 2018; Fleiner et al., 2016; Gallou-Guyot et al., 2020; Law et al., 2014b; McSween et al., 2019; Yang et al., 2020).

Dementia comprises of Alzheimer's disease, the most frequent form of dementia, as well as vascular dementia, frontotemporal dementia, and Lewy body disease, to name a few. Evidently, distinguishing the type of dementia is relevant for treatment planning. Often, however, dementia patients do not only have one but several pathologies. For instance, more than 80% of those with the Alzheimer's disease pathology also have vascular pathologies (Attems & Jellinger, 2014). Multiple microinfarct or large microinfarcts and vascular lesions in diverse subcortical regions can lead to atypical patterns of symptomatology (Jellinger, 2007). The heterogeneity of the pathology and symptomatology requires a person-tailored treatment plan. Moreover, dementia prognosis, treatment, and care challenges have heterogeneous consequences on the diagnosed individual, but also on their families, healthcare providers, and caregivers (Rodriguez et al., 2020; Winblad et al., 2016).

The multi-factorial causes of dementia, the multi-faceted nature of dementia symptoms, and the numerous consequences of a patient's cognitive impairment requires the development of a holistic approach to dementia prevention and care that allows for tailored treatment and intervention plans (Rodriguez et al., 2020).

As there are multiple causes of cognitive impairment (Albert et al., 2011), every individual's symptoms are different and each family is unique (Rodriguez et al., 2020), therefore, the responses given by medical professionals and communities should be as personalized as possible. Accordingly, an interdisciplinary approach to dementia prevention and care is essential for tackling the complex questions surrounding these heterogeneous diseases.

Interdisciplinary research is “a mode of research by teams or individuals that integrates information, data, techniques, tools, perspectives, concepts, and/or theories from two or more disciplines or bodies of specialized knowledge to advance fundamental understanding or to solve problems whose solutions are beyond the scope of a single discipline or area of research practice” (National Academy of Sciences, 2004)(Borrego & Newswander, 2010).

Integration of knowledge from several disciplines on dementia and the achievement of a detailed summary is necessary to develop optimized person-tailored treatment plans (Wagner et al., 2011). There is still a long way to go to achieve such a coordinated combination of different disciplines in dementia care and research; however, it is a necessary next step for unravelling dementia’s complex issues.

The specific characteristics of dementia patients, such as decreased executive functioning, reduced attentional and memory capacities (Baddeley et al., 1986; Perry, 1999), diminished ability to develop and perform new complex motor sequences, and impaired gait and balance performance (Allan et al., 2005; van Iersel et al., 2004), together with comorbidities that may exist as well as altered behaviour (like violence, sleep patterns, etc.) demand specific interventions based on an interdisciplinary approach (Divo et al., 2015; Tatsiopoulou et al., 2020).

This investigation aims to collect the perspectives of an interdisciplinary team on the implementation of an exercise program for people with MCI/dementia, or in other words to identify the main recommendations and concerns of different experts.

From the interdisciplinary approach, some questions emerged:

- What are the concerns of each area?
- What are the major recommendations of each area?
- What are the areas of expertise that should be considered in the program design?

Methods

Organisation and participants of the expert panel

The Expert panel’s structure and the participants chosen for the expert panel were organized by the Department of Sport of the University of Beira Interior. It was composed according to two main aspects: interdisciplinary variety and practical relevance. Interdisciplinary and methodological variety was achieved by inviting researchers from the motor and cognitive sciences as well as the humanities, social and natural sciences. Practical relevance was achieved by including researchers with direct experience in the development and evaluation of motor assessments or with experience in dementia research.

In the first phase, a meeting session with individuals of different expertise (Medical Neurologists, Neuropsychologists, Fitness instructors, Exercise Physiologists, Social Work Technicians, patients and caregivers/family) was organized.

Discussion and guiding questions during the expert panel

Prior to the first meeting, the Department of Sport Sciences developed guiding questions based on challenges in assessing motor performance in a population with MCI identified by the literature review. These questions included aspects such as the type, frequency, intensity and duration of exercise, the type of cognitive stimulation and the biochemical parameters which should be assessed together with a relational approach (language, motivation strategies, topics of interest) and the specifications of the program's implementation (location, decoration, lighting level, ambient sound level, type of music, type of floor, equipment to be used). Based on the results of the first meeting, the second meeting aimed to obtain specific recommendations in a smaller group context. It began with a summary of the results, which were then analyzed based on common research practices and one's own research experiences. In the next step, the guiding questions were again critically reflected upon and specific issues for each evaluation instrument were discussed in detail. As stated above, the discussion gradually became more specific. Finally, the instruments for physical and cognitive assessment were defined, and the entire team reached a consensus.

Experts' interviews

After reviewing the literature, semi-structured interviews were conducted with collaborators to discuss the content of the program, including the degree and intensity of cognitive–physical training, types of exercises, and any concerns regarding the intervention program.
Information was retrieved through semi-structured interviews that were based on three questions: (1) "What characteristics should be present in an exercise-based intervention for people with MCI?"; (2) "What kind of cognitive stimulation should be utilized?"; and (3) "What are the main concerns about exercise in relation to this population?"

Results

The main results are presented in Table 1.

Table 1.- Experts' interview: summary of findings

Expert	***Major recommendations***	***Major concerns***
Medical Neurologists (1)	▪ Importance of describing the criteria for inclusion and exclusion in the program; ▪ Importance of assessing general health status and identifying all comorbidities; ▪ Importance of a proper diagnosis of Dementia; ▪ Indication and suggestion of biochemical parameters to be evaluated; ▪ Recommendation of the use of technology to enhance movement and cognitive stimulation.	▪ Risk of falls; ▪ Danger of disorientation; ▪ Episodes of violence; ▪ Not wanting to participate; ▪ Beware of comorbidities (hypertensive, diabetics, cardiac patients, asthmatics); ▪ Inadequate dementia diagnosis.
Exercise Physiologist (2)	▪ The need to increase family awareness of the importance of Physical Activity in dementia; ▪ Prior to exercise, assess physical fitness; ▪ The need for a pre/post program test (assessment of differences in physical fitness); ▪ Individualize the type, intensity, frequency and duration of exercise; ▪ The exercise space should have adequate lighting, a non-slip floor, and no obstacles or unevenness.	▪ Resistance to participate; ▪ Ability to perform fitness tests; ▪ Control of exercise intensity; ▪ Adaptation of the exercises.
Neuropsychologist (3)	▪ The importance of enrolling families and caregivers; ▪ The need to educate families and caregivers about the importance of Physical Activity in dementia; ▪ Respect an individual's willingness or unwillingness to participate; ▪ Create a relationship of trust with the participant; ▪ The need for an interdisciplinary team to design appropriate cognitive stimulation. ▪ Stimulation of different cognitive abilities such as memory, attention, language, calculation and executive functions; ▪ Adapt to cultural context and individual educational level; ▪ Stimulation of the various senses (visual, auditory, tactile, verbal); ▪ The use of childhood memories.	▪ Participation resistance; ▪ Lack of family support; ▪ Inadequate dementia diagnosis; ▪ Ability of fitness instructors and sport scientists to mentor sessions in patients with dementia; ▪ Lack of ability to understand instructions; ▪ Inadequate cognitive stimulation.

Social Work Technicians (4)	▪ Promote the collaboration and involvement of the senior residence staff; ▪ Choose suitable timetables (mornings are better than afternoons for these activities); ▪ Coordinate the programme with other existing activities; ▪ Create a relationship of friendship and trust with the participant; ▪ Use appropriate language.	▪ Willingness to collaborate; ▪ Sensitivity to deal with people with MCI/D.
Fitness Instructors (5)	▪ The exercise professional should be a PA specialist for people with dementia; ▪ The program should focus on everyday materials that are available in any institution for the elderly or can be easily transported; ▪ Support materials; ▪ Tools should be adapted to physical and cognitive difficulties; ▪ Development of functional movement; ▪ Tasks with little difficulty; ▪ Work in small groups; ▪ Use of demonstration to exemplify the execution of exercises; ▪ Positive feedback to promote program continuity; ▪ Training of different physical abilities, endurance, strength, balance, flexibility; ▪ Type of language should be clear and simplified, adapted to people´s educational levels; ▪ Create a relationship of trust with the fitness instructor.	▪ Participation resistance; ▪ Adaptation of the exercises; ▪ Lack of understanding of exercise rules; ▪ Physical space for application of the program is not always the most adequate; ▪ Lack of didactic materials in the institutions.
Patients (6)	▪ Make sure the program is good for your health and carries no risks; ▪ Understand if the proposed tasks are up to their level; ▪ Make sure they are not "too old" to participate in the program.	▪ Resistance to participate; ▪ Weakened physical and cognitive conditions.
Caregivers (7)	▪ Ensuring the safety of the exercise program; ▪ Need to be sure it is an appropriate program for their relative; ▪ Ensure thoughtful, respectful and friendly treatment of their family member; ▪ Need to understand the benefits of exercise in Dementia; ▪ Want to ensure the confidentiality of the data collected and the conversations that take place during the program; ▪ Want to ensure that no image capture is made without prior consent; ▪ Reinforce the importance of the informed consent required for participation in the program.	▪ Lack of literacy about the importance of exercise in neurodegenerative diseases; ▪ Some resistance in the consent of their family members to participate; ▪ Capacity of the fitness instructor to deal with MCI/D; ▪ Possible risks of exercise.

After analyzing the table, common recommendations from all experts, recommendations from most experts and other more specific recommendations from some experts were identified.

Recommendations common to all experts stand out, such as: the importance of engaging families and caregivers; the need to educate families and caregivers about the importance of exercise in dementia; respecting a patient's willingness to participate; promoting the collaboration and involvement of the senior residence's staff; ensuring caring, respectful and friendly treatment; creating a relationship of trust with the exercise professional; the appropriate design of the exercise and cognitive stimulation; an appropriate schedule; and a safe environment.

The recommendations of most experts highlight the need for an interdisciplinary team to design appropriate cognitive stimulation; stimulate different cognitive abilities such as memory, attention, language, calculation, executive functions; adapt to the cultural context and individual educational level of each patient; stimulate the various senses (visual, auditory, tactile, verbal); use childhood memories; adapt tools to physical and cognitive difficulties; focus the program on everyday materials that are available in any institution for the elderly or can be easily transported; use clear and simplified language adapted to people`s educational levels; promote program continuity through positive feedback; develop functional movement; use tasks with little difficulty; work in small groups; use demonstrations to exemplify the execution of exercises; have adequate lighting, a non-slip floor, and no obstacles or unevenness in the exercise space; promote collaboration and involvement of senior residence's staff; choose appropriate times (mornings are better than afternoons for these activities); coordinate the program with other existing activities; and ensure the safety of the exercise program.

Some recommendations that stand out as more specific are the importance of describing the inclusion and exclusion criteria in the program; the importance of assessing general health status and identifying all comorbidities; the importance of a proper diagnosis of Dementia; indicating and suggesting biochemical parameters to be assessed; and recommending the use of technology to enhance movement and cognitive stimulation.

The importance of the role of family members in supporting people with the characteristics of MCI or Dementia should be emphasized. They play an important role in encouraging, motivating, and participating in programs that aim to help delay the onset of these diseases.

The main concerns common to all experts are related to the resistance of individuals to participate in programs, inadequate activities or exercises; the risk of falls; the lack of adaptation of exercises; the lack of an individual's ability to understand instructions; the physical space for the implementation of programs not always being the most adequate; and the lack of family support.

The concerns of most experts refer to the inadequate diagnosis of dementia; danger of disorientation; episodes of violence; willingness to collaborate; lack of sensitivity to deal with people with MCI/ Dementia; and lack of adequate exercise equipment in the nursing homes.

Discussion

Recent literature has presented evidence on the benefits of exercise combined with cognitive stimulation in people with dementia, including those living in nursing homes, as it has been found to improve cognition, agitation, mood, mobility, and functional ability (Brett et al., 2016; Henskens et al., 2018; Lee, 2018; Vseteckova et al., 2020). Despite this evidence, there continues to be a lack of focus on physical exercise in nursing homes, particularly for individuals with dementia (Brett et al., 2016).

Gebhard & Mir, (2021) justify the strong need for further research on physical exercise in nursing homes, especially considering the lack of targeted interventions, inadequate development of exercise programs and incomplete picture of motivating and hindering factors regarding physical activity in people living with dementia in care homes.

To design and implement a multi-component exercise program for people diagnosed with MCI/Dementia in nursing homes, it is necessary to involve an interdisciplinary team composed of the physician, psychotherapist, and exercise expert, but also nursing home staff and technicians, family/caregivers of the participant and the individual him/herself.

This paper aimed to identify the main recommendations and concerns of different experts in building an exercise program in working with people with MCI.

Based on the semi-structured interviews, some aspects were considered essential for the successful implementation of exercise programs for people with MCI, one of the main ones being the absolute need for the inclusion of families and caregivers.

In fact, family members are the people who are affectively closest to the individual with dementia, meaning they must often make decisions about him/her and his/her life and therefore consider themselves to be the experts regarding the person with dementia (Chenoweth et al., 2009; Harper et al., 2021). Thus, the importance of involving family members was unanimous for all the specialists interviewed.

This finding is supported by Brett et al., (2018) who states that encouraging staff's and family carers' involvement in the implementation of a new intervention program in people with dementia living in nursery homes can help to ensure success.

Considering the important role of families/caregivers in the implementation of an exercise programme in dementia, it is necessary that the family recognises the importance of exercise in dementia. This was another recommendation that emerged from the interviews conducted.

Caregivers of people with dementia reported the patient's well-being and maintaining the emotional relationship with them (Lindeza et al., 2020) as essential, as well as having the best health care, not only for dementia, but for other existing pathologies. Family members want their relatives to have a good life, with care focused on them as an individual and their specific characteristics (Harper et al., 2021).

Exercise is not one of the priorities of family members of people with dementia. Post et al., (2020) refer to the fact that the initial perceptions of family members were favorable to the idea of the exercise program and its potential benefits; nevertheless, there was some scepticism associated with the possibility of any benefit, with some family members thinking residents were '...too far gone'.

It is therefore fundamental to reinforce to the family members that the benefits of multi-component exercise in this population are significant, and that a sedentary lifestyle will contribute to an acceleration of the individual's physical and cognitive decline.

This change in family perceptions about exercise in dementia is a crucial aspect for the participation of individuals in exercise programs.

Just like family members, caregivers/staff in nursing homes need to recognise the benefits that an exercise program can present - and not just see it as "more work" - having to drive the service user to the program, having to reconcile activity schedules, etc.

Sampaio et al., (2021) emphasize this idea, stating that caregivers are the people who have more contact with institutionalized dementia patients and, as such, a caregiver's perception of exercise intervention is important.

Chu et al., (2022) reinforce the caregiver's intimate knowledge about the residents and their perception that physical activity not only increases social interactions while reducing loneliness, frustration and stress, but also improves well-being in residents with dementia.

Harper et al., (2021) highlight that caregivers of people with dementia are uniquely situated to provide insight into residents' preferences as the progressive disease affects residents' ability to express their own desires.

Therefore, promoting the collaboration and involvement of the nursery homes' caregivers is a key aspect to ensure implementation and participation in exercise programs.

Another important aspect to discuss is the perception of medical doctors, in regard to exercise for people with dementia. If the doctor recommends participation in an exercise program as a non-pharmacological therapy, the motivation to participate may increase. However, several doctors are sceptical about the benefits of this participation, considering that exercise does not bring significant improvements in the individual's condition.

According to Karuncharernpanit et al., (2016), in order to recommend exercise, medical doctors demand to know the specifications of the exercise (and present concerns regarding its adequacy), the advantages people believe exercise to have, and the proper way to exercise. Medical doctors mainly recommend aerobic exercise along with strength and balance training, and the major advantages acknowledged include preserving health and mobility as well as enhancing mood and sleep (Karuncharernpanit et al., 2016). Despite the increasing demand from its main advocates, interdisciplinary exercise programs are not of standard practice in the care of dementia. The views of doctors regarding the importance of exercise in the treatment of dementia are not well-known and it is therefore not incorporated into the usual care pathway for those with dementia (Karuncharernpanit et al., 2016).

Interdisciplinary exercise will need to be reframed to be more widely accepted as being relevant to dementia care. This requires educating upcoming health professionals on the potential benefits for dementia patients as well as convincing all those involved in the patient’s care that the investment is beneficial (Cations et al., 2020).

Physicians' perceptions of exercise in dementia may be altered by discussion in interdisciplinary groups, including exercise physiologists, fitness instructors and caregivers. Willingness to participate in exercise programs is also a particularly sensitive subject when dealing with people with MCI/Dementia. Harper et al., (2021) refer to the fact that individuals perceive the benefit of being physically active and are aware of the health-enhancing effects of physical activity; nevertheless, Gebhard & Mir., (2021) found that people living with dementia face more barriers than motivators where physical activity is concerned.

Encouragement from others and the socializing effects of physical activity are seen as additional motivators. Furthermore, it should be noted that initial scepticism towards exercise programs is quite typical among people living in nursing homes (Wu et al., 2015). People with dementia describe these communities as a low-stimulus environment and a place with rules and restrictions (Freund et al., 2018; Murad & Pyun, 2017), almost associated with a prison environment (Heggestad et al., 2013). This feeling of imprisonment can be an impediment when choosing to participate in existing programs in nursing homes, including exercise programs. Therefore, both the living environment and staff support are key aspects to an individual's willingness to participate in an exercise program.

Some experts interviewed have reported the importance of inclusion and exclusion criteria. A criterion that is too narrow can lead to a sample size that produces inconsequential amounts of data, but a criterion that is too broad can lead to data that is biased by external factors (Hornberger & Rangu, 2020). The clear definition of inclusion and exclusion criteria is an important methodologic item in program design (Rondão et al., 2022).

One of the major difficulties is the correct diagnosis of participants. As Dementia is not a well-known diagnosis, individuals with dementia are missing crucial clinical care and treatment measures. On a similar note, mild cognitive impairment (MCI) has not yet been adequately defined, diagnosed or treated, and screening is not currently recommended. It is important to scientifically analyze the methods of screening for dementia, including their sensitivity and specificity for identifying those affected in risk groups (Ashford et al., 2007; Morra & Donovick, 2014).

One of the problems raised by experts was the subject of communication. In order to continue to engage in decision-making and advocate on behalf of a patient with dementia, caregivers must first learn about the patient through communication. Despite efforts to improve communication between nursing home personnel, doctors, patients with dementia, and caretakers, caregiver dissatisfaction and unhappiness with this aspect remains high (Buhr et al., 2006; Burgio et al., 2001). This lack of communication is very tricky when it comes to developing interdisciplinary work. On the one hand, there is the use of technical terms (jargon) frequently used by medical doctors and psychotherapists, which can be a barrier to communication with nursing home staff and exercise technicians. On the other hand, there is a question of "power" in a team: doctors and university professors are considered to have more "power" and their opinions are hardly ever refuted by other team members.

Considering the results obtained, ten main aspects were considered important to highlight in the design and implementation of exercise programs:

1. Special care with the initial diagnosis

Talk about the diagnosis of comorbidities, the diagnosis of dementia, biochemical analyzes and also the fitness tests used.

2. Evaluating the effects of the program

Assess fitness levels combined with cognitive stimulation (dual task), functional fitness and the effect of exercise on oxidative stress involvement and Brain Derived Neurotrophic Factor (BDNF).

3. Involvement of psychologists, fitness instructors and Exercise Physiologists in individualizing both the exercise component and the cognitive stimulation componente.

Readjust cognitive stimulation in order to be adapted to the social and cultural context of a patient as the literacy level of the sample is low. Adapt all exercises to the physical abilities of the participants as fitness levels are also low.

4. Involvement of family/caregivers

Raise awareness by clarifying and informing caregivers about the importance of participating in a physical exercise program that is combined with cognitive stimulation.

5. Close collaboration with Social Work Technicians

Integrate Social Service Technicians as they facilitate both access to the program and a participant's involvement in the program. Also, they facilitate access to existing materials and infrastructure for use in the program.

6. Strategy to minimise the risk of falls/injuries

Choose locations for the intervention without physical barriers or any inclinations to facilitate walking, as well as strategically place rest and support points to ensure the safety of the participants.

7. Involvement of psychologists, fitness instructors and Exercise Physiologists in individualizing the progression of both the exercise and cognitive stimulation components

Have an interdisciplinary team as it allows the organization and planning of interventions to be more tailored and appropriate to the individuality of each participant and ensures that there is improved performance.

8. Participation in a training session on mental health

Implement a training session including the following topics: a better understanding of how the brain works, the importance of adapting the language, the relationship with the participants, how to transmit information, and what kind of tools to use. These points are crucial to the organization, planning and operationalization of the program.

9. Introduction of technology for cognitive stimulation

Use technological companies in the development of research to introduce digital platforms for cognitive stimulation, namely Cogweb, a cognitive training platform; Brain on Track, a cognitive monitoring platform; and Blaze Pod exergame, all of which work on physical and cognitive abilities simultaneously.

10. Development of strategies that lead to motivation/participation in the program

Adopt diverse strategies to ensure participation in the program, including the type of material used, the type of feedback given, the organization of exercises ranging from the simplest to the most complex, and promoting success in the execution of the exercises.

Overall, this study's intervention development process was successful, and the finalized intervention is prepared for practical use and further improvement through an experimental investigation. Through a process of evaluation and feasibility testing in a controlled experiment, it will be possible to explain how it worked, why it might not have worked, and how it could be further developed or improved.

Limitations

The experts interviewed were involved with the program - no external experts were contacted, which may bias the answers given, as they already understood the program that was to be implemented.

At times, there was difficulty in reconciling the language of the different experts and, therefore, it was challenging to come to the conclusion that they were saying the same thing but using different technical language and terms. This limitation was tentatively overcome by having two people in each interview and comparing the results obtained by each of them.

Conclusion

This investigation aimed to collect the perspectives of an interdisciplinary team on the implementation of an exercise program for people with MCI/dementia.

The areas of expertize that were considered for the design of the exercise program were: Medical Neurologists, Neuropsychologists, Fitness instructors, Exercise Physiologists, Social Work Technicians, and caregivers/family.

Major recommendations found were the importance of inclusion families and caregivers; the need to educate families and caregivers about the importance of exercise in dementia; respecting a patient's willingness to participate; promoting the collaboration and involvement of the senior residence's staff; ensuring caring, respectful and friendly treatment; creating a relationship of trust with the exercise professional; the appropriate design of exercise and cognitive stimulation; an appropriate schedule; and a safe environment.

The main concerns found are related to the resistance of dementia patients in participating in exercise programs, the inadequacy activities or exercises; the risk of falls; the lack of the adaptation of exercises; the difficulty in understanding instructions; the physical space for the implementation of programs not always being the most adequate; the lack of family support, the inadequate diagnosis of dementia; the danger of disorientation; the episodes of violence; the willingness of those involved in the care of dementai patients to collaborate; the lack of sensitivity in dealing with people with MCI/ Dementia; and the lack of adequate exercise equipment in nursing homes.

The benefits of interdisciplinary collaboration are widely heralded by scientists in many fields, but the effectiveness of alternative strategies to promote such collaboration is not well-understood. It is proposed more research be conducted on exercise programs for people with MCI/Dementia that include interdisciplinary contributions in order to improve the quality of interventions and services.

The recommendations and concerns found were used to design a multicomponent program specifically designed for people with MCI8/Dementia: the MEMO_MOVE program (Rondão et al., 2022) https://www.facebook.com/profile.php?id=100063619118105, https://memomove.wixsite.com/memomove.

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Institutional Review Board Statement: All the experimental procedures were approved according to the Declaration of Helsinki (UNESCO. Universal Declaration on Bioethics and Human Rights 2006) and were carried out with the approval of the Ethics Committee of the University of Beira Interior (reference code No. CE-UBI-PJ-2019-021).

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Conflicts of Interest: The authors declare no conflict of interest.

Chapter 4.

Study 3 – Physical fitness level of a population with mild cognitive impairment

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Physical fitness level of a population with mild cognitive impairment

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ABSTRACT

Older people are the fastest growing group in the world, and they experience a progressive loss of cognitive and physiological functions, leading to cognitive impairments and loss of functional motricity. The maintenance of physical activity and good physical fitness is important for functional independence. Information available about the physical activity and sedentary behaviour of people with cognitive impairment is scarce. Therefore, this study aims examine the physical fitness level in older persons with mild cognitive impairment. The cross-sectional study included older people ≥ 65 years of age. 36 nursing home residents (mean 79.36 years) from both genders participated in this study; all participants have mild cognitive impairment according to the Mini Mental State Examination. Physical fitness was assessed using the Rikli & Jones Test. Statistical analyses were conducted with the statistical software SPSS. Results show that physical fitness in a population of older persons with mild cognitive impairment is very poor, with severe consequences on functional independence. Therefore, promoting an active lifestyle among this population should be a crucial concern, to maintain motor abilities to perform daily tasks. **Keywords:** Mild cognitive impairment; Physical fitness; Aging; Rikli & Jones Test.

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Physical fitness level of a population with mild cognitive impairment

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Older people are the fastest growing group in the world, and they experience a progressive loss of cognitive and physiological functions, leading to cognitive impairments and loss of functional motricity. The maintenance of physical activity and good physical fitness is important for functional independence.

Information available about the physical activity and sedentary behaviour of people with cognitive impairment is scarce. Therefore, this study aims examine the physical fitness level in older persons with mild cognitive impairment. The cross-sectional study included older people ≥ 65 years of age. 36 nursing home residents (mean 79.36 years) from both genders participated in this study; all participants have mild cognitive impairment according to the Mini Mental State Examination. Physical fitness was assessed using the Rikli & Jones Test. Statistical analyses were conducted with the statistical software SPSS. Results show that physical fitness in a population of older persons with mild cognitive impairment is very poor, with severe consequences on functional independence. Therefore, promoting an active lifestyle among this population should be a crucial concern, to maintain motor abilities to perform daily tasks.

Keywords:
Mild cognitive impairment; Physical fitness; Aging; Rikli & Jones Test.

INTRODUCTION

Physical fitness is closely related to health-related quality of life among older people with dementia (Hesseberg et al., 2016), since it is essential to carry out daily task, to participate social life and to live autonomously (Donnezan et al., 2018). Prevention of decline in physical fitness is important since it is related to older person's independence and wellbeing. However, aging brings chronic diseases, cognitive impairment and hospitalization which have direct impact on physical fitness and ability to stay active (Hesseberg et al., 2016). Cognitive impairment may be associated with lower levels of physical fitness and become a serious threat to older people's independence and quality of life (Bárrios et al., 2013; Hesseberg et al., 2016; Pettersson et al., 2005). Therefore, the main objective of this study was to examine Physical fitness of individuals with mild cognitive impairment, in order to evaluate the need of a specific Physical activity program that improve their functional fitness status.

MATERIAL AND METHODS

Participants

This investigation is a cross-sectional study in individuals with mild cognitive impairment. A total of 36 nursing home residents (mean 79.36 years) from both genders participated in this study. Inclusion criteria: all participants have mild cognitive impairment according to the Mini Mental State Examination (Guerreiro et al., 1994). Exclusion criteria: clinical diagnosis of advanced dementia syndrome; uncontrolled hypertension (BP> 160/90 mmHg); frequent hypoglycaemia; severe congestive heart failure; acute myocardial infarction in the last year; severe anaemia (HB <8 g / dl); severe respiratory disease; severe osteoporosis; sensory deficit (vision / hearing) that disables collaboration in the physical exercise program; severe psychiatric disorders.

Measures

Evaluation of cognitive impairment was made according to the Mini Mental State Examination (Guerreiro, et al., 1994). Physical fitness was assessed using the Rikli & Jones Test (Rikli & Jones, 1999).

Procedures

Participants were completely free to participate in the study, after the presentation of researchers' affiliation, investigation goals and guaranty of total confidentiality. An informed consent was signed by participant and relative. All evaluation procedures were made by a qualified professional: Mini Mental State Examination by a physiologist and Physical fitness by a sport professional, PhD student.

RESULTS

The physical fitness of individuals evaluated is presented on Figure 1, revealing that the level of physicalfitness of patients with mild cognitive impairment is mainly too week or week.

DISCUSSION

The results show that the level of physical fitness of patients with mild cognitive impairment is low, revealing deficits in motor performance that may affect their level of independence and their ability to perform daily tasks. Literature shows results similar findings (Chang et al., 2016; Hesseberg et al., 2016; Song et al., 2018). These results support the need for a program of functional physical activity in these individuals, which slows the deterioration of their motor abilities and allows an improvement in aerobic capacity, balance, strength and generic motor skills.

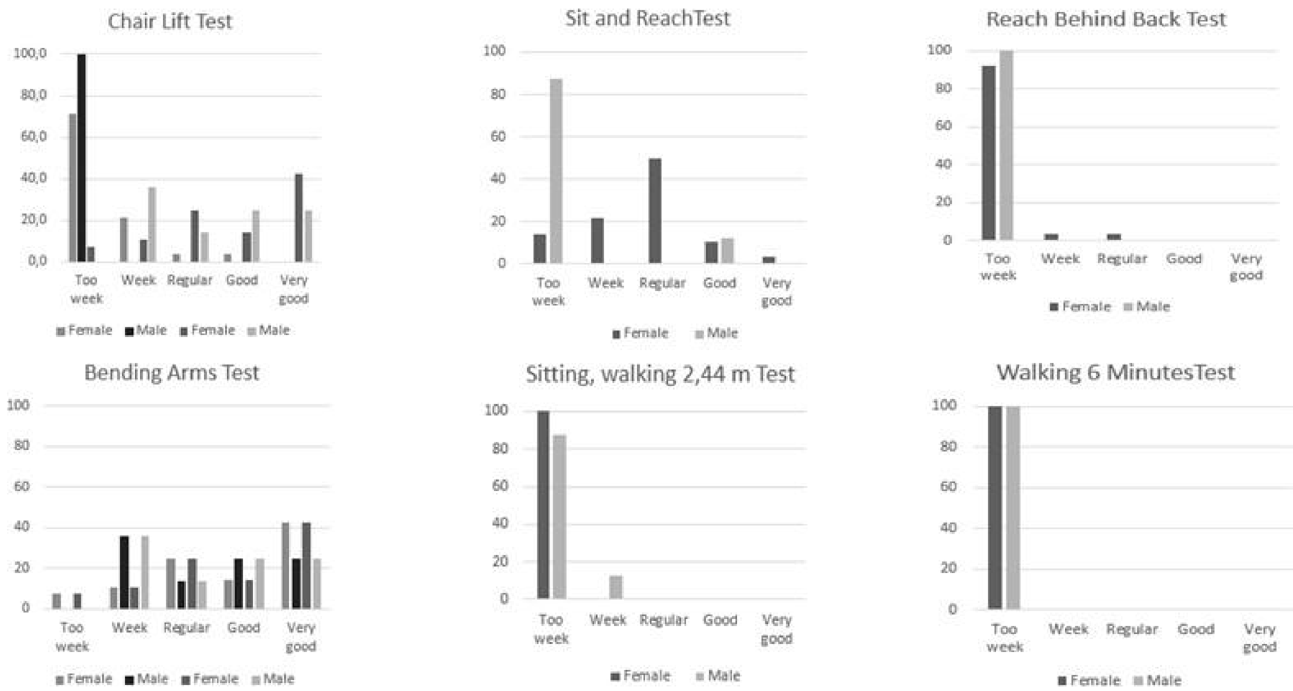

Figure 1.- Physical fitness of individuals with mild cognition impairments, according to Rikli & Jones Test.

CONCLUSIONS

Based on these results, authors designed a specific physical activity program to individuals with mild cognitive impairment: MEMO_MOVE program.

Chapter 5.

Study 4 – Development of a Combined Exercise and Cognitive Stimulation Intervention for People with Mild Cognitive Impairment—Designing the MEMO_MOVE PROGRAM.

International Journal of *Environmental Research and Public Health*

MDPI

Article

Development of a Combined Exercise and Cognitive Stimulation Intervention for People with Mild Cognitive Impairment—Designing the MEMO_MOVE PROGRAM

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Abstract: Dementia patients are at high risk for the decline of both physical and cognitive capacities, resulting in an increased risk of the loss of autonomy. Exercise is regarded as a non-pharmacological therapy for dementia, considering the potential benefits of preventing cognitive decline and improving physical fitness. In this paper, we aim to describe the different design stages for an exercise program combined with cognitive stimulation for a population with mild cognitive impairment, i.e., the MEMO_MOVE program. Methods: The intervention design followed the Medical Research Council's guidelines for complex interventions and was structured according to the six steps in quality intervention development (6SQuID). The intervention was described considering the Template for Intervention Description and Replication (TIDieR). In order to establish the intervention characteristics, a literature review was conducted to collate and analyze previous work, which provided a summary the type of exercise that should be implemented among this population. Results: The MEMO_MOVE program was structured and described, regarding (i) inclusion of a cognitive stimulation component; (ii) the kind of cognitive stimulation; and (iii) the type of exercise, duration, frequency, intensity, and program length. Conclusions: A systematic step-by-step process design was followed to create a specific intervention to promote physical fitness and cognitive stimulation in individuals with mild dementia.

Keywords: exercise program design; multimodal exercise for MCI/dementia; exercise characteristics for MCI/dementia

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1. Introduction

According to Alzheimer's Disease International (2021), worldwide, there are more than 10 million new cases of dementia per year, giving rise to a new case every 3.2 s [1].

Nichols and Vos (2021) have estimated that the number of people with dementia will rise from 57.4 million cases in 2019 to 152.8 million in 2050 [2]. Most of this increase will be seen in developing countries; however, 60% of people with dementia live in countries of low and middle income. By 2050, this figure is expected to rise to 71%. The combined prevalence of all causes of dementia, Alzheimer's disease, and vascular dementia has been reported to be 697, 324, and 116 per 10,000 people, respectively, corresponding to individuals aged 50 years and older. [3].

Dementia is a neurodegenerative syndrome characterized by a decline in functional capacity and cognition [4] consisting of a global and irreversible loss of cognitive ability, accompanied by a reduced ability to perform tasks of daily living as well as a range of further neuropsychiatric symptoms [5]. Dementia progresses at varying rates, affecting

Development of a Combined Exercise and Cognitive Stimulation Intervention for People with Mild Cognitive Impairment—Designing the MEMO_MOVE PROGRAM.

Abstract: Dementia patients are at high risk for the decline of both physical and cognitive capacities, resulting in an increased risk of the loss of autonomy. Exercise is regarded as a non-pharmacological therapy for dementia, considering the potential benefits of preventing cognitive decline and improving physical fitness. In this paper, we aim to describe the different design stages for an exercise program combined with cognitive stimulation for a population with mild cognitive impairment, i.e., the MEMO_MOVE program. Methods**:** The intervention design followed the Medical Research Council's guidelines for complex interventions and was structured according to the six steps in quality intervention development (6SQuID). The intervention was described considering the Template for Intervention Description and Replication (TIDieR). In order to establish the intervention characteristics, a literature review was conducted to collate and analyze previous work, which provided a summary the type of exercise that should be implemented among this population. Results: The MEMO_MOVE program was structured and described, regarding (i) inclusion of a cognitive stimulation component; (ii) the kind of cognitive stimulation; and (iii) the type of exercise, duration, frequency, intensity, and program length. Conclusions: A systematic step-by-step process design was followed to create a specific intervention to promote physical fitness and cognitive stimulation in individuals with mild dementia.

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Dementia is a neurodegenerative syndrome characterized by a decline in functional capacity and cognition (Petersen et al., 2001) consisting of a global and irreversible loss of cognitive ability, accompanied by a reduced ability to perform tasks of daily living as well as a range of further neuropsychiatric symptoms (Dening & Lloyd-Williams, 2020). Dementia progresses at varying rates, affecting individuals in different ways. (World Health Organization, 2019). In the absence of a cure, treatment and care focuses on improving the lives of people with dementia along with their career/family life through early diagnosis, information/counseling, physical and mental health support, and addressing behavioral and psychological problems (Lewis, Livsey, Naughton, & Burton, 2020).

Feter et al (2021) note that dementia is usually preceded by mild cognitive impairment (MCI), which is an important risk factor for dementia presented as a symptomatic phase of neurodegeneration marked by cognitive impairment (Feter et al., 2021). MCI is commonly misunderstood as a normal part of aging and permits a crucial window of opportunity into dementia prevention, planning, and policy (Falck, Davis, & Liu-Ambrose, 2017).

Physical activity (PA), by increasing aerobic capacity and cerebral blood flow, appears to help reduce chronic inflammation in the central nervous system, increasing neuroplasticity and promoting the reorganization of neural circuits(Erickson et al., 2011). Huang et al. (2022) emphasize that exercise may exert protective effects on cognitive function by (i) increasing levels of growth factors, such as brain-derived neurotrophic factor and insulin-like growth factor 1; (ii) regulating inflammatory cytokines; (iii) alleviating oxidative stress; (iv) increasing cerebral blood flow; (v) reducing Aβ concentration; and (vi) inhibiting tau phosphorylation(Huang et al., 2022, p. 2).

High levels of leisure-time physical activity leads to a 64% reduction in the risk of dementia progression in individuals with MCI (Feter et al., 2021; Grande et al., 2014), and PA is associated with a lower incidence of MCI and dementia. (Beckett et al., 2021; Blondell, Hammersley-Mather, & Veerman, 2014; Guure, Ibrahim, Adam, & Said, 2017; Nuzum et al., 2020). Thus, PA is considered an effective non-pharmacological strategy to mitigate or slow the progression of dementia-related degenerative diseases (Erickson et al., 2019; Maliszewska-Cyna, Lynch, Jordan Oore, Michael Nagy, & Aubert, 2017; Paillard, Rolland, & de Souto Barreto, 2015).

Programs have been developed in recent years to increase cognitive and motor function in older adults with MCI (Brasure et al., n.d.; Fleiner, Leucht, Förstl, Zijlstra, & Haussermann, 2016; Gallou-Guyot, Mandigout, Combourieu-Donnezan, Bherer, & Perrochon, 2020; Law, Barnett, Yau, & Gray, 2014; McSween et al., 2019; Yang et al., 2020). These interventions consist of exercise or multimodal programs, including exercise and cognitive stimulation, which are defined as interventions for people with dementia through providing a variety of enjoyable activities as well as an overall stimulus for thinking, concentration and memory, usually in a social-social setting, such as a small group (Woods, Aguirre, Spector, & Orrell, 2012).

The combination of cognitive and physical exercise (simultaneous cognitive-motor dual tasking) appears to have a greater benefit on cognitive and physical functions than one individual (either cognitive or physical) task training exercise in MCI (Gallou-Guyot et al., 2020; Gheysen et al., 2018; Karssemeijer et al., 2017; Tait, Duckham, Milte, Main, & Daly, 2017; Varela-Vásquez, Minobes-Molina, & Jerez-Roig, 2020). Combining physical training with cognitive training in a functional context may contribute to helping cognitively impaired older adults develop skills for everyday activities, fostering some autonomy(Zhang, Low, Gwynn, & Clemson, 2019).

Given the potential benefits of PA in both intellectual skills and functional physical fitness, exercise programs, often combined with cognitive stimulation, have been incorporated into the activities proposed for this population and implemented in nursing homes, day centers, community centers, health centers, among others.

Taking into account the proliferation of these programs, it is important to consider their objectives as well as what types of exercises and related characteristics should be implemented.

Moore et al. (2016) reinforce this idea, stating that recent literature presents the benefits of PA interventions in patients with dementia although the amount/type of PA required for these benefits remains unclear(Moore et al., 2016). Tait et al., (2017) are of the same mind that regular exercise has shown some cognitive benefits for individuals with MCI and agree that the optimal type and dose (frequency, intensity, duration) of exercise remains unclear(Tait et al., 2017).

In fact, different types of interventions (exercise type, intensity, duration, free frequency, among others) lead to different outcomes in terms of functional fitness and cognitive function (Guure et al., 2017). Lewis et al., (2020) stress that in order to prescribe and recommend any exercise intervention, it is necessary to define its frequency, intensity, type, and time (FITT principle). The amount (ITF) of exercise performed may be a crucial factor for outcomes when considering people with dementia. Due to the diversity of interventions (Brasure et al., n.d.), it is important to observe that the relationship of PA interventions in preventing cognitive decline or dementia in older adults is largely insufficient: different exercises lead to different outcomes.

Therefore, identifying optimal qualitative (namely the type of exercise) and quantitative (e.g., frequency, duration, intensity, and temporal proximity of cognitive and motor training) training characteristics which effectively and sustainably increase individual cognitive reserve and show impact on activities of daily living is an important point to be investigated (Herold, Hamacher, Schega, & Müller, 2018).

This paper aims to describe the process of developing an exercise intervention using formal models of intervention development while establishing a theoretical framework that supports the design of a multicomponent intervention: MEMO_MOVE - which is specific, theoretically considered and evidence-based for people with mild dementia and MCI.

Before implementing the program, some questions should be addressed:

- What kind of exercise intervention and cognitive stimulation seems to be more effective for dementia patients?
- What is the FITT plan that best improves physical fitness (functional ability, fitness, walking, equilibrium, muscular strength) and cognitive outcomes (cognitive function and cognitive ability)?
- Is there sufficient evidence to favor one or more types of exercise for dementia patients?

This article was constructed in order to help address the fact that there are few published studies on the development of interventions; in other words, it is an article based on originality and novelty.

2. Materials and Methods

2.1. Intervention Design

To develop an intervention program for a population with MCI, some steps must be taken into account. The intervention design followed the Medical Research Council guidelines for complex interventions described by Craig et al., (2008) (Craig et al., 2008), and updated by Skivington et al., (2021) (Skivington et al., 2021). In order to structure the intervention, the six steps in quality intervention development (6SQuID) proposed by Wight et al., 2016 were followed: (1) Define and understand the problem and its causes; (2) Identify factors with greatest scope for change; (3) Identify how to bring about change; (4) Identify how to deliver the change; (5) Test and refine on a small scale and (6) Collect sufficient evidence of effectiveness to justify rigorous evaluation/implementation.

With the purpose of improving comprehension when reporting the intervention design, this article was guided by the Template for Intervention Description and Replication (TIDieR) checklist and guide (Hoffmann et al., 2014), considering all 12 items (brief name, why, what (materials), what (procedure), who provided, how, where, when and how much, tailoring, modifications, how well (planned), how well (actual)) (Craig et al., 2008; Hoffmann et al., 2014; Skivington et al., 2021; Wight, Wimbush, Jepson, & Doi, 2016).

2.2. Theorical Framework Development

For the theoretical background of the program, this article followed the work presented by Booth et al, (2018). Furthermore, a literature review was conducted aiming to collate and analyze previous work investigating exercise interventions in adults with MCI therefore providing a clear summary of what kind of exercise should be implemented to improve both physical fitness and cognition among this population. We are particularly interested in identifying what FITT plan best improves physical fitness and cognitive outcomes.

The electronic databases, WEB OF SCIENCE, SCOPUS, PUBMED and the COCHRANE ELECTRONIC LIBRARY were systematically examined, using the following conjugation of terms: (1) ["exercise" or "physical activity"], (2) ["mild cognitive impairment" or "dementia"] and [Dual task or multimodal]. The search was conducted from September to December 2021.

The results from the literature search were selected from the initial search if they met with the following criteria: (1) included an adult population with MCI or dementia recognized through cognitive testing (e.g., Mini Mental State Examination) or diagnosis (e.g., Dementia, Alzheimer's disease); (2) exercise-based intervention; (3) exercise program completely described (FITT); (4) results concerning physical fitness and cognitive performance and (5) manuscripts written in English.

Exclusion criteria encompassed: (1) exercise interventions in which the aim was the improvement of other factors other than physical fitness or cognition, such as the improvement of sleep patterns, general health, quality of life, pain management, psychological health and/or improving psychological parameters, namely mood or depression; (2) lifestyle interventions; (3) revision of exercise guidelines or recommendations; (4) the use of specific exercise programs such as tai chi, yoga or dance; (5) patients that present psychiatric diseases and other comorbid medical conditions (6) exercise programs not explicit and (7) manuscripts written in languages other than English.

Due to the number of articles identified, a further exclusion criterion of articles published before 2015 was introduced to ensure identification of recent evidence and focus on material published after this year.

This process yielded 26 studies to be evaluated (Figure 1), all of which were screened according to the PRISMA systematic review protocol (Liberati et al., 2009; Moher, Schulz, Simera, & Altman, 2010). The search was performed by CR (first author). Two independent reviewers (DE and PM) assessed the included studies for their methodological quality; any discrepancies were discussed until a consensus was definitively reached.

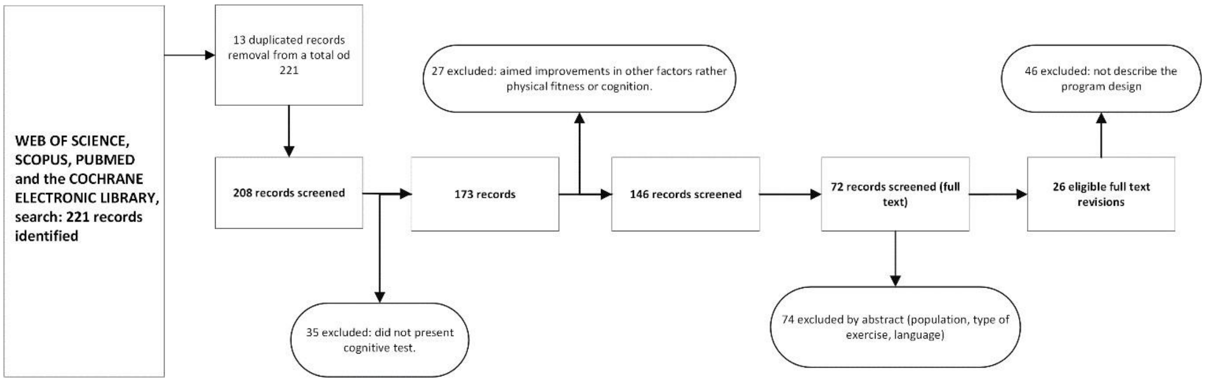

Figure 1.- Flow diagram of the review articles.

3. Results

The rationale for intervention components ("why") and equipment or procedures used ("what") were established from the 26 eligible studies. The main result of this article is the intervention description according to the TIDieR checklist.
Name: MEMO_MOVE—Multicomponent exercise intervention for people with MCI.

3.1. Why: Rationale, Theory, and Goal (Program Design)

Exercise is a promising nonpharmacological therapy in preventing the decline of cognitive function (Huang et al., 2022, p. 20). Numerous randomized controlled trials (Cammisuli et al., 2018; Du et al., 2018; Groot et al., 2016) have reported the positive effects of exercise on cognitive function and neuropsychiatric symptoms in patients with cognitive impairment. Interventional studies demonstrate that physical exercise improves certain domains of cognitive and affective functions in older adults (McSween et al., 2019) and potentially enhances brain neuroplasticity (Mellow et al., 2020), preventing cognitive decline. Arrieta et al., (2020) also refer to the fact that physical exercise can enhance hippocampal neurogenesis and neuronal plasticity; thereby, it should counteract the negative effects of aging (Arrieta et al., 2020).
Besides cognitive impairment, older adults often present with physical impairment (Gallou-Guyot et al., 2020; Makizako et al., 2011), increasing the risk of falls and, in turn, leading to a loss of autonomy. However, the decrease in functional physical aptitude can be delayed by the practice of physical exercise (Lam et al., 2018; Pitkälä et al., 2013). Thus, PA may have a beneficial role not only in cognitive skills, but also in the physical fitness of individuals with MCI.

Regarding the type of intervention, a **first decision** must be considered in our decision tree: "simple" exercise program or "combined" exercise with cognitive stimulation (Figure 2).

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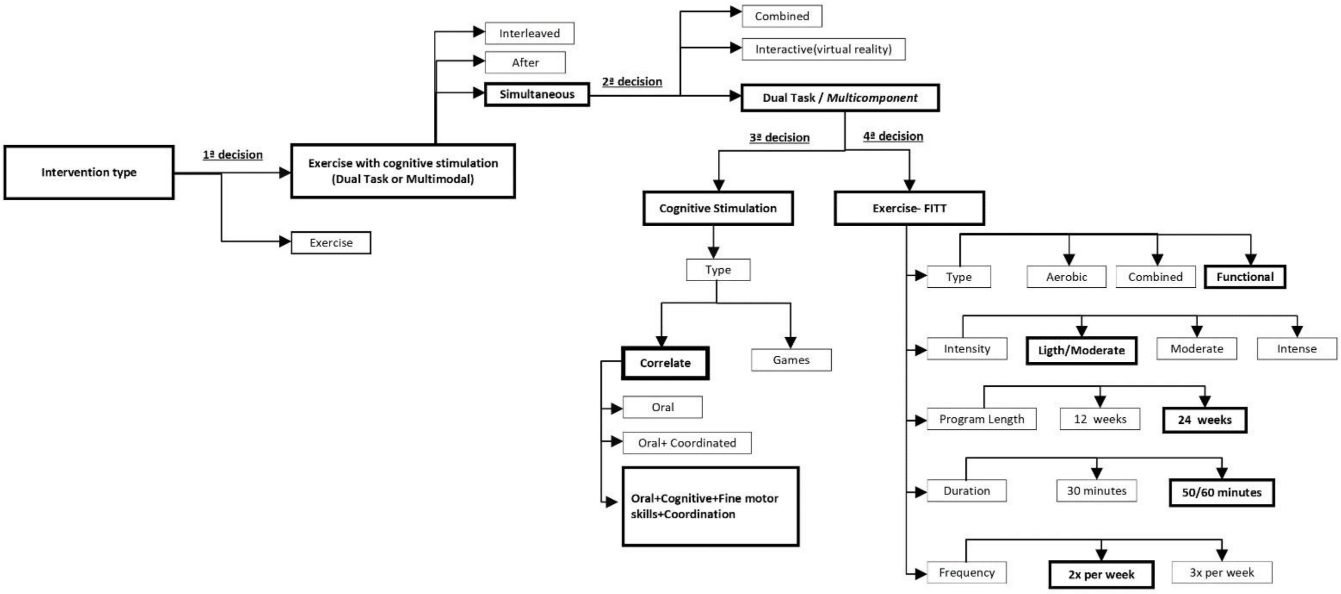

Figure 2. MEMO_MOVE: design decision tree.

The recent literature has considered that dual task or multicomponent exercise is more advantageous than simple exercise in this population since working simultaneously on the physical and cognitive components allows for more stimuli while enhancing neural regeneration by increasing blood flow to the brain, promoting neural growth, maintaining brain function, and improving brain plasticity (Makizako et al., 2011; Morita et al., 2018) A combined physical and cognitive rehabilitation program leads to significant improvements in physical fitness, also improving the cognitive performance (Bruderer-Hofstetter et al., 2018; Callisaya et al., 2021; Gavelin et al., 2021; Gill et al., 2016; Gregory et al., 2016; Karssemeijer et al., 2017; Kitazawa et al., 2015; Park et al., 2019; Parvin et al., 2020; M. G. Silva et al., 2018; Sok et al., 2021; Tay et al., 2016; Zhang et al., 2019).

Therefore, our option was to design a multicomponent exercise combined withcognitive stimulation.

Anderson-Hanley et al., (2012) (Anderson-Hanley et al., 2012) classifies the combined exercise and cognitive interventions into:

- “combined/sequential” interventions, wherein the components are administered sequentially/in tandem (Barnes et al., 2013; Karssemeijer et al., 2017; Law et al., 2014; Lipardo, Aseron, Kwan, & Tsang, 2017; Rahe et al., 2015; C. Wang et al., 2014).
- “dual-task/multicomponent” interventions, wherein components are administered simultaneously, but are typically separate tasks (e.g., reciting numbers backwards while walking) (Bherer, 2015; Coelho et al., 2013; Desjardins-Crepeau et al., 2016; Eggenberger, Theill, Holenstein, Schumacher, & de Bruin, 2015; Forte et al., 2013; Schaefer &

Schumacher, 2011; Theill, Schumacher, Adelsberger, Martin, & Jäncke, 2013; Yokoyama et al., 2015), which can be further contrasted with:

- interactive interventions, as in exergaming, in which the actions in one realm affect the other (e.g., pedaling and steering controls progress in a virtual world and attainment of goals) (Anderson-Hanley et al., 2012; Bamidis et al., 2015; González-Palau et al., 2014; Maillot, Perrot, & Hartley, 2012; Schoene, Valenzuela, Lord, & de Bruin, 2014; Styliadis, Kartsidis, Paraskevopoulos, Ioannides, & Bamidis, 2015).

According to these authors, a **second decision** must be considered in our decision tree: sequential, dual task/multicomponent or interactive intervention (Figure 2).

Tait et al., (2017) concluded that there are inconsistent findings with regard to the cognitive benefits of sequential training in comparison to cognitive or exercise training alone. In contrast, simultaneous (dual task) training interventions have significantly improved cognition in both healthy and older clinical populations.

Interactive interventions can provide an integrated physical and cognitive improvement (Eggenberger et al., 2015; Lauenroth et al., 2016; Stanmore et al., 2017; S. Wang et al., 2016)however, this option cannot be considered due to the reality of the materials available.

Therefore, dual task exercise/multicomponent intervention was the option chosen: cognitive stimulation was incorporated into the sessions; simultaneously combined with resistance or aerobic training.

3.2. A Third Decision Concerns the Type of Cognitive Stimulation

Cognitive stimulation is an intervention for people with dementia that offers a very wide variety of enjoyable activities. Providing general stimulation of thinking, concentration and memory, usually in a social setting such as a small group, or even individually, cognitive stimulation involves a range of activities which aim to stimulate cognitive abilities such as attention, memory, language, thinking (including the discussion of past and pre-envisioned events and topics of interest), word games, puzzles, music, and hands-on activities such as indoor baking or gardening (Woods et al., 2012).

Cognitive training studies recommend that training for executive functions (e.g., working memory) improves the efficiency of the prefrontal network, which provides support for brain function in the face of cognitive decline. While physical activity preserves neuronal structural integrity and brain volume (hardware), cognitive activity strengthens the functioning and plasticity of neural circuits (software), thus supporting cognitive reserve in different ways, (Cheng et al., 2016).

From the 26 studies retrieved in the literature review, we conclude that the main cognitive stimuli used were: composing poems (Bae et al., 2020; Makizako et al., 2011; Suzuki et al., 2012); special stair training combined with counting (Bae et al., 2020; Gill et al., 2016; Öhman et al., 2016; Park et al., 2019); semantic/phonemic verbal fluency tasks (Gill et al., 2016; Y. Kim, Chae, & Yang, 2021); word games (Y. Kim et al., 2021; Park et al., 2019); mathematical calculations (Y. Kim et al., 2021; Rezola-Pardo et al., 2019); forward and backward counting (Lemke et al., 2019); memory games (cards, sounds or movements) (Delbroek, Vermeylen, & Spildooren, 2017); reality-directed orientation training (Venturelli et al., 2016); computer aided cognitive training with stimulation (oral, memory, verbal fluency, spatial learning, attention, executive functions, orientation) (Combourieu Donnezan, Perrot, Belleville, Bloch, & Kemoun, 2018; Karssemeijer et al., 2017); cognitive exercises based on horticultural intervention (Shimada et al., 2017) and walking while singing and playing instruments (Chen & Pei, 2018).

Considering this data in conjunction with the type of equipment available for this intervention, the cognitive stimulation will comprise exercise based on word games, mathematical calculations, forward and backward counting, computer exercises (Cogweb – www.cogweb.pt and brain on track – www.brainontrack.com), exergames (Blaze pod – www.blazepode.com) and balance platforms (Physio Sensing – www.physiosensing.net).

This stimulation is implemented in two sets of exercises: (1) repetitive - we repeated some exercises in order to promote evolution and apply the use of acquired skills and (2) alternated – in each session, we introduced different cognitive exercises in order to maintain the effect of innovation/surprise and motivation.

Example: one day they performed arithmetic tasks (one or two-digit subtraction), played a word game (in which the technician said a category and the user had to say as many words related to that topic as possible), while simultaneously performing squats with the help of a chair.

Another day they tried to change the direction of their walk from front to back or left to right according to a whistle pattern, while counting up or down in twos or threes. In another exercise, they were encouraged to say as many animal names as possible while walking up and down a step. Also, coordinative circuits combined with cognitive tasks were performed: at one station they had to associate a part of a certain category with a picture, at a second station they performed memory tasks with letters, at a third station they had to say the names of people beginning with a certain letter, and at a fourth station they completed puzzles; along the circuit there were tasks of dynamic balance, static balance, and strength with calisthenics exercises.

3.3. The Fourth Decision Addresses the Exercise Characterization (FITT)

Concerning *type*, the intervention within the literature review presented aerobic training, strength training, and functional training as the most commonly used.

For our study, functional training was chosen due to the characteristics of the participants who sometimes present physical weaknesses, making it difficult to apply any aerobic type of training. Our exercise program combined strength, balance and endurance exercises, as well as cognitive stimulation (Gallou-Guyot et al., 2020; Gavelin et al., 2021; Gheysen et al., 2018; Gill et al., 2016; Gregory et al., 2017, 2016; Karssemeijer et al., 2017; Makizako et al., 2011; Morita et al., 2018; Park et al., 2019; Parvin et al., 2020; Rezola-Pardo et al., 2019; Zhang et al., 2019).

Considering *frequency*, according to the literature review, intervention performed 2-3 times per week was the usual frequency applied. A frequency of 2 times per week was chosen for our program (Combourieu Donnezan et al., 2018; Delbroek et al., 2017; Hyuma Makizako et al., 2012; Lemke et al., 2019; Park et al., 2019; Parvin et al., 2020; Rezola-Pardo et al., 2019; Suzuki et al., 2012).

Regarding *duration (session time)*, programs from table 1 refer to 45 to 60 minutes as a regular training program. We adopted the same duration: 50-60 minutes (Callisaya et al., 2021; Gill et al., 2016; Makizako et al., 2011; Parvin et al., 2020; Rezola-Pardo et al., 2019; Sok et al., 2021).

About *duration (program time)* the program lasted six months, which is similar to several programs presented in Table 1 (Callisaya et al., 2021; Coelho et al., 2013; H. K. Kim, Mendonça, Howson, Brotchie, & Andreazza, 2015; Makizako et al., 2011).

Finally, regarding *intensity*, literature (Gill et al., 2016; Parvin et al., 2020; M. G. Silva et al., 2018) recommends light to moderate intensity. In order to individualize the training, a fitness evaluation was initially performed, and the intensity was specifically adapted to each subject. Due to the capacities observed among participants, light to moderate intensity was applied.

Table 1.- Literature review: summary of findings.

No	Study ID	Sample Size	Diagnosis/Test	Duration (Weeks)	Frequency	Intensity	Exercise Component	Cognitive Component	Cognitive/Motor Outcome	Control Group
1	Makizako et al., 2012 [95]	50	Dementia/MMSE	24	90 min/2 days a week	Moderate	Aerobic exercises, strength training, balance retraining	Poem composition, stairs stepping while counting 3 backwards, waking on balance board while counting 3 backward	Gait functions	Standard care
2	Suzuki et al., 2012 [83]	50	MCI/MMSE	52	90 min/3 days a week	Moderate	Aerobic exercises, strength training, balance retraining	Poem composition, special ladder training	Gait functions, memory, executive function	Health education
3	Coelho et al., 2013 [67]	27	Alzheimer/MMSE	16	60 min/3 days a week	65% to 75% HRmax moderate	Strength/resistance training, aerobic capacity, flexibility, balance, agility	Cognitive activities focused attention, planned organization, abstraction, motor sequencing, and mental flexibility	Frontal cognitive function	Standard care
4	Suzuki et al., 2013 [102]	100	MCI//MMSE	24	90 min/2 days a week	Not clear	Aerobic exercises, balance retraining, dual task training	Poem creation, special ladder training	Gait functions, memory	Health education
5	Gill et al., 2016 [53]	44	MCI/MoCA	26 plus/26 follow up	50 + 45 min/2 or 3 days a week	Not clear	Aerobic exercises, lower extremity strength training	Semantic/phonemic verbal fluency tasks, random athematic calculations	Gait functions, memory, executive function	Standard care
6	Heath et al., 2016 [103]	63	Dementia/MMSE	24	60 min/3 days a week	Moderate to high intensity (65–85% HRmax)	Aerobic exercise, strength/balance training	Special square stepping exercise involving memory, executive functions, pattern recognition	Executive functions	Standard care
7	Öhman et al., 2016 [85]	210	AD/MMSE	52	60 min/7 days a week	Not clear	Aerobic, strength, endurance, and balance training	Dual tasking with, ball games, dancing, calculation, and memory games	Gait functions, executive function, memory	Standard care
8	Venturelli et al., 2016 [90]	80	AD/MMSE	12	60 min/5 days a week	Not clear	Brisk walking	Reality orientation method	Gait functions	Standard care
9	Silva et al., 2017 [104]	127	AD/MMSE	24/28 follow up	60 min/3 days a week	Moderate to high intensity (65–85% HRmax)	Aerobic exercises, resistance training, stretching	Mind motor training (special square stepping games)	Gait functions	Standard care
10	Delbroek et al., 2017 [89]	20	MCI/MoCA	6	30 min/2 days a week	Not Clear	BioRescue training, aerobic exercises, balance retraining, weight bearing	Memory games, attention maze, dual task training	Gait functions, gait and balance	Standard care
11	Gregory et al., 2017 [94]	56	Dementia/MMSE	26	40 min/3 days/week	Moderate to high intensity (65–85% HRmax)	Aerobic exercise	Executive function training: verbal fluency, memory, and arithmetic	Cognitive functions and gait	Standard care
12	Hagovská et al., 2017 [105]	80	MCI/ACE	10	60 min/2 days a week	Not clear	Leg strengthening exercises, balance training	CogniPlus, memory, attention, executive function, visual motor training	Gait functions, memory, executive function, attention, balance	Health education
13	Karssemeijer et al., 2017 [28]	742	MCI/MMSE	12	30–120 min/3 days a week	Not clear	Aerobic training a single	Computer-aided; cognitive (oral, memory, verbal fluency, spatial learning, attention, executive functions, orientation	Cognitive and motor functions	Standard care
14	Maffei et al., 2017 [106]	113	MCI/MMSE	28	60 min/5 days a week	Not clear	Aerobic exercises, strength, control, and flexibility training	Attention, memory, learning, and meta cognitive training	Gait functions, executive function, attention	Non-musical cognitive task and walk

15	Shimada et al., 2017 [92]	308	MCI/RAVLT/MMSE	40 plus/+ 12 follow up	90 min/1 day a week	Not clear	Aerobic exercises, balance retraining, dual task training	Cognitive training (horticultural intervention)	Gait functions, memory, executive function	Standard care
16	Chen et al., 2018 [93]	28	Dementia/ MMSE	8	60 min/1 day week	Not clear	Functional activities, dual task walking	Walking while singing, playing instruments, cognitive load stepping	Executive function, balance, gait functions,	Standard care
17	Donnezan et al., 2018 [91]	69	MCI/MMSE	12	60 min/2 days week	Moderate 60% HRmax	Aerobic training on bicycles, balance retraining.	Game software "HAPPYneuron" and Presco	Attention, executive functions, balance, gait functions	Standard care
18	Wiloth et al., 2018 [100]	99	Dementia/ MMSE	10	90 min/2 days week	Not clear	Dual task walking, sit to stand maneuver	Game based training (motor-cognitive exercises)	Executive functions	Standard care
19	Lemke et al., 2019 [88]	105	Dementia/ MMSE	10 plus/+12 follow up	90 min/2 days week	Not clear	10 m walk, dual tasking	DT Serial low/high demand calculation (2–3 forward and backward calculation)	Gait functions	Standard care
20	de Oliveira Silva at al., 2019 [101]	52	MCI/AD/CDR	12	60 min/2 days week	70–80% (VO_{2max}) or 80% of HRmax	Balance, aerobic, and strength training and stretching	Executive functions, verbal training, selective attention	Mobility and executive function	Health education
21	Park et al., 2019 [56]	49	MCI/MMSE	12	110 min/2 days week	Moderate	Aerobic exercises included stair stepping, resistance walking and stair climbing, and agility stair walking	Word games and numerical calculations	Cognitive function and physical function	Standard care
22	Rezola-Pardo et al., 2019 [87]	85	MCI/AD/MMSE	12	60 min/2 days week	Moderate	Strength and balance exercises	Verbal training and arithmetic calculation	Physical performance and gait speed, cognitive functions	Standard care
23	Zhang et al., 2019 [31]	Not clear	MCI/	Not clear	Not clear	Not clear	Strength and balance training	Attention and executive function	Cognitive and motor functions	Not clear
24	Bae et al., 2020 [84]	280	MCI/MMSE	40	90 min/1 day week	Moderate	Aerobic exercises, balance strength training	Calculation, word games, poems citing, challenging cognitive tasks	Gait Functions, memory, executive function, motor functions	Standard care
25	Parvin et al., 2020 [57]	32	DA/MoCA	12	40 to 60 min/2 days week	Moderate	Muscle endurance, balance, flexibility, and aerobic exercises	Short-term and working memory, attention and executive function	Cognitive and motor function	Standard care
26	Kim et al., 2021 [86]	20	MCI/MMSE	12	60–90 min/1 day week	Moderate	Strength, rubber band	Remembered the names and main uses; counting numbers; planning and solving complex story problems	Balance and gait	Standard care

About "duration (program time)", the program lasted six months, which is similar to several programs presented in Table 1 (Callisaya et al., 2021; Coelho et al., 2013; Heath et al., 2016; Makizako et al., 2011).

Finally, regarding "intensity", the literature (Gill et al., 2016; Parvin et al., 2020; N. C. B. S. Silva et al., 2017) recommended light to moderate intensity. In order to individualize the training, a fitness evaluation was initially performed, and the intensity was specifically adapted to each subject. Due to the capacities observed among participants, light to moderate intensity was applied.

3.4. What—Materials: Provider, Participant, and Equipment

The MEMO_MOVE provider is a consortium of a university (Universidade da Beira Interior), a research center (Research Center in Sports Sciences, Health Sciences and Human Development), and the Fundão City Council. The consortium aims to partner sport science with a community program tailored to people with MCI/dementia.

Regarding participants, the intervention sessions will be provided in nursing homes. Through the collaboration of the technical directors of the respective institutions, it will be possible to make a preselection of possible participants.

Before being selected for the interventions, all participants (or their families/tutors) must sign an informed consent form.

An initial cognitive evaluation will be performed by a specialized technician in the area of Psychology using the Mini Mental State Examination Test Battery (Rikli & Jones, 1999), which allows for the assessment of the inclusion of the participants in the study as all participants had to have mild cognitive impairment. Regarding physical fitness, the Rikli and Jones test batteries and the Short Performance Battery Test will be applied.

Exclusion criteria include: clinical diagnosis of advanced dementia syndrome, uncontrolled hypertension (BP > 160/90 mmHg), frequent hypoglycemia, severe congestive heart disease, acute myocardial infarction in the past year, severe anemia (HB < 8 g/dL), severe respiratory diseases, severe osteoporosis, sensory deficit (vision/hearing) that prevents collaboration in the physical exercise program, and psychiatric disorders.

Materials and equipment to be used in the MEMO_MOVE program were trialed during a pilot study in which six people with MCI undertook five supervised, multicomponent exercise interventions.

Equipment selected for intervention sessions will be diversified according to the exercises planned for each intervention and will comprise of dumbbells of varying weights, flares, motor skills kits, therapeutic balls, educational games (such as cards, dominoes, and association games), and pedals.

3.5. What—Procedure: Provider Training, Assessment, and Intervention Session

The intervention providers include physical education teachers, exercise physiologists, and psychologists. Their training includes theoretical sessions (with sport scientists and neurologists) and practical sessions (a pilot study oriented by senior fitness instructors and exercise physiologists).

Regarding assessment, participants are divided between an experimental group (EG) and a control group (CG).

Cognitive evaluation is performed using the Mini Mental State Examination Test Battery and physical fitness is evaluated by the Rikli & Jones Test Battery (Rikli & Jones, 1999) and Short Physical Battery Test (Ronai & Gallo, 2019), applied by a Physical Education Teacher and PhD student.

Blood samples are collected in collaboration with a clinical laboratory (Affidea, www.affidea.pt (accessed on 15 January 2019)).

Assessments are made before (baseline) and after intervention.

Participants' presence in the session and the exercises performed is recorded daily.

The intervention focuses on the application of exercises that aim to work some physical and cognitive capacities within the dual task model, with the physical capacity as the main task and the cognitive capacity as the secondary one.

Functional exercises are performed within functional circuits: upper and lower limb strength using dumbbells or the weight of the body (calisthenics); dynamic and static balance and flexibility; some cognitive functions such as attention, memory, calculation, language, and executive functions were worked on as well.

3.6. Where Intervention Location

The intervention sessions will occur in nursing homes ((1) Centro Paroquial e Bem-Estar Social de Valverde, (2) Hotel Senior Prestige do Fundão, and (3) Centro Paroquial de Assistência de Souto da Casa).

3.7. How: Method of Delivery

The intervention is delivered face-to-face in a group setting with exercises individualized to the users' conditions.

To increase motivation and session participation, the self-determination method is used (Booth et al., 2018) which involves:

Communication strategies, for instance, taking the time to speak and hear the participant; using clear, simple language to explain the exercises; acknowledging the participant's feelings and mood; using verbal and body language, using a friendly secure voice; promoting participant's communication.

Motivational strategies, for example, recognizing progress and skills, providing positive feedback, adapting exercise complexity to participants' skills, using colorful materials, using music and images related to the cultural/social backgrounds of participants, providing different exercises, stimulating socialization in small groups.

3.8. Tailoring the Intervention

According to Booth et al. (2018), a central principle of the intervention is that it is individually tailored to the abilities, comorbidities, interests, and goals of the participant. The authors emphasized the need to adapt interventions to overcome content-specificity barriers (Booth et al., 2018)

The MEMO_MOVE program was tested in a feasibility study, which will be the basis for further refinement in the future.

Some barriers encountered in the development and implementation of the program include:

- The motivation of individuals with MCI to exercise and perform the cognitive tasks;
- The resistance of family members to participation in the program;
- Difficulty in the medical diagnosis of dementia;
- Logistical difficulties in participating in the program (transport, timetables).

How these barriers were addressed:

- Promotion of a one-to-one trial session, where an affective/trusting bond and proximity with the individual was created. The interpersonal relationship has proven to be a fundamental factor for adherence and participation in the program. The exercises should have a playful character and fit in with the cultural and social experiences of each person.
- Inviting families to participate in the sessions, explaining the advantages in terms of functional autonomy and brain stimulation.
- Integration of a team of psychologists who help to improve the diagnosis of individual's cognitive capacities, as well as help to adapt cognitive stimulation to each person.
- Choosing a central and easily accessible location, with timetables that are compatible with the lifestyles of the participants.

4. Discussion

4.1. Summary of Findings

A dual task training intervention program combining physical exercise and cognitive stimulation was developed to support people with MCI, aiming to help participants to improve both physical and cognitive abilities. A literature review was used to design the program. It is suggested that the intervention should include some application criteria as follows: a sample base ranging from 30 to 100 participants; a program duration of 24 weeks; a frequency of twice a week; and the intensity should vary between light, moderate and intense while always taking into consideration the physical frailties of the users.

Based on this analysis, the MEMO_MOVE intervention program was designed to be delivered to populations living in communities with MCI or in senior housing and subsequently be self-managed.

4.2. Strengths and Limitations

As previously mentioned, the MEMO_MOVE program resulted from a consortium between the University of Beira Interior, CIDESD, and Fundão City Council. This is an advantageous point as it allies scientific research with the ability to intervene in municipal community programs.

Another strong point is the people responsible for the program, including scientific leaders (sport scientist, PhD), the people responsible for the orientation and implementation (PhD student), and the consultants (psychologists and technicians); the capacity of the multidisciplinary team that designed and implemented the program is fundamental to its success.

A pretest was conducted to evaluate the materials used and the type of cognitive stimulation with more acceptance. This was very important because it showed the motivation, communication skills, and relationship of the intervention team with this population.

As for the limitations, the main one to mention has to do with the lack of a more specific diagnosis of dementia, since the population recruited was identified either by a family doctor or by psychologists from the nursing homes without a defined medical diagnosis of the type and state of dementia.

Another limitation has to do with the acceptance of the program by both family members and nursing home managers.

5. Conclusions

Implementation and Recommendations

As referenced by Booth et al. (2018), the Council's complex intervention guidelines are broad, providing a general framework that covers all aspects of development from theory identification to evaluation by randomized controlled trial and implementation. However, there is little detail, especially in the critical early stages. In general, there are few published intervention development studies (Hagovská et al., 2017).

This article was constructed in order to contribute to closing this gap in the literature.

The developed intervention is not yet sufficiently researched to be recommended as a clinical exercise program, as its effectiveness has not yet been evaluated and the results need to be investigated.

In any case, the development process within the intervention has reached its goals and the described intervention is ready to be implemented, starting as a feasibility trial through a pilot study preferably with the participation of 20 to 30 individuals.
As further evaluation of the effectiveness of the program's implementation is required, investigation of any obtained future results is recommended.

Author Contributions: Conceptualization, C.A.d.M.R. and D.E.; methodology, C.A.d.M.R.; software, C.A.d.M.R.; validation, C.A.d.M.R., D.E. and M.P.G.M.; formal analysis, C.A.d.M.R.; investigation, C.A.d.M.R.; resources, D.E.; data curation, C.A.d.M.R.; writing—original draft preparation, C.A.d.M.R.; writing—review and editing, D.E.; visualization, D.E.; supervision, M.P.G.M.; project administration, D.E.; funding acquisition, D.E. and M.P.G.M. All authors have read and agreed to the published version of the manuscript.

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Chapter 6.

Study 5 - Multicomponent exercise program effects on fitness and cognitive function of elderlies with mild cognitive impairment: Involvement of oxidative stress and BDNF.

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Multicomponent exercise program effects on fitness and cognitive function of elderlies with mild cognitive impairment: Involvement of oxidative stress and BDNF

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Multicomponent exercise program effects on fitness and cognitive function of elderlies with mild cognitive impairment: involvement of oxidative stress and BDNF

Abstract

Regular exercise has been shown to be one of the most important lifestyle influences on improving functional performance, decreasing morbidity and all-cause of mortality among older people. However, and although there is some evidence on the effects of aerobic training on oxidative stress, there is little information on the effects of multicomponent exercise (dual task training), combination of exercise with cognitive stimulation) on oxidative stress. With this in mind, the aim of this study was to verify the effects of a multicomponent exercise program on physical fitness and cognitive function in the elderly with mild cognitive impairment: involvement of oxidative stress and Brain Derived Neurotrophic Factor (BDNF).

At baseline, 37 elderly nursing home residents with mild cognitive impairment were divided into two groups: control group (CG, n = 12: 81.8 years) and experimental group (EG, n = 25: 83.2 years).

These elderlies followed multicomponent exercise training for 24 weeks, with two sessions per week, 45-50 minutes per session. The exercises included both aerobic and strength exercises, considering functional movements and light to moderate intensity. Cognitive stimulation comprehended exercises based on word games, puzzles, mathematical calculations, forward and backward counting, computer exercises, exergames and games on a balanced platform.

Physical assessments (weight, height, body mass index), health and functional parameters (fitness tests: Chair stand , Arm Curls, Chair sit-&-Reach , 8-Ft Up-&-Go Back Scratch , Six min walking, Feet together , Semi Tandem, Full Tandem) lipid profile (Total Cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL) and Triglycerides) and measures of lipid peroxidation damage, thiobarbituric acid reactive substances (TBARS), total antioxidant capacity (TAC) and BDNF were measured in plasma, on which analyses were performed before and after the 24 weeks of the multicomponent exercise intervention. The results showed an overall improvement in physical and functional performance. Regarding biochemical measures, multicomponent exercises lead to a significant decrease in oxidative damage. The results indicate that muticomponent exercise training induces benefits in functional capacity and reduces oxidative stress damage.

Keywords: Alzheimer, MCI, Dual Task, BDNF, Oxidative Stress.

1. Introduction

During aging, brain tissue atrophy and dysfunction is accompanied by a decrease in learning, memory and hippocampal neurogenesis that frequently leads to mild cognitive impairment (MCI)(Wang et al., 2016). MCI is defined as a cognitive decline greater than that expected for an individual's age and education level, which does not affect most daily activities but have a high risk of progressing to dementia, particularly Alzheimer (Gauthier et al., 2006). In fact, it has been proposed that the annual progression rates of MCI to dementia range from 10% to 15% (*Risk reduction of cognitive decline and dementia: WHO guidelines*, sem data). There are no curative treatments for dementia or MCI but it has been estimated that 3% of dementia cases could be prevented by increasing levels of physical activity and exercise for preventing and eventually slowing down the pathological process and dementia-related problems (Sadowsky & Galvin, 2012). In fact, physical exercise has been related to cognitive function(s) through a variety of cellular and molecular processes that induce angiogenesis, neurogenesis and synaptogenesis, thus improving learning, memory, and brain plasticity (van Praag et al., 1999).

Some of the aforementioned mechanisms that contribute to modulate the exercise-induced cognitive improvement, are neurotrophins (Radak et al., 2007) and oxidative stress (Cobley et al., 2013). Brain-Derived Neurotrophic Factor (BDNF) is the most abundant neurotrophin, and though it is synthetized in peripheral tissues such as muscle, liver, adipose tissue, endothelial an immune cells, 75% of its synthesis occur in different types of brain cells and can be transported outside the brain through the blood–brain barrier (Bathina & Das, 2015). BDNF appears essential for neuronal survival during the development and formation of neural networks of the peripheral and central nervous systems and regulates synaptogenesis, synaptic transmission and plasticity by/through/via its tyrosine kinase receptor B (TrkB) (DeLaRosa et al., 2019; Molinari et al., 2020). BDNF and TrkB expression in the hippocampus and temporal cortex decrease over the years, in humans, which has been related with the increased problems in learning and memory (Webster et al., 2006). Acute exercise induces an increase in BDNF levels comparatively with resting conditions, which return to baseline levels within minutes following exercise cessation (Currie et al., 2009). The effects of chronic exercise in BDNF have not been consistent, with literature reporting no significant changes (Ogonovszky et al., 2005; Schiffer et al., 2009; Schulz et al., 2004), an increase (Erickson et al., 2011b; Voss et al., 2013; Zoladz et al., sem data), or even a decrease in resting values, suggesting that the mode and workload characteristics of the exercise program should be a decisive factor.

Reactive oxygen species (ROS) are highly reactive chemical compounds generated during normal metabolic processes, and, in excess, can damage macromolecules such as lipids, proteins, and deoxyribonucleic acid (DNA), causing cellular dysfunction and possibly death (*Free radical involvement in neuropsychiatric illnesses - PubMed*, sem data). The antioxidant defense system reduces the action of ROS, both preventing, scavenging, and repairing them. Oxidative stress (OS) involves an imbalance between pro-oxidant processes and the antioxidant defense system in favor of the former (Lohr et al., 2006; Sies & Jones, 2020). An accumulation of oxidized proteins, lipids peroxides and DNA oxidatively damaged in the brain potentiates neurodegeneration and impairs cognitive function (Radak et al., 2007), which has been demonstrated to be underly one of the main molecular mechanisms of brain aging and neurodegenerative disorders like Parkinson's disease, Alzheimer's disease and Huntington's disease (Federico et al., 2012). *In the study of vitro* animals it is suggested that oxidative stress, mitochondrial function, and BDNF have a complex and reciprocal relationship. Mitochondria organelles have a crucial role in adenosine triphosphate (ATP) production through oxidative phosphorylation, a process performed by the electron transport chain (ETC) complexes I through V, and is related to the levels of intra and extracellular BDNF (Kim et al., 2015; Markham et al., 2012). Moreover, BDNF interacts with ATPase, improving the mitochondrial respiratory coupling (Markham et al., 2004, 2012). Additional studies have shown an inverse relation(ship) between oxidative stress and BDNF levels, indicating that BDNF may play a protective role against oxidative damage in neurons (He & Katusic, 2012; Valvassori et al., 2015) possibly through the increase of cells' antioxidant capacity (He & Katusic, 2012).

Therefore, physical exercise may mitigate age-related cognitive decline through the modulation of factors participating in the crosstalk between skeletal muscle and the brain, such as neurotrophins and oxidative stress. Several studies described a reduction in markers of oxidative stress in resting conditions after the implementation of exercise programs (Barbosa et al., 2010; Gabriel et al., 2012).

Regarding the kind of exercise intervention more recommended to this population, recent systematic reviews and meta-analysis (Bruderer-Hofstetter et al., 2018; Gavelin et al., 2021; Gheysen et al., 2018; Karssemeijer et al., 2017) concluded that dual task or multicomponent exercise is more advantageous than simple exercise in MCI individuals, since working simultaneously on the physical and cognitive components allows for more stimuli, enhancing neural regeneration by increasing blood flow to the brain, promoting neural growth, maintaining brain function, and improving brain plasticity (Bherer, 2015; Morita et al., 2018). Combining physical and cognitive rehabilitation programs leads to significant improvements in physical fitness, also improving the cognitive performance , (Bruderer-

Hofstetter et al., 2018; Gavelin et al., 2021; Gheysen et al., 2018; Karssemeijer et al., 2017; Zhang et al., 2019b).

Considering that aging results in decreased physical and cognitive capacities, particularly more pronounced in frailty populations, and that regular exercise improves the function of most of the organs, can multicomponent exercise prevent or attenuate decline of physical and cognitive function of elderlies with MCI? Moreover, considering the role of oxidative stress in mediating cell adaptation to exercise, and its relationship with BDNF, which changes are we able to observe in these parameters and how are they related with functional variations in elderlies with MCI? Regarding this, the aim of this study is to analyze the effect of a multicomponent exercise program with stimulation in fitness, cognitive function, plasmatic lipidic profile, oxidative stress and BDNF of elderlies with mild cognitive impairment.

2. Methods

2.1 Participants

Thirty-seven individuals aged between 64 and 97 years old (=82.6; SD=6.8), 73% female, 27% male, living in nursing homes, were included in the study, and divided into two groups: experimental group (EG, n=25), submitted to 24-weeks of multicomponent exercise workout combined with cognitive stimulation (dual task), and a control group (CG, n=12). The participants were recruited in five different nursing homes located in Beira Interior, Portugal, that allowed participation in the study. Inclusion criteria were mild cognitive impairment and aged above 60 years old. Exclusion criteria included: clinical diagnosis of advanced dementia syndrome; uncontrolled hypertension (BP > 160/90 mmHg); frequent hypoglycemia; severe congestive heart; acute myocardial infarction in the last year; severe anemia (HB < 8 $g.dl^{-1}$); severe respiratory illnesses; severe osteoporosis; sensory deficit (vision/hearing) that makes it impossible to collaborate in the physical exercise program; and severe psychiatric disorders (Figure 1).

Prior to inclusion in the study, all candidates were carefully selected by a psychologist and a neurologist who performed cognitive assessments according to the standardized Mini Mental State Examination (MMSE) and those with a diagnosis of MCI were selected.

2.1.2 Test Procedures

All measurements were performed in five different nursing homes. Tests were supervised and applied to both groups before and after the application of the exercise program (baseline and post-training) by the same researchers. Each subject was familiarized with the procedures and aims of the study and gave their written informed consent. All the experimental procedures were approved according to the Declaration of Helsinki (UNESCO. Universal Declaration on Bioethics and Human Rights 2006) and were carried out with the approval of the Ethics Committee of the University of Beira Interior (reference code No. CE-UBI-PJ-2019 -021).

2.1.3 Anthropometric measurement

Height (cm) was measured with a stadiometer (Cabral, model 14) with a scale of 0.10 cm, and total body weight (kg) was measured to the nearest 0.1 kg on a digital scale (Tanita, type BF511). Subjects were measured wearing shorts and t-shirts (shoes and socks were removed).

2.1.4 Physical Fitness Assessment

Physical fitness was assessed according to Rikli and Jones battery procedures (Rikli & Jones, 1999). Participants performed six tests: 2.44m up-and-go test (to assess agility and dynamic balance), stand-up test (to measure lower body strength), 6-minute walk test (6MWT, to assess aerobic endurance), arm curls (to measure upper body strength), sitting and reaching, and reach behind the back (to assess upper body flexibility).

2.1.5 Measurement of cognitive function

Cognitive performance was assessed by a psychologist using the MMSE questionnaire (Opasso et al., 2016), translated and validated for the Portuguese population (Guerreiro & Bras, 2015). This instrument consists of 11 items in a total of 5 domains: orientation scale (time and place), memory (recording and recall), attention/counting skill (numbering), language skill (remembering names, 3-stage order, copying and repetition) and comprehension/judgment. A total score categorizes the individual on a scale of cognitive function ranging from 0 to 30. MMSE normative cut-of values for the Portuguese population are 22 (for 0–2 years of literacy), 24 (for 3–6 years of literacy) and 27 (for more than 6 years of literacy) (Morgado et al., 2009).

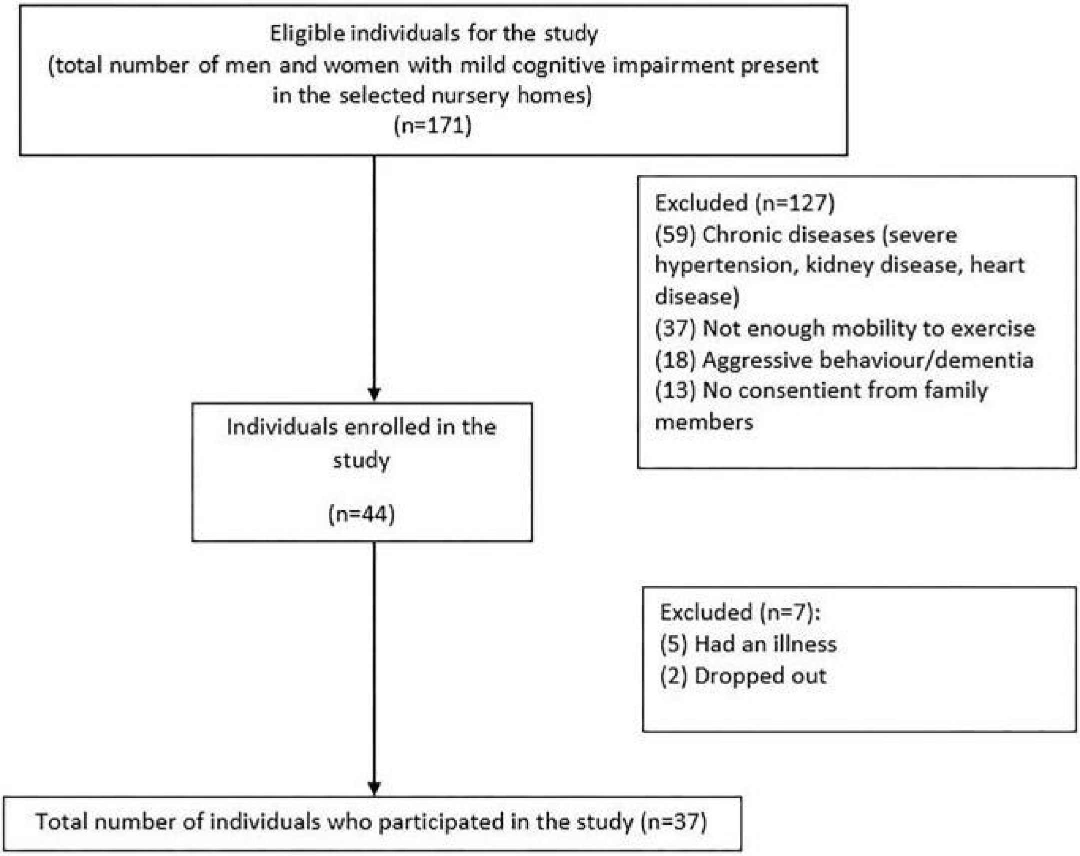

Figure 1 – Flowchard with inclusion and exclusion of the participants

2.1.6 Blood sample collection

A venous blood sample (4mL) was taken from each subject, between 8:30 and 10:00 a.m. in fasting conditions, and collected in ethylenediaminetetraacetic acid (EDTA) test tubes to prevent coagulation. The collected samples were then subjected to centrifugation at 3000 rpm for 10 min and the separated plasma was stored in Eppendorf tubes at -80°C for future analysis. The time between the last exercise session and blood sampling was between 48 and 72 hours after exercise.

2.1.7 Total protein determination

Total protein concentration in plasma was spectrophotometrically estimated according to biuret method, using serum albumin as standard (Gornall et al., 1949).

2.1.8 Lipid peroxidation

Nonspecific lipid peroxidation level in plasma was measured by determining the levels of lipid peroxides as the amount of thiobarbituric acid reactive substances (TBARS) formed, according to Wills (Wills, 1987) with some modifications. Plasma samples of 100 µL were taken and mixed with 200 µL trichloroacetic acid (10 %) and centrifuged at ~ 15,000×g for 1 min. Then, 200 µL of supernatant were taken and mixed with 200 µL of thiobarbituric acid (TBA) reagent (1 % thiobarbituric acid). The mixture was heated at 80– 90 °C for 10 min and cooled down at room temperature for 20 min. Lipid peroxidation was estimated by the appearance of malondialdehyde (MDA) which was quantified spectrophotometrically by reading the absorbance at 535 nm. The amount of (MDA) formed was calculated using molar extinction coefficient (ε) of 1.56×10^5 $M^{-1}cm^{-1}$, and the results were expressed as MDA concentration (nmol mg^{-1} of protein).

2.1.9 Total antioxidant capacity (TAC)

The total antioxidant capacity (TAC) in plasma was determined using the 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS) radical-scavenging activity measured by a procedure previously reported (Özgen et al., 2006), with slight modifications. A solution was prepared with $ABTS^{\bullet+}$ (7 mM) and potassium persulfate (140 mM) in 5 mL of distilled water. The solution was held/kept/stored at room temperature, in the dark, for 12–16 h before use. The $ABTS^{\bullet+}$ solution was diluted in acetate buffer (100 mM, pH 4.5), in order to obtain an absorbance of 0.7 at 734 nm. Fresh $ABTS^{\bullet+}$ solution was prepared for each analysis. To obtain Trolox equivalent, a standard solution was prepared at 0 (control), 1.25, 2.50, 5.00, 7.50, 10.00, 15.00, and 20.00 µM. To measure the antioxidant capacity of the samples, three different sample volumes were used. The antioxidant capacity of the samples was expressed in terms of the Trolox equivalent activity.

2.2.1 Brain-Derived Neurotrophic Factor (BDNF)

Plasma BDNF concentrations were analyzed by enzyme immunoassay using ELISA kits by Millipore (Temecula, CA, USA) according to the manufacturers' description and the protocol used by (Rojas Vega et al., 2006). The intensity of light was detected by a photometer (Microplate reader, ThermoFisher, New York, USA) with a 450 nm filter.

2.2.2 Intervention: Physical exercise training and cognitive stimulation (Dual Task)

Considering literature recommendations (Bruderer-Hofstetter et al., 2018; Gavelin et al., 2021; Gheysen et al., 2018; Karssemeijer et al., 2017; Zhang et al., 2019b), a multicomponent exercise intervention was implemented, where the cognitive stimulation was incorporated into the sessions; simultaneously combined with resistance or aerobic training.

Regarding the type of cognitive stimulation for people with MCI, (Woods et al., 2012) refers that they should be offered a range of enjoyable activities providing general stimulation for thinking, concentration and memory usually in a social setting, such as a small group, involving a wide range of activities that aim to stimulate thinking and memory, including discussion of past and present events and topics of interest, word games, puzzles, music and practical activities such as baking or indoor gardening (Woods et al., 2012).

Taking into account these recommendations together with the type of equipment available to this intervention, the cognitive stimulation comprehended exercises based on word games, puzzles, mathematical calculations, forward and backward counting, computer exercises (Cogweb – www.cogweb.pt and brain on track – www.brainontrack.com), exergames (Blaze pod – www.blazepode.com) and games on a balance platform (Physio Sensing – www.physiosensing.net).

Cogweb and Brain on Track being cognitive stimulation platforms were combined with physical exercise, the users cycling while solving the exercises. The Blaze Pod and Physio Sensing are platforms that work physical abilities such as speed, balance, coordination, and these were combined with cognitive stimulation with counting, naming, and calculating.

This stimulation was implemented in two sets of exercises: (1) repetitive - we kept some exercises in order to promote evolution and applying the use of acquired skills, and (2) alternated – in each session we introduced different cognitive exercises, in order to maintain the innovative effect and motivation.

The cognitive stimulation exercises were progressively inserted as the individuals performed the motor tasks with gradual degrees of difficulty, the exercises contemplated cognitive functions such as: attention, memory, calculation, language and executive functions. Stretching and relaxation for 5-10 minutes was included at the end of the exercise session.

Concerning the type of exercise, functional training was chosen due to the characteristics of the participants (frailty). Subjects followed physical training for 24 weeks, with two sessions per week, 45-50 minutes per session, on non-consecutive days. Each session was divided into three components: 20-25 min of aerobic exercise(s) plus cognitive stimulation, 10-15 min of strength exercise(s) plus cognitive stimulation, and 5-10 min of stretching and cool-down. Aerobic exercises were walking, walking on circuits with functional tasks and pedaling. The intensity of the aerobic component was moderate to low, considering the individuals' physical conditions. No perceived exertion scales or cardio frequencies were used, (however,) visual indicators were used as external signs of fatigue such as respiratory rate, speech fluency, and blushing (Riley et al., 2018; Solomon, 2006). The strength exercises were mostly calisthenics for the lower and upper limbs, and for arm flexion, dumbbells between 1kg to 3kg were used. The intensity of the strength component varied between 65% and 75% of the maximum of one repetition per minute (1RM), three sets of 8-12 repetitions in the first 4 weeks, and three sets of 12-16 repetitions in the following weeks.

To calculate the (1RM) the indirect method, repetitions test was used given the frailty of the study population.

2.2.3 Statistical Procedures

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) software version 21. The alpha level was set to 0.05, and data results were shown as means ± SDs. The normality of distribution was checked with the Shapiro-Wilk test, and homogeneity of variance was tested by Levene’s statistics. The effect of physical exercise on physical fitness variables, total MMSE score, Lipid profile, BDNF, TAC and MDA, was assayed using General Linear Model (GLM), repeated measures. For the non-parametric variables (Chair sit-&-Reach, Six/6 min walking, MMSE subscales, and total cholesterol) a Mann-Whitney test was performed for intra-group comparisons.

3. Results

The respective mean values and standard deviation (SD) of age and education of the sample are described in Table 1.

Table 1 – Mean ± standard deviation values of age and education.

Variables	CG ($N = 12$)	EG ($N = 25$)
Age (years)	81.8 ± 8.9	83.2 ± 5.5
Education		
Can neither read nor write	7	8
1–11 years of schooling	5	16
Higher education	0	1

Anthropometric and functional variables variance along the 24 weeks of intervention are described in table 2.

Table 2 – Mean ± standard deviation values of weight, body mass index (BMI), and functional variables, before and after intervention of exercise program.

Variables	CG ($N = 12$)		EG ($N = 25$)	
	Baseline	Post	Baseline	Post
Weight (Kg)	71.9 ± 13.5	72.6 ± 4.13	69.7 ± 14.1	69.9 ± 2.8
BMI (Kg/m^2)	28.1 ± 4.9	28.3 ± 5.1	28.6 ± 4.6	28.5 ± 4.7
Chair stand (no. of stands)	6.3 ± 5.0	5.3 ± 1.8	6.8 ± 5.6	8.2 ± 1.1#
Arm Curls (n° of reps)	18.6 ± 4.8	17.0 ± 4.8	16.5 ± 4.5	21.1 ± 3.8#
Chair sit-&-Reach (cm +/–)	(–)4.7 ± 8.7	(–) 6.4 ± 8.7*	(–) 3.1 ± 8.3	0.4 ± 6.4*
8-Ft Up-&-Go (s)	16.8 ± 14.2	18.9 ± 15.2	21.1 ± 11.7	17.2 ± 10.8#
Back scratch (cm +/–)	(–)30.1 ± 5.6	(–)34.9 ± 5.5	(–)37.2 ± 18.1	(–)31.7 ± 17.9 #
Six min walking (m)	145.3 ± 140.1	117.3 ± 126.0*	183.7 ± 192.8	204.3 ± 195.7
Feet together (s)	9.3 ± 1.6	9.3 ± 1.6	10.0 ± 0.0	9.8 ± 0.8
Semi Tandem (s)	6.8 ± 3.9	4.7 ± 3.3*	8.8 ± 3.1	8.8 ± 3.1
Full Tandem (s)	3.8 ± 4.1	1.9 ± 3.2*	6.2 ± 4.1	7.0 ± 4.1
SPBT	1.5 ± 1.0	0.9 ± 0.5*	2.3 ± 0.7	2.4 ± 0.9

#Between groups significant variation between baseline and post-intervention moment.
*Intragroup significant difference between baseline and post-intervention moment.
BMI, *body mass index;* CG, control group; EG, experimental group; SPBT, short performance battery test.

From baseline to week 24, GLM-repeated measures revealed that no body composition changes were observed in both groups, but significant variations in strength parameters were observed in both groups, in upper limbs (Arm Curl, p=0.000), lower limbs (Chair stand, p=0.003), agility and dynamic balance (8-Ft Up-&-Go) (p=0.002), and upper limbs flexibility (Back Scratch) (p=0.002).

Nonparametric test(s) revealed that lower limbs flexibility (Chair sit-&-Reach) decreased in the CG (p=0.007) and increased in the EG (p=0.007). Considering the remaining parameters, no significant changes were observed in the EG, while the CG decreased performance in the six minute walking test (p=0.032), Semi Tanden test (p=0.004), Full Tanden (p=0.017), and SPBT (p=0.020).

Cognitive function (MMSE) was significantly different between groups at baseline (CG=15.0±4.4; EG=13.1±3.9) and after 24 weeks of intervention (CG=18.2±2.6; EG=19.8±3.2), with multicomponent exercise exerting a significant effect in the variation of both groups' mental function (p=0.000). MMSE subscale variations with the intervention can be observed in Figure 2.

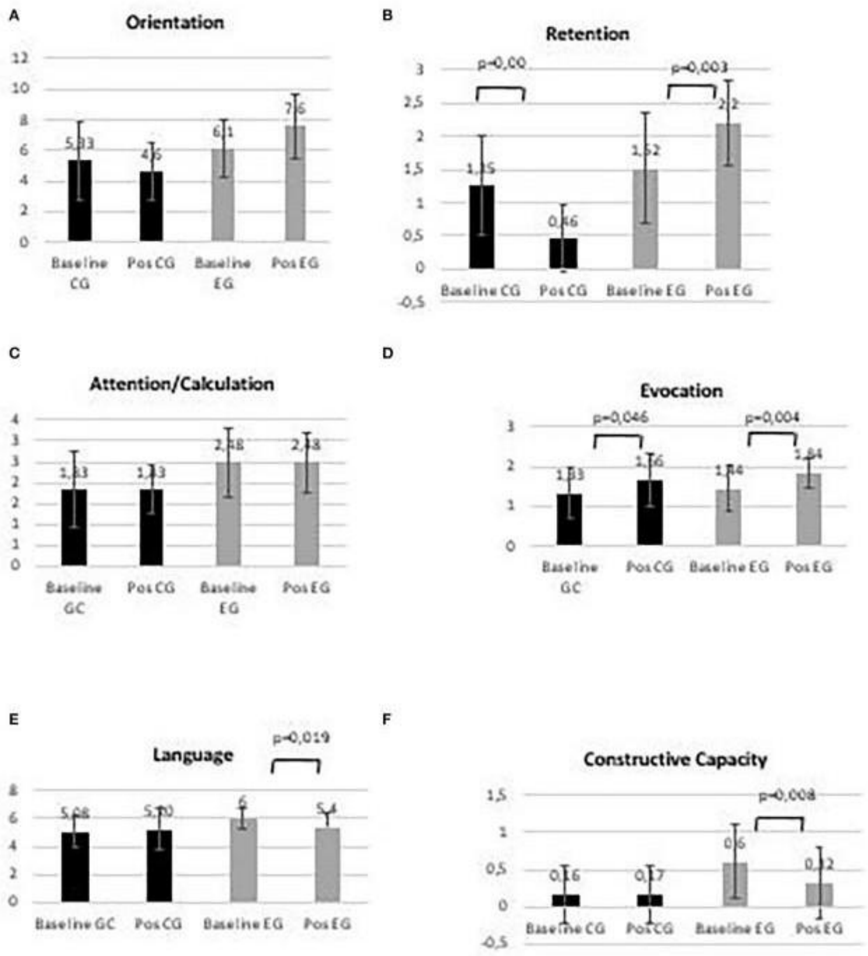

Figure 2 – Control group (CG) and experimental group (EG), (A) Orientation, (B) Retention, (C) Attention/Calculation, (D) Evocation, (E) Language, (F) Constructive capacity in baseline and post intervention period.

No significant changes in Orientation and Attention/Calculation between baseline and post intervention period was observed in both groups. Significant differences between baseline and post intervention period were observed in both groups for the Retention (p=0.0.000 and p=0.003, for CG and EG, respectively). An increase in Evocation between baseline and post intervention period were observed in both groups (p=0.046 and p=0.004, for CG and EG, respectively). Language and Constructive Capacity decreased in the EG, between baseline and post intervention period (p=0.019 and p=0.008, respectively).

Plasmatic Lipidic profile variations during the intervention period can be observed in Figure 3.

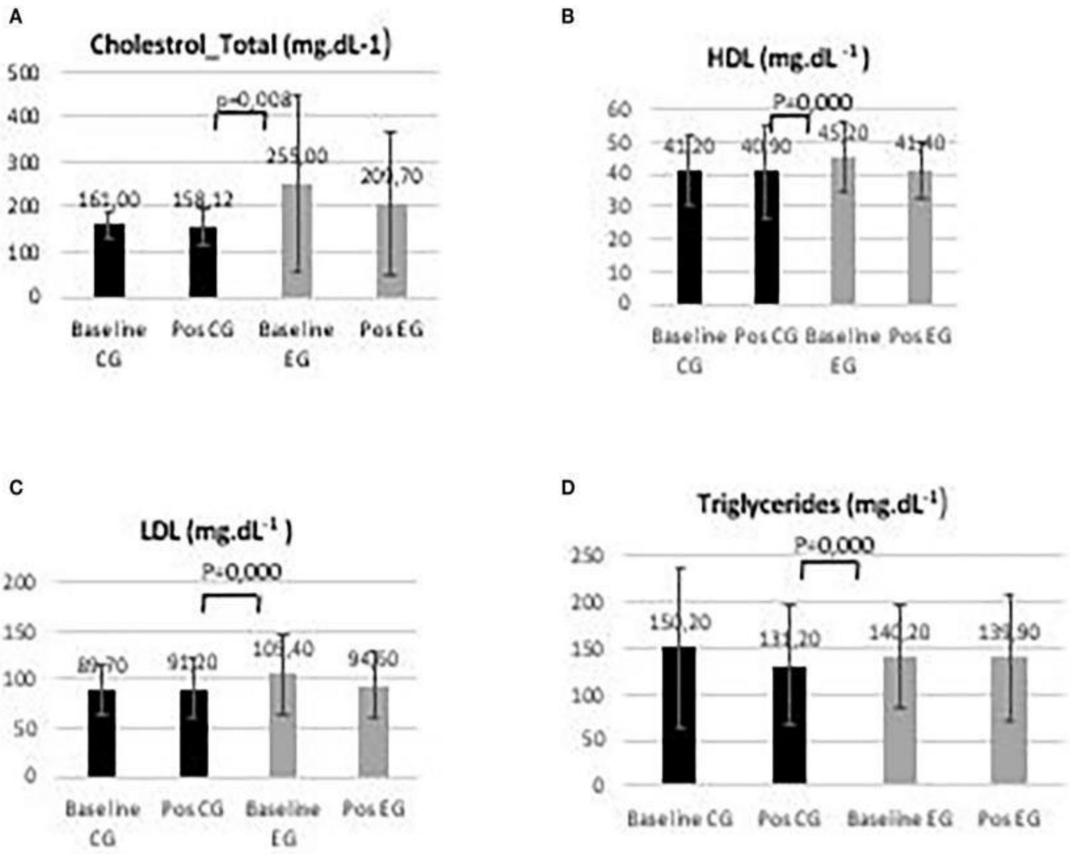

Figure 3 –Control group (CG) and experimental group (EG), (A) Plasmatic Lipidic Profile Cholestrol Total, (B) High Density Lipoprotein, HDL, (C) Low Density Lipoprotein, LDL, (D) Thriglycerides in baseline and post intervention period.

Regarding lipidic profile variables, there was significantly different variations between groups in Total Cholesterol (p=0.008), HDL (p=0.000), LDL (p=0.000) and triglycerides (p=0.000) between baseline and post intervention.

Plasmatic biochemical parameters of BDNF, lipid peroxidation (TBARs) and Total antioxidant capacity (TAC) variations during the intervention period can be observed in the Figure 4.

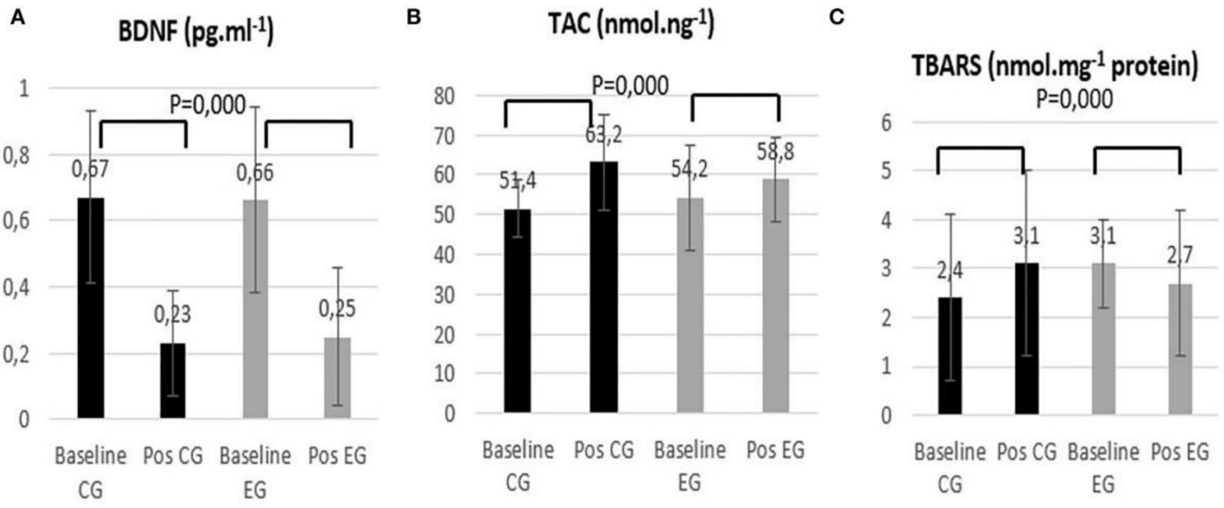

Figure 4 –Control group (CG) and experimental group (EG), (A) Brain Derived Neurotrofic Factor, BDNF, (B) Total Antioxidant Capacity,TAC, (C) Thiobarbituric Acid Reactive Substances, TBARS(D) in baseline and post intervention period.

Considering of plasmatic concentration of BDNF, there was a significant decrease in both groups between the baseline and post intervention (p=0,000). Total Antioxidant capacity increased in both groups (p=0,000). With respect to TBARS, it is possible to notice that while the CG increased lipid peroxidation (p=0,000) damage, EG decreased (p=0,000).

4. Discussion

This study aimed to analyze the effect of a multicomponent physical exercise program with stimulation on fitness, cognitive function, plasmatic lipidic profile, oxidative stress and BDNF of elderlies with MCI. Our results revealed a significantly crucially positive fitness improvement in the EG, while the CG decreased in almost all the fitness variables. These results enhance the importance of regular exercise in delaying the aging process. This is even more important considering the fragility of the elderlies living in nursing homes.

Values obtained describe a sample with a BMI above the recommended values and values in the physical fitness parameters lower than those indicated for healthy elderly people of the same age (Rikli & Jones, 2013; Sampaio et al., 2019; São Romão Preto et al., 2015). Nevertheless, these results are corroborated by other studies also developed with elderlies living in nursing homes (São Romão Preto et al., 2015)[#] significant variation between groups; [*]intragroup significant differences between baseline and post intervention moment; BMI (*Body Mass Index);* Control Group (CG) and Experimental Group (EG); SPBT (Short Performance Batery Test).

Indeed, although the aging process induces physical and physiological impairments, such as decreased muscular strength, power, and mobility in all elderly people, they seem to be more pronounced in those who spend long periods of time physically inactive (e.g., sitting, watching TV) (Oesen et al., 2015; Sampaio et al., 2019). This is a very common reality in nursing homes (Oesen et al., 2015; Sampaio et al., 2019; Scarabottolo et al., 2017) which may explain the low levels of functional fitness of our sample. It should also be added that several studies report an inverse association between the level of daily physical activity and cognitive function in the elderly (Brett et al., 2016; Marmeleira et al., 2017), agravated by the aging process (Chougnet et al., 2015; Grimmer et al., 2019; Scarabottolo et al., 2017). Regarding the CG, a significant loss of all parameters of functional fitness after 6 months without intervention was observed. On the other hand, in the EG, it was possible to observe a significant improvement in several parameters, and in the remaining ones there was no decrease in the performance of the elderly, which clearly indicate the benefits of physical exercise in delaying the loss of functionality associated with age. Although these results are corroborated by other studies (Lobo et al., 2011; Pedrero-Chamizo et al., 2012; Scarabottolo et al., 2017), it is important to emphasize the characteristics of the implemented exercise program. In this case, strength exercises were privileged, due to the sample frailty, enhancing balance and reducing the risk of falling (Borges et al., 2015; Coelho et al., 2013; Schwenk et al., 2010; Shin & An, 2014; Sobol et al., 2016), combined with functional circuits and dual tasks situations (the primary task was motor and the secondary task was cognitive)(He et al., 2018), to stimulate cognitive ability.

Regarding cognitive function, the values reveal the existence of a cognitive deficit in both groups, more pronounced in the EG. Contrary to our expectations, both groups showed an increase in total cognitive ability at the post-test moment compared to the baseline situation. Nevertheless, this improvement was more expressive in the experimental group. One would expect a maintenance or decrease in cognitive function in the CG, as a result of the aging process, as it has been described in other studies (Gregory et al., 2017; Rezola-Pardo et al., 2019; Zhang et al., 2019b). However, some variables were not controlled during the study and could explain the enhancement of cognitive function, particularly in the non-intervened group. In fact, other strategies has also been recommended in the treatment of MCI, such the use of antioxidants, medication and lifestyle changes (Ataollahi Eshkoor et al., 2015; DeCarli, 2003; Odawara, 2012).

Considering the six MMSE subscales, the results also raise some inconsistencies. Despite the intense and diverse cognitive stimulation, the variable that changed in a distinct and significant way was retention, which decreased in the CG and increased in the EG. In the remaining variables, results are not very coherent as there were improvements/losses or maintenance in both groups. These results may be justified, in part, by uncontrolled factors independent of the program performed and already mentioned above, but may also express limitations of the instrument used in the assessment of cognitive function. The MMSE has several advantages of use, namely its translation and validation into more than 50 languages (Carnero-Pardo, 2014) which makes it possible to find comparative norms in the most varied circumstances, evaluates different cognitive domains, is easy to apply and interpret and establishes cut-off points for cognitive deficits (Guerreiro & Bras, 2015) according to education level. Thus, this instrument seems, from the outset, to fit the population studied, as approximately 40% of the sample is illiterate, 57% have between 1 and 12 years of schooling, and 2% have higher education. The sample's schooling made it impossible to use other validated instruments, such as the montreal Cognitive Assessment (MOCA) (Hobson, 2015). On the other hand, the MMSE has several limitations, including the fact that it was not created specifically for the detection of Dementia. This explains why most of its score is due to orientation (10 points) and language (8 points) and only 3 of its 30 points assess memory, a cognitive domain that is primarily and early affected in MCI (Carnero-Pardo, 2014), and that was the most affected by our multicomponent exercise program, also found in another study (Grober & Sliwinski, 1991). Executive functions are also underrepresented in the MMSE, making it an instrument with little sensitivity to frontal dysfunctions (Carnero-Pardo, 2014). The MMSE contains several items that do not provide much discriminatory ability on the whole, especially in MCI or Dementia.

Regarding the lipid profile, significant variations were observed between groups. The values of the sample at baseline show normal or close to normal values, which, given its high body mass index, suggests taking medication and/or taking care of food and other healthy lifestyle habits (Barnard et al., 2014; Barre et al., 2011). The exercise intervention may have helped to accentuate some of these improvements observed in the EG.

BDNF variations were very similar in both groups, decreasing between the two evaluation moments. These results contradict somewhat our expectations, as BDNF is an important neurotrophin involved in neuroplasticity and cognitive function, so an increase in BDNF in the EG would be expected. However, despite the results of studies carried out in animals, particularly mice, they are quite consistent in showing an increase in BDNF with different modes of exercise(s), whereas in humans the results are very controversial, with some reporting an increase (K. I. Erickson et al., 2011b; Voss et al., 2013; Zoladz et al., sem data), others no change (Church et al., 2016; Goekint et al., 2010) and others decrease (De la Rosa et al., 2019). BDNF is known to induce rapid excitation and transmitter release, and to facilitate long-term potentiation through TrkB receptors and MAP kinase activation (Kafitz et al., 1999). MAP kinase activation is involved in mitochondria biogenesis, a cell-signaling pathway also stimulated by exercise, particularly intense exercise (Radak & Taylor, 2019). So, we would expect an increase in energy capacity production resulting both from BDNF and exercise, which could explain the increase in cognitive function.

However, in our study BDNF decreased in both groups, suggesting an age-dependent effect more relevant than exercise. Our results also failed to prove the importance of BDNF in the cognitive function of the elderly with MCI, once the CG revealed the same cognitive and BDNF variation as EG.

Regarding the Oxidative stress parameters, we found a very beneficial effect of multicomponent exercise as it induced a significant decrease in oxidative damage (TBARs) in the EG, also corroborated in the literature in studies with independent elderly people (Mota et al., 2019; Soares et al., 2015). This result can be explained through the multicomponent exercise effect in the activation of redox-sensitive signaling pathways such as NF-B, heat-shock transcriptional factor 1 (HSF-1), and P53 pathways, as well as mitogen-activated protein kinase (MAPK) and an increase in antioxidant capacity (Ji, 2006), also found in this study. However, results describing the multicomponent exercise related changes in oxidative stress of elderlies living in nursing homes were difficult to find. Regarding the CG, an increase in oxidative damage was observed, despite the antioxidant capacity having also increased, which suggests that a more intense generation of reactive oxygen species occurred in this group. This variation of the oxidative stress parameters in the CG also pointed out to the influence of possible uncontrolled variables in the study (food, supplementation and medication) that might have influenced TAC.

5. Conclusions

Results suggest that a multicomponent exercise training program (aerobic and strength exercises combined with cognitive stimulation) in institutionalized elderly with MCI is effective for improving physical fitness, memory and reducing damage induced by oxidative stress. The combined exercise program may be a method to mitigate the aging processes associated with oxidative stress. Additional studies are necessary to clarify the role of regular exercise in BDNF and its effect on cognitive function. It is suggested that future studies with elderlies with MCI should take into consideration food and medication.

Contribution to the Field Statement

Cognitive ability can be impaired by a variety of neuropathological conditions, such as neurodegenerative diseases, in which abnormal accumulation of certain proteins can cause silent chronic inflammatory processes. In this context, physical activity, by altering brain metabolism, increasing aerobic fitness and cerebral blood flow, appears to contribute to reducing chronic inflammation in the central nervous system, increasing neuroplasticity, promoting reorganization of neural circuits, and improving cognitive function.

We believe that physical exercise is very beneficial in delaying this pathology, we suggest that more research be done on the various exercise programs in order to try to find a more effective answer.

Study Limitations

This study has some limitations, namely (1) the sample size (37 participants, predominantly female); (2) the fact that overall, participants were classified as overweight and obese; (3) the age (participants were very old) and (4) several participants were polymedicated and this aspect is not taken into account.

Another limitation concerns the lack of control of several variations, like diet, use of antioxidants supplementation, medication, and lifestyle changes. These variables may explain the improvement in cognitive function, particularly in the non-intervention group. It is also important to refer as limitation the presence of some differences between groups in some baseline measurements.

Chapter 7: General Discussion

This thesis is part of a research project associated with a community program to evaluate the effect of a multi-component exercise program on different biochemical parameters, physical fitness and cognitive abilities, in people with MCI/Dementia - MEMO_MOVE program.

Various research techniques were used to carried out this intervention: rigorous quantitative and qualitative data were used, analyzed according to a standard procedure, and synthesized equally.

The use of mixed approaches was well defined in the research, and there was a strong justification for this. The approaches used allowed for continuous improvement of the study and research, confirmed individually recognized results to increase overall validity, and supported each other (Polit & Beck, 2010).

First, a review of the literature on exercise programs for people with MCI/Dementia was conducted. From an initial search of 1815 reviews, only 41 met the defined criteria; however, only 29 showed sufficient methodological quality to be considered in this critical review. Based on the current findings, patients with dementia may benefit from various exercise programs to improve global cognition, especially in the early to moderate phase of the disease (Maillot et al., 2012), ranging from aerobic exercise, strength exercise, multi-component exercise, and dual task exercises. There is a wide variety of exercise programs and it becomes difficult to say that one is better than the other. So, since different programs work different components, the most appropriate will be to do a multi-modal program with dual task and possibly exergames.

A recent literature has presented evidence on the benefits of exercise combined with cognitive stimulation in people with dementia, including those living in nursing homes, as it has been found to improve cognition, agitation, mood, mobility, and functional capacity (Brett et al., 2016; Henskens et al., 2018; Lee, 2018; Vseteckova et al., 2020).

To be able to have an effective exercise program it is necessary to have a multidisciplinary team consisting of a physician, psychotherapist, and exercise specialist, but also staff and coaches of the elderly, family/caregivers of the participant, and the individual themselves.

The next step was to check which inputs from experts from different fields identified as the main recommendations and concerns in building an exercise program for working with people with ICM. There are some studies that address the importance of multidisciplinary teams, the integration of knowledge from various disciplines about dementia, and conducting a detailed summary is necessary to develop optimal treatment plans tailored to individuals (Wagner et al., 2011); however, to our knowledge, this is the first article to report recommendations and constraints from experts in this population with institutionalized MCI.

The most important recommendations were: reinforcing the importance of physical activity in preventing dementia in institutions; respecting the patient's desire for participation; encouraging the cooperation and involvement of nursing home residents; ensuring attentive, respectful, and kind treatment; developing a trusting relationship with the physical activity professional. The main concerns identified are related to: patient resistance to participation in exercise programs; inappropriate activities or exercises; risk of falls; lack of adaptation to exercise; difficulty in understanding the orientations; the physical environment to implement the program sometimes is not the most appropriate; lack of family support; inadequate diagnosis of dementia; risk of disorientation, and adverse episodes.

The next phase was to design the intervention program based on the literature review and experts' opinion.

The goal was to describe the design of a combined exercise and cognitive stimulation intervention for people with MCI, focusing on interdisciplinary and transdisciplinary perspectives.

To assist people with MCI and help participants advance both their physical and cognitive abilities, a cognitive stimulation intervention program was designed, focusing on interdisciplinary and transdisciplinary perspectives. The design of the program was based on a literature review. To achieve results, it was recommended that the intervention contain the following application criteria: the program should last at least 24 weeks, have a minimium frequency of twice a week, and vary in intensity between light, moderate, and intense, always taking into account the physical limitations of the users.

The MEMO_MOVE intervention program was created based on this analysis to be offered to populations living in senior housing or communities with MCI.

The MEMO_MOVE initiative was the result of a collaboration between the Fundão City Council, CIDESD, and the University of Beira Interior. This was a proficous community outreach project that linked scientific research with the ability to participate in multicultural community programs.

Another strength of this project was the team behind the program, which included the scientific leaders (a sports scientist, a PhD), the people responsible for its planning and implementation (a PhD student), and the advisors (psychologists and technical experts). The capacity of the multidisciplinary team that developed and implemented the program was crucial to its success.

A preliminary test was conducted to evaluate the materials used and the type of cognitive stimulation that received the most favorable feedback by elederlies with MCI. This was quite significant, since it demonstrated the motivation, communication skills, and relationship that the intervention team had with this population.

Following the program's implementation, we continued with study 4, which looked for the biochemical changes induced the designed multi-component exercise program on physical fitness and cognitive function in elderly persons with mild cognitive impairment.

There are a few reasons to study oxidative stress and BDNF. One of the most proeminent biological theory of aging support by research is the Oxidative Stress Theory. According to this theory, the biological changes associated with aging are a consequence of increased oxidative stress, resulting from increased ROS production, reduced antioxidant capacity, and reduced ability to repair the resulting damage (Buffenstein et al., 2008; Gemma et al., 2007). This increased oxidative stress is involved in both normal (disease-free) aging, and aging aggravated by the presence of disease, where dementias has been included (Tönnies & Trushina, 2017). Therefore, given that chronic exercise reduces oxidative stress in individuals of different ages (refs), we aimed to see if the same occurred in older adults with MCI. Dual task exercise was used to stimulate cognitive function resulting not only from improving the individual's overall metabolism, but also to stimulate neuroplasticity. The literature has described an important role of BDNF in neurogenesis and synaptogenesis (Yang et al., 2020), possibly modulated by oxidative stress (Valvassori et al,. 2022), which made it an eligible variable to be studied in this research. The results indicated that physical and functional performance had generally improved. Multi-component exercise significantly reduces oxidative damage. However, the BDNF changes in our study were very similar in both groups, suggesting that aging process has a major effect than this physical exercise program. Additional studies are needed to clarify the effect of multicomponent exercise training with dual task in oxidative stress damage and neurotrophines modulation in people with MCI.

Chapter 8. Overall Conclusions

This thesis aimed to design and implement an exercise program that includes cognitive stimulation target to people with MCI/Dementia and evaluate the caused effects on fitness, cognitive function, including the role of oxidative stress and BDNF.
From the critical review based on revision articles concerned the evidenced effects of physical exercise in people with MCI were made, the main conclusions retrieved were that there are scientific evidence regarding the benefits that patients with dementia have from various exercise programs to improve global cognition, especially in the early to moderate stage of the disease.
The interdisciplinary teamwork provide some important recommendations regarding program design and implementation, such as such as the importance of including families and caregivers; the need to educate families and caregivers about the importance of physical exercise in dementia; respect the patient's will to participate; promote the collaboration and involvement of the senior residence staff; ensure attentive, respectful, and friendly treatment; create a relationship of trust with the exercise professional; the appropriate design of physical exercise and cognitive stimulation; an appropriate schedule; and a safe environment. Additionally, the main concerns were related to dementia patients' resistance to participate in exercise programs, inappropriate activities or exercises; the risk of falls; the lack of exercises' adaptation; the difficulty in understanding instructions; the physical space for the implementation of programs not always being the most adequate; the lack of family support; the inadequate diagnosis of dementia; the danger of disorientation; episodes of violence; the willingness of people involved in the care of demented patients to collaborate; the lack of sensitivity in the treatment of people with MCI/Dementia; and the lack of adequate exercise equipment in nursing homes.

The evaluation of the physical fitness level in older persons with mild cognitive impairment was assessed, evidencing that is very poor among this population, particularly in aerobic capacity (walking 6 minutes test), strength of lower limbs (chair lift test) and flexibility (sit and reach test and reach behind back test). This result emphasizes the need of specific exercise intervention to this population.
The MEMO_MOVE program was designed from a literature review that provided a summary of the type of exercise that should be implemented among this population. The MEMO_MOVE program was then described, regarding (i) inclusion of a cognitive

stimulation component; (ii) the kind of cognitive stimulation; and (iii) the type of exercise, duration, frequency, intensity, and program length.

The exercise program created from the recommendations and issues identified by (Rondão et al., 2022) was the MEMO_MOVE program, which is a multicomponent program designed specifically for people with MCI8/Dementia. https://memomove.wixsite.com/memomove https://www.facebook.com/profile.php?id=100063619118105.

After the identification of the key aspects to include in the exercise program for subjects with MCI, and paying attention to the main recommendations and constrains identified by the professionals that take care of these people, a study to evaluate the effects of a multicomponent exercise program on cognitive function and physical fitness in elderly people with mild cognitive impairment and to identify the role of oxidative stress and brain derived neurotrophic factor (BDNF), had been carried out. The main results showed an overall improvement in physical and functional performance. Regarding cognitive function, there were significant improvements in the cognitive performance, particularly in retention and recall capacity. Significant different variations between groups in Total Cholesterol between baseline and post intervention period, occurred. The plasma biochemical parameters of BDNF, decrease in both groups between baseline and post intervention. Total antioxidant capacity increased in both groups, however while CG increased lipid peroxidation, EG decreased it.

The results suggest that a multicomponent exercise training program (aerobic and strength exercises combined with cognitive stimulation) in institutionalized elderly with MCI is effective in improving physical fitness, memory and reducing oxidative stress-induced damage.

More research is needed to explain the role of regular exercise on BDNF and its effect on cognitive function, and future research with older adults with MCI should consider nutrition and medication.

Limitations

Throughout the research some limitations were identified, some were presented throughout this research in the respective articles.
In general, we could identify as a limitation the physical and cognitive condition of elderly people in nursing homes.
The importance of testing more individualized sessions, as well as studying other biochemical parameters such as those associated with the inflammatory response.

Practical implications

The research project started in nursing homes, after its conclusion and analysis of the data, it evolved into a space in the community due to the positive results, the municipality of Fundão embraced the project, making it an answer for its citizens.
Having a multidisciplinary team allowed innovation in terms of cognitive stimulation and physical exercise with the introduction of technology, such as (Cogweb, Brain on Track, Sios Life, Play Memo_Move, Physio Sense, Blaze Pods).
This project raised awareness of the importance of exercise with cognitive stimulation in improving/maintaining physical fitness and cognitive skills, which led to a great demand from individuals and caregivers, resulting in a waiting list to attend the program.
The creation of specific equipment like Play Memo_Move.

Figure 1 – Play Memo_Move

Suggestions for future investigations

For the future, it is intended to evaluate another type of intervention, to apply other types of exercise (intensities and loads) on the effect of biochemical parameters (oxidative stress, ABTS and BDNF);

Replication of the program in a non-institutionalized population;

Evaluation of the effects of the program on the parameters of physical fitness, cognitive and biochemical performance;

Introduction of technology for cognitive stimulation and physical fitness (cognitive stimulation platforms and exergames);

Development of technology and exercise support equipment, such as "Play Memo_Move" among others;

Compilation of a book with specific training sessions;

Creation of a new support program for Parkinson's patients, highly recommended by neurologists and clinical psychologists.

Chapter 9. References

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Chapter 3

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Chapter 6

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Chapter 10 - Attachments

Informed Consent

Centro Hospitalar Cova da Beira, EPE

IMPRESSO

Consentimento livre e informado

MEMO_MOVE

Código: CHCB.IMP.CINVEST.18 | Edição: 2 | Revisão: 0

Catarina Alexandra de Melo Rondão, doutoranda em Exercício e Saúde da Universidade da Beira Interior, a realizar um trabalho de investigação subordinado ao tema **Avaliação dos efeitos de um programa de exercício físico com componente de estimulação cognitiva (programa *dual task*) na aptidão física e funcional, composição corporal e capacidade cognitiva em pacientes com défice cognitivo ligeiro - Estudo piloto: Implementação do programa MEMO_MOVE,** vem solicitar a sua colaboração neste estudo. Informo que a sua participação é voluntária, podendo desistir a qualquer momento sem que por isso venha a ser prejudicado nos cuidados de saúde prestados pelo CHCB. Informo ainda que a sua privacidade será respeitada, todos os dados recolhidos serão confidenciais e não serão fornecidas quaisquer compensações.

Objetivo do trabalho de investigação: O objetivo principal deste estudo é avaliar os efeitos de um programa de exercício físico que compreenda uma estimulação cognitiva (programa dual task) na aptidão física e funcional, na composição corporal e na capacidade cognitiva em pacientes com défice cognitivo ligeiro. Como objetivo secundário pretende ainda avaliar-se o efeito do mesmo programa de exercícios no stress oxidativo, nos dados de ADN e na capacidade de reparação do ADN nos linfócitos, na mesma população. Para este objetivo pretendem usar-se sobras de análises sanguíneas, que permitirão avaliar os seguintes parâmetros: (1) Ficha Lipídica; (2) Fator Neurotrófico Derivado do Cérebro (BDNF, *Brain-derived neurotrophic factor*); (3) substâncias reativas ao ácido tiobarbitúrico (TBARs, *Thiobarbituric acid reactive substances*); (4) Danos de ADN (ensaio do cometa ou Eletroforese em Gel de Célula Única) e (4) Capacidade antioxidante total (TAC).

Critérios de inclusão: diagnóstico clinico de défice cognitivo ligeiro ou síndrome demencial em estado ligeiro; não cumprimento das atuais diretrizes de atividade física recomendada (<150 min por semana) pelo American College of Sports Medicine.

Critérios de exclusão: diagnóstico clínico de síndrome demencial em estado avançado; hipertensão não controlada (TA>160/90 mmHg); hipoglicémias frequentes; insuficiência cárdica congestiva grave; enfarte agudo do miocárdio no ultimo ano; anemia grave (HB<8g/dl); patologia respiratória grave; osteoporose grave; défice sensorial (visão/audição) que incapacite a colaboração no programa de exercício físico; alterações psiquiátricas graves.

Procedimentos necessários: A aptidão física e funcional será avaliada por intermédio de testes físicos de desempenho; a composição corporal será avaliada por bioimpedância e a capacidade cognitiva através de avaliação neuro psicológica através do teste psicológico Montereal Congnitive Assessement MOCA VERSÃO PORTUGUESA – 7.1 (Versão Portuguesa: Freitas, S., Simões, M. R., Santana, I., Martins, C. & Nasreddine, Z. (2013). Montreal Cognitive Assessment (MoCA): Versão 1. Coimbra: Faculdade de Psicologia e de Ciências da Educação da Universidade de Coimbra).

Os parâmetros bioquímicos que se pretendem avaliar necessitam de sobras de sangue de análises de rotina.

Estes procedimentos metodológicos serão realizados em instalações do Centro Hospitalar da Cova da Beira.

As sessões de exercício físico serão orientadas em instalações da do Centro Hospitalar da Cova da Beira, com grupos de 3 a 5 pacientes, 2 vezes por semana ao longo de 16 semanas.

Risco / Benefício da sua participação: Não existe risco pois o exercício será adaptado a cada doente e só realizarão os exercícios os doentes indicados segundos os critérios clínicos. O benefício será diminuição da fadiga, aumento da força muscular, flexibilidade e da qualidade de vida, diminuição da dor e náuseas.

Duração da participação no estudo: 16 semanas para cada paciente.

Nº aproximado de participantes: 40 pacientes. Contacto para esclarecimento de dúvidas: 966628885

Consentimento informado – Aluno / Investigador

Ao assinar esta página está a confirmar o seguinte:

* Entregou esta informação;

* Explicou o propósito deste trabalho;

* Explicou e respondeu a todas as questões e dúvidas apresentadas pelo participante ou representante legal.

____

Nome do Aluno / Investigador

________________________________ ___/___/___

Assinatura do Aluno / Investigador Data

Consentimento informado – Participante

Ao assinar esta página está a confirmar o seguinte:
* O Sr. (a) leu e compreendeu todas as informações desta informação, e teve tempo para as ponderar;
* Todas as suas questões foram respondidas satisfatoriamente;
* Se não percebeu qualquer das palavras, solicitou ao aluno/investigador uma explicação, tendo este esclarecido todas as dúvidas;
* O Sr. (a) recebeu uma cópia desta informação, para a manter consigo.

____________________ ____________________

Nome do Participante (Legível) Representante Legal

____________________ ___/___/___

(Assinatura do Participante ou Representante Legal) Data

Comissão de Ética
Universidade da Beira Interior

comissaodeetica@ubi.pt
Convento de Santo António
6201-001 Covilhã | Portugal

Parecer relativo ao processo n.º CE-UBI-Pj-2019-021:ID1239

Na sua reunião de 9 de abril de 2019 a Comissão de Ética apreciou a documentação científica submetida referente ao pedido de parecer do projeto ***"Avaliação dos efeitos de um programa de exercício físico com componente de estimulação cognitiva (programa dual task) na aptidão física e funcional, composição corporal e capacidade cognitiva em pacientes com défice cognitivo ligeiro - Estudo piloto: Implementação do programa MEMO_MOVE"***, da proponente **Dulce Esteves,** a que atribuiu o código n.º CE-UBI-Pj-2019-021.

Na sua análise não identificou matéria que ofenda os princípios éticos e morais sendo de parecer que o estudo em causa pode ser aprovado. Dado o conteúdo do trabalho deverá ser solicitada autorização ao Encarregado da Proteção de Dados da(s) entidade(s) envolvida(s).

Covilhã e UBI, 6 de maio de 2019

O Presidente da Comissão de Ética

Professor Doutor José António Martinez Souto de Oliveira
Professor Catedrático

Registration of the trademark Memo_Move

inpi instituto nacional da propriedade industrial

MARCA NACIONAL Nº 594846

Síntese do Processo

Nº do Pedido	33383
Data de Apresentação	19-01-2018
Data do Pedido	19-01-2018
Tipo de Modalidade	Não aplicável a este processo
Fase Actual	REGISTO CONCEDIDO
Data de Início da Fase	05-04-2018
Data de Fim Previsto	---
Situação de Taxas	NÃO HÁ RENOVAÇÕES A PAGAMENTO
Data de Início da Sit.	05-04-2018
Data de Fim Previsto da Sit.	04-10-2027
Taxas Pagas	1
Taxas Devidas	0
Data da Última DIU	---
BPI 1ª Publicação	26-01-2018
Data do Despacho	02-04-2018
BPI do Despacho	05-04-2018
Data de Início de Vigência	02-04-2018
Data Limite de Vigência	---
Titulares	UNIVERSIDADE DA BEIRA INTERIOR
Mandatário	JOÃO PEREIRA DA CRUZ
Classificação de Nice	41 42 44
Processo em Tribunal	NÃO
Tribunal	---

MEMO_MOVE - PROGRAMA DE EXERCÍCIOS COM ESTIMULAÇÃO COGNITIVA PARA ADULTOS COM DÉFICE COGNITIVO LIGEIRO

Tipo de Sinal: VERBAL

inpi instituto nacional da propriedade industrial

MARCA NACIONAL Nº 594847

Síntese do Processo

Nº do Pedido	33384
Data de Apresentação	19-01-2018
Data do Pedido	19-01-2018
Tipo de Modalidade	Não aplicável a este processo
Fase Actual	REGISTO CONCEDIDO
Data de Início da Fase	05-04-2018
Data de Fim Previsto	---
Situação de Taxas	NÃO HÁ RENOVAÇÕES A PAGAMENTO
Data de Início da Sit.	05-04-2018
Data de Fim Previsto da Sit.	04-10-2027
Taxas Pagas	1
Taxas Devidas	0
Data da Última DIU	---
BPI 1ª Publicação	26-01-2018
Data do Despacho	02-04-2018
BPI do Despacho	05-04-2018
Data de Início de Vigência	02-04-2018
Data Limite de Vigência	---
Titulares	UNIVERSIDADE DA BEIRA INTERIOR
Mandatário	---
Classificação de Nice	41 42 44

MEMO_MOVE

Tipo de Sinal: VERBAL

Links

- https://www.facebook.com/profile.php?id=100063619118105
- https://fb.watch/bXlvG-KBeg/
- https://www.facebook.com/profile.php?id=100063454274474

Awards

- As part of the European project URBACT/SIBDEV, Memo_Move won funding for the creation of an outdoor Exargame called Play Memo_Move. https://youtu.be/qR73fNHeXNU

Photos

Aerobic training - Functional Circuit

Strength training

Balance

Cognitive stimulation

Exergames