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Contributions of a 6-month Multicomponent Training Intervention on Individuals Diagnosed with Major Neurocognitive Disorder

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Porto, 2022

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The present thesis was written with the purpose of obtaining a doctoral degree in Physical Activity and Health designed by Research Centre in Physical Activity, Health and Leisure, Faculty of Sports, University of Porto, under the Decree-Law No. 74/2006 from March 24th.

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KEYWORDS: DEMENTIA, PHYSICAL ACTIVITY, PHYSICAL EXERCISE, OLDER ADULTS, COGNITION, FUNCTIONALITY.

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Porto, 5 de outubro de 2022

Flávia Alexandra Borges Machado

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DIRETIVAS LEGAIS

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Flávia Alexandra Borges Machado

Flávia Alexandra Borges Machado

Em memória dos meus avós

Aos meus sobrinhos Manuel, Francisco, Maria Leonor e Inês

A todas as pessoas que vivem com demência e seus familiares

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RESUMO

Introdução: A perturbação neurocognitiva major (PNC), comummente designada de demência, é caracterizada por um declínio cognitivo significativo que afeta a independência dos indivíduos no desempenho das atividades de vida diária (AVD). Evidências científicas sugerem que o exercício físico poderá ter um impacto positivo na progressão da PNC e na gestão dos sintomas. Mas os dados são ainda insuficientes quanto aos efeitos de metodologias de treino específicas, particularmente o treino multicomponente (TM). ***Objetivos***: Esta tese teve como principal objetivo investigar o impacto de um programa de TM com a duração de seis meses na capacidade funcional e função cognitiva de indivíduos com PNC major. Secundariamente, visou examinar os efeitos desta intervenção nos parâmetros funcionais e psicossociais; analisar a relação entre indicadores físicos e de qualidade de vida; e explorar os fatores que influenciam a adesão ao exercício físico. ***Métodos***: A tese inseriu-se num projeto mais amplo, o "Body & Brain", que incluiu um estudo controlado, não randomizado, conduzido em múltiplos contextos. O grupo experimental recebeu sessões de exercício físico bissemanais (60 minutos) subdivididas em aquecimento, treino específico (e.g., coordenação/equilíbrio, força e capacidade aeróbia) de intensidade ligeira a moderada, e relaxamento. O grupo de controlo recebeu sessões mensais de carácter social. ***Resultados***: O TM beneficia a capacidade funcional dos indivíduos com PNC; porém, permanece incerto o efeito que o TM poderá ter na função cognitiva, sintomas neuropsiquiátricos, qualidade de vida e independência nas AVD. Foi possível identificar vários fatores promotores de adesão a este tipo de exercício físico, dos quais se destacam: a antecipação de ganhos, a necessidade de atividades estimulantes, o aconselhamento dos profissionais de saúde e o envolvimento dos cuidadores informais. ***Conclusões***: Esta tese oferece informações relevantes sobre os benefícios do TM e sobre os fatores que podem aumentar a taxa de sucesso de futuras intervenções.

PALAVRAS-CHAVE: DEMÊNCIA, ATIVIDADE FÍSICA, EXERCÍCIO FÍSICO, IDOSOS, COGNIÇÃO, FUNCIONALIDADE.

ABSTRACT

Background: Major neurocognitive disorder (NCD), also designated as dementia, is characterized by a significant cognitive decline that affects individuals' independence in activities of daily living (ADL). Evidence suggests that physical exercise might have a positive impact on NCD progression and symptoms management. But data is still scarce about the effects of specific types of physical exercise, particularly multicomponent training (MT). ***Aims***: This thesis had as primary aim to investigate the contribution of a 6-month MT intervention on the physical and cognitive functions of individuals with major NCD. Secondarily, it aimed to examine its effects on functional and psychosocial outcomes and analyze the relation between physical indicators and quality of life. It also intended to explore the factors that influence adherence to physical exercise. ***Methods***: This thesis is nested in a wider project, the "Body & Brain", which is a two-arm quasi-experimental controlled trial, conducted in multicentered settings. Experimental group received bi-weekly sessions (60 minutes) subdivided in warm-up, specific training (e.g., coordination/balance, strength, and aerobics) at light-to-moderate intensity and cool down. Control group received monthly social activity sessions. ***Results***: MT benefits individuals' functional capacity; however, it remains unclear if MT can exert a significant effect on cognitive function, neuropsychiatric symptoms, quality of life, and ADL independence. Also, it was possible to identify a set of factors that influence the involvement in this type of intervention: the anticipated gains, the need for a stimulating activity, the healthcare professional's advice, and the engagement and compliance of informal caregivers. ***Conclusions***: This thesis provides several insights on the benefits of MT and on factors that may increase the success rate of future interventions.

KEYWORDS: DEMENTIA, PHYSICAL ACTIVITY, PHYSICAL EXERCISE, OLDER ADULTS, COGNITION, FUNCTIONALITY.

LIST OF ABBREVIATIONS AND SYMBOLS

ACSM	American College of Sports Medicine
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive
ADCS-ADL-sev	Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory for Severe Alzheimer's Disease
ADI	Alzheimer's Disease International
ADL	Activities of daily living
ASMI	Appendicular skeletal muscle mass index
BDNF	Brain-derived neurotrophic factor
BI	Barthel Index
BMI	Body Mass Index
BNT	Boston Naming Test
BPSD	Behavioral and psychological symptoms of dementia
CDR	Clinical Dementia Rating
CG	Control group
COREQ	Consolidated Criteria for Reporting Qualitative Research
COVID-19	Coronavirus disease
DALYs	Disability-adjusted life years
DSM-5	Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition – Text Revision
DXA	Dual energy X-ray absorptiometry
EG	Experimental group
EMA	European Medicines Agency
EWGSOP	European Working Group on Sarcopenia in Older People
FDA	U.S. Food and Drug Administration

FITT	Frequency, intensity, type, and time variables
GBD	Global Burden of Diseases, Injuries and Risk Factors Study
GDO	Global Dementia Observatory
HIC	High-income countries
HRmax	Maximal heart rate
ICD-10	International Classification of Diseases and Related Health Problems – 10^{th} Revision
ICD-11	International Classification of Diseases and Related Health Problems – 11^{th} Revision
IG	Intervention group
IGF-1	Insulin-like growth factor-1
IPDJ	Instituto Português do Desporto e Juventude
JTT	Jebsen Total Time
KATZ-ADL	Katz Index of ADLs
LbD	Lewy-body dementia
LMIC	Low-and-middle income countries
MCI	Mild cognitive impairment
MD	Mixed dementia
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
MT	Multicomponent training
NCD	Neurocognitive disorder
NH	Nursing home
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association
NPI	Neuropsychiatric Inventory
PA	Physical activity
PD	Parkinson’s disease
PET	Positron emission tomography
PRISMA	Preferred Reporting Items for Systematic Reviews and

	Meta-analysis
QoL	Quality of life
QoL-AD	Quality of Life – Alzheimer's Disease
RCT	Randomized controlled trial
SD	Subcortical dementia
SFT	Senior Fitness Test
SHARE	Survey of Health, Ageing and Retirement in Europe
SPBB	Short Physical Performance Battery
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TESTEX	Tool for the Assessment of Study Quality and Reporting in Exercise
TUG	Timed-Up and Go Test
UD	Undefined dementia
VaD	Vascular disease
VIF	Variance Inflation Factor
WHO	World Health Organization
WW-FINGERS	World-Wide Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
YLDs	Healthy life lost due to disability
YPAS	Yale Physical Activity Survey

LIST OF ARTICLES

CORE ARTICLES

The six articles listed below are the core structure of this thesis, presented by its order of appearance. Three are published, and the other three are currently under review by international scientific journals with peer-review.

Borges-Machado F, Lima N, Farinatti P, Poton R, Ribeiro O, Carvalho J. (2021) Effectiveness of multicomponent exercise interventions in older adults with dementia: a meta-analysis. *The Gerontologist*. 61(8): e449-e462. doi: 10.1093/geront/gnaa091

Borges-Machado F, Barros D, Teixeira L, Ribeiro O, Carvalho J. (2021) Contribution of a multicomponent intervention on functional capacity and independence on activities of daily living in individuals with major neurocognitive disorder. *BMC Geriatrics*. 21:625. doi: 10.1186/s12877-021-02591-2

Borges-Machado F, Teixeira L, Carvalho J, Ribeiro O. (*under review*) Does multicomponent training work for dementia? Exploring the effects on cognition, neuropsychiatric symptoms, and quality of life.

Borges-Machado F, Barros D, Teixeira L, Ribeiro O, Carvalho J. (2021) Health-related physical indicators and self-rated quality of life in older adults with neurocognitive disorder. *Quality of Life Research*. Aug 30(8): 2255-2264. doi: 10.1007/s11136-021-02828-y

Borges-Machado F, Barros D, Silva P, Marques P, Carvalho J, Ribeiro O. (*under review*) Contributing factors for (non)adherence to a physical exercise program for people with neurocognitive disorder from the caregiver's point-of-view.

Borges-Machado F, Barros D, Silva P, Marques P, Carvalho J, Ribeiro O. (*under review*) Should caregivers also be included in physical exercise-based interventions for people with a neurocognitive disorder?

OTHER PUBLICATIONS PRODUCED WITHIN THE SCOPE OF THE THESIS

Articles

Carvalho J, **Borges-Machado F**, Barros D, Sampaio A, Marques-Aleixo I, Bohn L, Pizarro A, Magalhães J, Ribeiro O. (2021) Body & Brain: effects of a multicomponent exercise intervention on physical and cognitive function of adults with dementia - study protocol for a quasi-experimental controlled trial. *BMC Geriatrics.* 21(1):156. doi: 10.1186/s12877-021-02104-1

Borges-Machado F, Barros D, Ribeiro O, Carvalho J. (2020) The Effects Of COVID-19 Home confinement in dementia care: physical and cognitive decline, severe neuropsychiatric symptoms, and increased caregiving burden. *American Journal of Alzheimer's Disease & Other Dementias*. 35: 1-9. doi: 10.1177/1533317520976720

Barros D, **Borges-Machado F**, Ribeiro O, Carvalho J. (2020) Dementia and COVID-19: The ones not to be forgotten. *American Journal of Alzheimer's Disease & Other Dementias. Jan-Dec* 35: 1533317520947505. doi: 10.1177/1533317520947505

Borges-Machado F, Ribeiro O, Sampaio A, Marques-Aleixo I, Meireles J, Carvalho J. (2019) Feasibility and impact of a multicomponent exercise intervention in patients with Alzheimer's disease: A pilot study. *American Journal of Alzheimer's Disease & Other Dementias*, 34(2): 95-103. doi: 10.1177/1533317518813555

Marques-Aleixo I, Sampaio A, Bohn L, **Machado F,** Barros D, Ribeiro O, Carvalho J, Magalhães J. (*under review*) Neuropsychiatric symptoms in individuals with major neurocognitive disorder are associated with poorer physical fitness, neurotrophic and inflammatory outcomes.

Book Chapter

Borges-Machado F, Barros D, Ribeiro O, Carvalho J. (2021) Body & Brain: Adaptação online de um programa de exercício físico multicomponente para pessoas com demência. *E-Book do IV Seminário Internacional Alzheimer Viseu: Conhecer, Compreender e Intervir*. Eds. José Carreira, Lia Araújo, Maria João Amante, Paula Xavier & Susana Fonseca. Escola Superior de Educação do Instituto Politécnico de Viseu, Portugal. doi: 10.34633/978-989-54743-7-0

Research related with some articles were presented as poster or oral communication in national and international scientific meetings and conferences. Whitin the PhD timeframe, the candidate:

a) presented 7 posters and 2 oral communications;
b) co-authored 11 posters and 2 oral communications;
c) was invited as a speaker to 5 national scientific conferences and to 2 international scientific conferences;
d) published 11 abstracts in scientific journals' special numbers: 2 national and 9 international;
e) published 5 abstracts in conference proceedings: 3 national and 2 international.

All contributions are listed in the candidate's *Curriculum Vitae* and **Appendix 1.**

GENERAL INTRODUCTION

Neurocognitive disorders (NCD) encompass a group of conditions that affect the brain and in which the primary clinical deficit is in the cognitive function. Extensively denominated as dementia, this syndrome is characterized by a decline from a previously attained level of functioning and interferes with daily independence (American Psychiatric Association, 2013). It is estimated that there are nearly 217 549 community-dwelling individuals living with dementia in Portugal (Gonçalves-Pereira et al., 2021). According to the Alzheimer Europe estimations, it is expected that in 2050 the number of people with dementia (346 905) in Portugal will represent 3.82% of the total population (Alzheimer Europe, 2019). In parallel, data from the Eurobarometer 472 on Sport and Physical Activity revealed that nearly 70% of the Portuguese respondents never exercise or play sports (Eurobarometer, 2018). International data on physical inactivity and sedentarism is particularly alarming when concerning individuals with major NCD (van Alphen, Volkers, et al., 2016), and the national paradigm should not be different.

In line with a more comprehensive and person-centered care approach (World Health Organization, 2021b), individuals with NCD should have access to potential (non-)pharmacological disease-modifying treatment options and, in this sense, a significant body of research has demonstrated the potential co-adjuvant effect of physical activity, and particularly physical exercise (American College of Sports Medicine, 2021; Izquierdo, Merchant, et al., 2021; Livingston et al., 2020). But the field of research on physical exercise interventions for individuals already diagnosed with major NCD is relatively recent (Forbes et al., 2015; Heyn et al., 2004; Skinner et al., 2018; Sofi et al., 2010), particularly when considering the multicomponent training (MT) methodology (Hernandez et al., 2015; Hong, 2018; Perrochon et al., 2015; Prick et al., 2017; Suzuki et al., 2013). Previous studies showed that MT programs (i.e., combining cardiorespiratory endurance, strength and balance training) are feasible and well-tolerated (Borges-Machado et al., 2019; Hernandez et al., 2015), but further evidence is still needed on the beneficial impact in older people with major NCD.

This work is presented in 10 chapters. **Chapter 1** presents an overview of NCD definition, diagnostic criteria and symptoms, main subtypes, epidemiological data, risk and prognostic factors and global impact, with a focus on post-diagnostic treatment, care, and support. This chapter also reflects on the effect of sedentarism, physical (in-)activity, and physical exercise in preventing and delaying the progression of NCD; it also outlines the role of physical exercise as a co-adjuvant therapeutic approach for major NCD management, particularly using MT methodology. **Chapter 2** includes the thesis' primary and secondary objectives. **Chapter 3** provides a description of the thesis' design and setting, methodology and COVID-19 contingency plan. **Chapter 4** includes a *systematic review* which synthesizes the existing evidence about the effects of MT on physical fitness, cognition, and ADL independence, and identifies moderation patterns of those effects regarding FITT variables. **Chapter 5** includes the *original study I* and demonstrates the effects of a 6-month MT intervention on functional capacity (e.g., lower body function, mobility, and gait speed) and ADL independence in older adults with NCD; the chapter also includes a study exploring the impact of the same intervention on cognitive function, neuropsychiatric symptoms, and quality of life (*original study II*). **Chapter 6** includes a cross-sectional study on the association between health-related physical indicators and self-rated quality of life in older adults with NCD (*original study III*). **Chapter 7** includes two qualitative studies that demonstrate the factors that influence individuals' adherence to a community-based physical exercise intervention. The main research findings and limitations are integrated and discussed in **Chapter 8**. Finally, **Chapters 9** and **10** grant the recommendations for future research and clinical practice, and main conclusions, respectively.

PART I – State of Art

Chapter 1. Background

This chapter provides an overview of the definition, diagnostic criteria, symptoms, severity, and main subtypes of neurocognitive disorders (NCD). Epidemiological data is presented, along with risk and prognostic factors, highlighting international and national scenarios. This chapter also offers an insight into the literature regarding the global impacts of major NCD, and (non-) pharmacological treatments available, reflecting on the impact of sedentarism, physical (in-)activity and physical exercise in preventing cognitive decline, minor and major NCD, and delaying the progression of NCD. Specifically, it focuses on the co-adjuvant role of physical exercise after major NCD diagnosis, particularly considering the multicomponent training (MT) methodology.

1.1 Neurocognitive Disorder

1.1.1 Definition, diagnostic criteria, and symptomatology

For decades now that dementia has been defined as an acquired loss of two or more cognitive abilities (often memory with at least one other domain) caused by injury or multiple brain diseases, usually of chronic or progressive nature (Arvanitakis et al., 2019; McKhann et al., 1984; McKhann et al., 2011; World Health Organization, 2016). The *International Classification of Diseases and Related Health Problems – 10th Revision* (ICD-10)[1] (World Health Organization, 2016) dementia categorization has been used in clinical practice for years, and despite the new classification ("Neurocognitive Disorders") in the *11th Revision* (ICD-11) (World Health Organization, 2022), it is still characterized by the presence of marked impairment in two or more cognitive domains, but not restricted to memory. However, recent changes in the *Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition* (DSM-5) (American

[1] It matters to highlight that at the time of this thesis planning and development, the ICD-11 hadn't been released.

Psychiatric Association, 2013) have recognized that this syndrome may be diagnosed in case of marked impairment in a single cognitive domain (Arvanitakis et al., 2019). Apart from other differences (e.g., subsection replacement and revision on the mild cognitive impairment [MCI] definition) (Sachs-Ericsson & Blazer, 2015) this alteration has brought significant changes to dementia classification and diagnosis, and, for this reason, this newest edition of the DSM guided the theoretical framework of the present thesis. One of its major changes concerns the use of the term “major NCD” in place of “dementia”, and “mild NCD” instead of “MCI” (American Psychiatric Association, 2013; Sachs-Ericsson & Blazer, 2015).

Specifically, the DSM-5 NCD category encompasses the group of acquired disorders in which the primary clinical deficit is in the cognitive function (American Psychiatric Association, 2013). The core diagnostic feature of NCD is evidence of a decline (significant if major NCD or modest if mild NCD) from a previous level of performance in one or more cognitive domains (i.e., complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on both (Criterion A): 1) concern of the individual, a knowledgeable informant, or the clinician; and 2) substantial or modest impairment (in case of major or mild NCD, respectively) in cognitive performance objectively measured or clinically quantified. Criterion B relates to the individual’s ability to independently perform activities of daily living (ADL), in which individuals with major NCD require assistance, at least with complex instrumental ADL, since the cognitive deficits interferes with daily functioning. Individuals with mild NCD may need more time, effort, or compensatory strategies to complete complex instrumental ADL, but the cognitive deficits do not interfere with their capacity to independently perform everyday activities. Lastly, diagnostic criteria C and D specify that the cognitive deficits (both in case of major or mild NCD) do not occur exclusively in the context of a *delirium* and are not better explained by another mental disorders (e.g., major depressive disorder, schizophrenia) (American Psychiatric Association, 2013).

Major and mild NCD are primarily subtyped according to the known (or presumed) etiological or pathological entity (or entities) underlying the cognitive decline (e.g., neurological, or medical condition that affects the brain, trauma, nutritional deficiency, chronic use of specific substances or medications, or exposure to heavy metals or other toxins). In this regard, the combination of several diagnostic features, such as time course, associated behavioral and functional symptoms, and characteristic domains affected, enable clinicians to distinguish subtypes from each other (i.e., due to frontotemporal lobar degeneration, traumatic brain injury, Parkinson's disease, Huntington's disease, prion disease, or multiple etiologies) (American Psychiatric Association, 2013).

As described in the DSM-5, along with etiological subtype specification, clinicians should specify if the cognitive decline is accompanied or not by clinically significant behavioral disturbances (e.g., psychotic symptoms, mood disturbances, agitation, apathy or other behavioral symptoms) and current severity (i.e., mild, moderate or severe) (American Psychiatric Association, 2013). As a matter of fact, evidence for distinct behavioral specifiers in NCD have been described, particularly in the areas of psychotic symptoms and depression. Psychotic disorders are common in a wide variety of NCD: at the mild-to-moderate stage of major NCD due to Lewy body disease, Alzheimer's disease and frontotemporal lobar degeneration. Paranoia, visual hallucinations, and other delusions are also common features of NCD. Depression may occur in early stages of mild or major NCD due to Alzheimer's disease and Parkinson's disease as an emotional reaction to the diagnosis. In addition, early during NCD, apathy may be observed as result of loss of motivation to conduct daily activities or hobbies. Other mood disturbances like anxiety and elation may also be present. Agitation, characterized as disruptive motor or vocal activity, tends to arise at moderate-to-severe stages of major NCD, and may occur in the setting of frustration or confusion, or as a combative behavior. Other behavioral symptoms as wandering, verbal, or sexual disinhibition, hyperphagia, hoarding, and sleep disturbances (e.g., insomnia, hypersomnia, and circadian rhythm alterations) may also need clinical attention (American Psychiatric Association, 2013; Cloak & Al Khalili, 2022). In addition, diagnostic biomarkers may come into play in the assessment of specific etiological subtypes, particularly blood-based laboratory tests and/or neuroimaging scans, such as positron emission tomography (PET) and magnetic resonance imaging (MRI) (American Psychiatric Association, 2013; Arvanitakis et al., 2019), for example, to study the amyloid beta-42 deposition in Alzheimer’s disease.

Notwithstanding, as highlighted in DSM-5, it becomes harder to differentiate among NCD subtypes because there are multiple potential sources of neurocognitive decline, as result of the increased prevalence of medical illness and sensory deficits as one ages. Like age, living situation, sociocultural norms, and occupation issues, individuals’ sex may affect the level of awareness and concern of cognitive and behavioral symptoms which, in turn, may complicate diagnosis or treatment (e.g., females that are older have more comorbidities) (American Psychiatric Association, 2013; Livingston et al., 2020). As it will be addressed in the following sections, there are also sex differences in the incidence of some NCD subtypes (American Psychiatric Association, 2013).

1.1.2 Severity and subtypes

The development and course of NCD varies across etiological subtypes, since some begin at a specific time and remain static (e.g., related to traumatic brain injury or stroke) and others may fluctuate over time (e.g., months or years) (American Psychiatric Association, 2013; Arvanitakis et al., 2019; Gale et al., 2018). As presented in **Table 1**, NCD due to neurodegenerative diseases like frontotemporal lobar degeneration or Alzheimer’s disease are typically marked by insidious onset and gradual progression, and these patterns of onset and progression of cognitive deficits and associated features are useful in differential diagnosis (American Psychiatric Association, 2013). Complementarily to diagnostic criteria information, it matters to outline some particularities and associated features of the more prevalent subtypes (i.e., due to Alzheimer’s disease, vascular disease, frontotemporal lobar degeneration, Lewy bodies disease, Parkinson’s disease, and multiple etiologies).

Table 1. Diagnostic criteria of the most prevalent NCD subtypes according to DSM-5

<table>
<tr><th colspan="5">Alzheimer's disease</th><th>Frontotemporal degeneration [c]</th><th>Lewy bodies disease [d]</th><th>Vascular disease [e]</th><th>Parkinson's disease [f]</th><th>Multiple etiologies</th></tr>
<tr><td>A</td><td colspan="9">The criteria are met for major or mild NCD</td></tr>
<tr><td>B</td><td colspan="4">Insidious onset and gradual progression of impairment (at least two domains for major NCD)</td><td>Insidious onset and gradual progression</td><td>Insidious onset and gradual progression</td><td>Clinical features are consistent with a vascular etiology, as suggested by either of the following:

1. Onset of the cognitive deficits is temporally related to cerebrovascular event

2. Prominent decline in complex attention (including processing speed) and frontal-executive function</td><td>The disturbance occurs in the setting of established PD</td><td>Evidence from the clinical history, physical examination, or laboratory findings that the NCD is a pathophysiological consequence of more than one etiological process, excluding substances</td></tr>
<tr><td rowspan="3">C</td><td colspan="4">Criteria are met for:</td><td>Either (1) or (2):</td><td>Combination of core and suggestive diagnostic features for either probable or possible NCD:</td><td rowspan="3">Evidence of the presence of cerebrovascular disease (from history, physical examination and/or neuroimaging), considered sufficient to account for the neurocognitive deficits</td><td rowspan="3">There is insidious onset and gradual progression of impairment</td><td rowspan="3">The cognitive deficits are not better explained by another mental disorder and do not occur exclusively during the course of a delirium</td></tr>
<tr><td colspan="2">Major NCD[a]</td><td colspan="2">Mild NCD[b]</td><td rowspan="2">1. Behavioral variant:

a) Three or more symptoms:
i. Behavioral disinhibition
ii. Apathy or inertia
iii. Loss of sympathy or empathy
iv. Perseverative, stereotyped or compulsive/ritualistic behavior
v. Hyperorality and dietary changes

b) Prominent decline in social cognition and/r executive abilities</td><td rowspan="2">1. Core diagnostic features:

a) Fluctuation cognition with pronounced variations in alertness and attention

b) Visual hallucinations (recurrent) that are well detailed and formed

c) Spontaneous features of parkinsonism (onset after the development of cognitive decline)</td></tr>
<tr><td>Probable</td><td>Possible</td><td>Probable</td><td>Possible</td></tr>
</table>

	1.Evidence of a causative AD genetic mutation 2. All three are present: a) Clear evidence of decline in memory, learning and (at least) one other cognitive domain b) Steadily progressive, gradual decline in cognition without extended plateaus c) No evidence of mixed etiology	1.Evidence of decline in memory and learning 2.Steadily progressive, gradual decline in cognition without extended plateaus 3. No evidence of mixed etiology	2. Language variant: a) Prominent decline in language ability (speech production, word finding, object naming, grammar, or word comprehension)	2. Suggestive diagnostic features: a) Rapid eye movement sleep behavior disorder b) Severe neuroleptic sensitivity			
D	The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance or another disorder (mental, neurological, or systemic)		Relative sparing of learning and memory and perceptual-motor function	The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance or another disorder (mental, neurological, or systemic)	The symptoms are not better explained by another brain disease or systemic disorder	The NCD is not attributable to another medical condition, and is not better explained by another mental disorder	N/A
E	N/A		The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance or another disorder (mental, neurological, or systemic)	N/A	N/A	N/A	N/A

a – Probable AD is diagnosed if either one of the two following is present; otherwise, possible AD should be diagnosed. b – Probable AD is diagnosed if there is evidence of a causative AD genetic mutation (genetic testing or family history); otherwise, possible AD should be diagnosed if all three criteria are present. c – Probable frontotemporal NCD is diagnosed if either of the following is present (evidence of causative genetic mutation or evidence of disproportionate frontal and/or temporal lobe involvement); otherwise, possible frontotemporal NCD should be diagnosed (no evidence of genetic mutation, and neuroimaging has not been performed). d – For probable major or mild NCD with Lewy bodies, the individual presents one suggestive feature and one or more core features, or two core features only; for possible major or mild NCD with Lewy bodies, the individual has only one core feature, or one or more suggestive features. e – Probable vascular NCD is diagnosed if one of the following is present (clinical criteria are neuroimaging-supported, or neurocognitive syndrome is temporally related to one or more documented cerebrovascular events, or both clinical and genetic evidence of cerebrovascular disease is present); otherwise, possible vascular NCD should be diagnosed. f – Major or mild NCD probably due to PD should be diagnosed if both of the following are present (no evidence of mixed etiology, and the PD clearly precedes the onset of the NCD); otherwise, major or mild NCD possibly due to PD should be diagnosed if one of the two previous criterion is met. AD – Alzheimer's Disease; N/A – Not Applicable; NCD – Neurocognitive Disorder; PD – Parkinson's Disease. Note: Table content was adapted from DSM-5 – Section II, Diagnostic Criteria and Codes, Neurocognitive Disorders, pages 591 to 643 (American Psychiatric Association, 2013)

The onset of symptoms of Alzheimer's disease usually appears in the eighth and ninth decades of life, accounting for 60 to 90% of all cases worldwide, depending on the setting and diagnostic criteria (American Psychiatric Association, 2013). Early-onset forms, in which symptoms emerge before the age of 65 years, represent less than 5% of all cases, and are often related to known causative genetic mutations (American Psychiatric Association, 2013; Gale et al., 2018). Individuals at severe stages are eventually bedbound and mute; however, this may be a consequence of advanced age and associated comorbidities rather than the course and management of the disease. At the moderately severe stages of major NCD, psychotic features, agitation, combativeness, irritability, and wandering are common, and only at late stages in the disease, the gait disturbances, dysphagia, incontinence, myoclonus, and seizures are observed (American Psychiatric Association, 2013). Nevertheless, procedural memory (e.g., dancing, play musical instruments) and social functioning may be relatively preserved for extended periods (American Psychiatric Association, 2013; Arvanitakis et al., 2019).

Major or mild frontotemporal NCD is gradually progressive, and its onset usually occurs in the sixth decade of life and, for this reason, often negatively affects family life and workplace. Even though the criteria must be met for either the behavioral or the language variant to make the diagnosis, given the distinct patterns of brain atrophy and neuropathology, many individuals present features of both variants. The functional impairment due to behavioral changes and language dysfunction (e.g., socially inappropriate behaviors, hyperorality, impulsive wandering) may lead to premature institutionalization (American Psychiatric Association, 2013; Arvanitakis et al., 2019). Extrapyramidal features may be prominent in some cases, as well as motor neuron disease (e.g., muscle atrophy, weakness) (American Psychiatric Association, 2013; Gale et al., 2018).

Lewy bodies disease is characterized by fluctuations in levels of alertness and cognition. The gradual progression of deficits in complex attention and executive function (over months or years, with occasional plateaus) is manifested early in the course of the disorder, at least a year before the onset of parkinsonism, typically observed from the sixth decade of life (American Psychiatric Association, 2013; Gale et al., 2018). Recurrent falls and syncope, episodes of loss of consciousness (transient and unexplained), orthostatic hypotension and urinary incontinence may be observed in individuals with major or mild NCD due to Lewy bodies. Also, bradykinesia, rigidity, stooped posture, and slow and shuffling gait may be associated with parkinsonism. Hallucinations (visual, auditory, and nonvisual), systematized delusions, and delusional misidentification are common, as well as depression. Moreover, the motor and autonomic impairments may also cause problems with transferring, eating, and sleeping and, therefore, affect individuals' daily functionality and quality of life (American Psychiatric Association, 2013; Arvanitakis et al., 2019).

Cerebrovascular disease etiology may vary from large vessel stroke to microvascular disease and affect different extensions and locations of the brain (e.g., focal, multifocal, or diffuse). Therefore, some individuals with major or mild vascular NCD may present an acute stepwise or fluctuating decline in cognition and even show partial improvements and periods of stability. Conversely, other patients may have gradual onset and slow progression, punctuated by acute events that lead to a rapid development of deficits followed by relative stability (American Psychiatric Association, 2013; Arvanitakis et al., 2019). Emotional lability, depression, abulia, personality and mood changes are commonly associated with this disorder. Major or mild vascular NCD prevalence increases exponentially in individuals aged 65 years and older and are commonly associated with physical deficits that increase disability and dependency levels (American Psychiatric Association, 2013; Arvanitakis et al., 2019).

Parkinson's disease onset typically occurs between the sixth and the ninth decades, and its more prevalent in males (American Psychiatric Association, 2013). Common behavioral features include apathy, depressed and anxious moods, hallucinations, delusions, personality changes, and sleep disturbances (e.g., rapid eye movement and excessive daytime sleepiness). The multiple pathological features – particularly in older individuals – the co-occurrence of mood disturbances (depression or apathy) and the associated motor symptoms may diminish individuals' functional abilities (American Psychiatric Association, 2013; Gale et al., 2018).

Lastly, the diagnosis of multiple etiologies is given when there is evidence that several medical conditions have played a probable role in the development of the NCD (American Psychiatric Association, 2013). The category "unspecified NCD" is used in situations in which the symptoms characteristic of NCD are present but do not fully meet any of the diagnostic criteria, and for this reason, a precise etiology cannot be determined (American Psychiatric Association, 2013).

Some subtypes occur exclusively or primarily in late life, whereas others are distributed throughout the lifespan. The prevalence of NCD varies widely by geographic regions and etiological subtype, and among individuals aged 60 years and more, the prevalence increases steeply with age (American Psychiatric Association, 2013; Livingston et al., 2020). Predictions about future trends in dementia prevalence suggest substantial increases in overall prevalence related to aging population (Livingston et al., 2020).

1.1.3 Epidemiology

Today, more than 55.2 million people worldwide are diagnosed with dementia[2], and it is estimated that in 2030 there will be around 78 million (Gauthier et al., 2021; World Health Organization, 2021b). More importantly, according to a recent report of the Alzheimer's Disease International (ADI), these numbers are underestimated due to the lack of awareness about the signs and symptoms of the disease, geographical and cultural biases, and lack of access to trained clinicians and resources (Gauthier et al., 2021).

[2]As mentioned in the DSM-5, the term dementia is subsumed under the newly named entity major NCD and may be used in settings where physicians and patients are knowledgeable of this term. In the present thesis, the terms MCI and dementia referring to, respectively, mild, and major NCD, will be used interchangeably and whenever mentioned by the consulted bibliography.

Dementia is the greatest global challenge for health and social care in the 21st century, representing one of the leading causes of care dependency and disability in old age, both in high-income countries (HIC) and low-and-middle income countries (LMIC) (Livingston et al., 2017; OECD, 2021a; World Health Organization, 2021b). In what concerns the disease burden, dementia is among the top ten causes of years of healthy life lost due to disability (YLDs) in people aged 60 years and older. When considering all ages, dementia is the twenty-fifth leading cause of disability-adjusted life years (DALYs) (World Health Organization, 2021b), disproportionally affecting women.

Considered as the seventh leading cause of death in 2019, dementia is one of the most common neurological disorders, mainly affecting older adults (World Health Organization, 2021b). After the World Health Organization (WHO) Western Pacific Region (20.1 million), the European Region has the second highest number (14.1 million) of people with dementia, followed by the Region of the Americas with 10.3 million people (World Health Organization, 2021b). Across the six WHO regions, and globally, the prevalence of dementia is higher among women, probably due to potential biological reasons, differential exposure to protective and risk factors across the life course, and longer life expectancy, among other factors (World Health Organization, 2021b).

A recent study conducted by the *Global Burden of Diseases, Injuries and Risk Factors Study* (GBD) showed comprehensive country-level estimations of dementia prevalence, considering the projected trends in exposure to known dementia modifiable risk factors (GBD 2019 Dementia Forecasting Collaborators, 2022). According to this study projections, in most regions, increases in age-standardized dementia prevalence due to rises in the prevalence of GBD risk factors (i.e., body mass index, fasting plasma glucose and smoking) were counterbalanced with decreases in age-standardized prevalence due to rises in average educational attainment. In other words, this study's results reinforce efforts should be made to alter the expected trends in risk factors prevalence to observe larger changes in age-specific dementia prevalence. Finally, findings also suggest that population aging will lead to 2.7 times more dementia cases globally than in 2019, being estimated that in 2050 there will be 152.8 million people with dementia worldwide. Of these, 351 504 cases will be in Portugal (GBD 2019 Dementia Forecasting Collaborators, 2022).

Like in other countries, epidemiological data on the prevalence of dementia and MCI in Portugal is limited (Alzheimer Europe, 2019; Gonçalves-Pereira et al., 2021). Results from two different studies conducted by Nunes et al. (2010) and Ruano et al. (2019), including individuals aged 55 or more years from urban areas in the north of Portugal revealed similar data on dementia prevalence: 1.6% and 1.3%, respectively. In both studies, vascular disease contributed to a significant number of cases. In contrast, following the *10/66 Dementia Research Group*, Gonçalves-Pereira et al. (2017) determined a dementia prevalence rate of 4.35% in community-dwelling older adults from an urban site in the southern area of Portugal (according to DSM-IV-TR criteria), being Alzheimer's Disease the most frequent cause. Despite the methodological differences and the heterogenic results, these studies' findings highlight that further research is needed to appropriately determine the prevalence and incidence of major and mild NCDs in Portugal (Alzheimer Europe, 2019; Direcção-Geral da Saúde, 2016; Gonçalves-Pereira et al., 2021; OECD, 2021a; Santana et al., 2015). This gap has also been identified in 2018 and recognized as a priority for the definition of a health plan for dementia in Portugal (Diário da República, 2ª Serie, n.º 116, 19th June). Moreover, given the higher burden of vascular and cerebrovascular diseases, particularly in the northern region (OECD, 2021a, 2021b), and the potential significant contribution that these diseases may have in the epidemiology of cognitive impairment among the Portuguese population, efforts should be made regarding their prevention and management.

With the rising prevalence and absence of neuroprotective pharmaceutical treatments, there is an emergent need to focus on strategies that may prevent and/or delay the progression of cognitive decline and dementia (Alty et al., 2020; Livingston et al., 2020). As alleged by the Alzheimer's Association (2021), several groups of researchers have estimated the potential impact of cost savings of future interventions that either slow the onset of dementia or reduce the symptoms. Therefore, the understanding of risk and prognostic factors, as well of protective factors (e.g., physical activity), is determinant to reduce the global burden of dementia (World Health Organization, 2019, 2021b).

1.1.4 Risk and prognostic factors

Age is the strongest risk factor for major and mild NCD, due to the increased risk of neurodegenerative and cerebrovascular diseases. Nonetheless, risk factors vary between sexes (Gauthier et al., 2021; World Health Organization, 2019), etiological subtypes and, also, by age at onset within etiological subtypes (American Psychiatric Association, 2013). Other non-modifiable risk factors include gene polymorphisms, race/ethnicity and family history (World Health Organization, 2017, 2019). Overall, the female sex is associated with a higher prevalence of major NCD, greatly attributable to a longer lifespan (American Psychiatric Association, 2013). Over the last decades, several studies have shown a relationship between the development of MCI and dementia with several modifiable risk factors, which are potentially to be targeted for the prevention of dementia, and/or delay of the progression of cognitive decline (Alzheimer's Disease International, 2015; Livingston et al., 2017; World Health Organization, 2019).

The 2020 *Lancet Commission* report on dementia prevention, intervention and care highlighted 12 potentially modifiable risk factors that together, if addressed, might prevent, or delay up to 40% of dementia cases worldwide (Livingston et al., 2020). From early life (i.e., low education), to midlife (i.e., hypertension, obesity, hearing impairment, traumatic brain injury, excessive alcohol consumption) and later life (i.e., smoking, depression, physical inactivity, social isolation, diabetes, air pollution), these factors influence individuals' cognitive reserve and trigger neuropathological developments (e.g., amyloid or tau-mediated, vascular or inflammatory) (Livingston et al., 2020). Evidence suggests that some of the late-life factors, such as depression, physical inactivity and social isolation might have a bidirectional impact and, therefore, are also part of the prodrome stages of dementia. On the other hand, there are still controversies whether sleep disturbances and nutrition and dietary components might have a direct impact on dementia neuropathology (Livingston et al., 2020; Sabbagh et al., 2022). Although the etiology of dementia is still shifting, and not all dementia subtypes are preventable, as recommended by Livingston et al. (2020), population-wide and individually targeted interventions are necessary – particularly at LMIC – to counteract the rising prevalence of dementia or, at least, to delay its onset or progression.

About 10 years ago, dementia was identified by the WHO as a public health priority (World Health Organization, 2012). In 2017, the same entity published the *Global Action Plan on the Public Health Response to Dementia 2017-2025* with the goal to improve the lives of individuals living with dementia, their caregivers and families, and decrease the impact of dementia on them as well as on communities and countries (World Health Organization, 2017). In this sense, in 2019, the WHO established risk reduction guidelines for cognitive decline and dementia in order to support health and social care professionals to provide evidence-based, multisectoral, sex and culturally appropriated interventions to general population, targeting the modifiable dementia risk factors that are shared with other noncommunicable diseases (e.g., physical activity and cognitive interventions, cardiovascular risk factors management as excessive weight, hypertension, diabetes mellitus and dyslipidemia) (World Health Organization, 2019).

According to the *Global Dementia Observatory* (GDO) data, only 35 countries (out of 62) reported having a dementia risk reduction plan or guidelines and, of these, over 70% are HIC and most are in the European Region (not including Portugal). Of the 28 GDO countries reporting risk reduction campaigns by television, radio, or social media, most of them are HIC with just 8 LMIC. In result, worldwide population awareness of the possibility of dementia risk reduction is limited, requiring greater efforts in population-level health education and awareness (World Health Organization, 2021b).

After the diagnosis, people living with dementia should have access to “person-centered, rights-based health and social services, when and where they need it, without financial hardship” (World Health Organization, 2021b, p. 141). But, the complex care needs, and the high levels of dependency and morbidity are associated with tremendous societal costs attributed to several direct and indirect factors like medical care, social care and informal care (World Health Organization, 2021b).

1.1.5 Impacts of major NCD: global costs and informal caregiving

The global costs of dementia, in 2019, were estimated to be 1.3 trillion U.S. dollars, and although most people with dementia live in LMIC, nearly 75% of these costs occurred in HIC. Globally, and particularly in LMIC, a significant portion of the dementia care costs are attributable to informal care, reflecting the lack or scarcity of available formal resources and, consequently, placing a heavy burden on families and caregivers (World Health Organization, 2021b).

As the population ages and the number of people being diagnosed with dementia increases, so does the number of individuals who find themselves in the role of caregivers, frequently without the training or knowledge to manage the condition and provide appropriate care (Gauthier et al., 2021; GBD 2019 Dementia Forecasting Collaborators, 2022). Recent reports from the WHO Member States showed that informal caregivers, in 2019, provided over 89 billion hours of care when only accounting the time dedicated to ADL support, this amount of time would increase to approximately 133 billion hours if considering the time dedicated to supervision (World Health Organization, 2021b). As identified by the WHO, caregiving also disproportionately affects women, who contribute to approximately 70% of the global hours of informal care, especially in LMIC (Alzheimer's Association, 2021; Alzheimer's Disease International, 2022; World Health Organization, 2021b).

Results from a cross-sectional study conducted in Portugal on the cost of informal caregiving in dementia, confirmed a well-known profile of informal caregivers (female, aged between 45 and 65 years old, living with care-receivers, with low educational level, and low income) and revealed a total cost of €619.8/per month for each dyad, representing 77.5% of their monthly income and, in consequence, possibly limiting the continuum of care at home (Pires et al., 2020). More recently, another national study estimated the disease burden and societal costs associated with Alzheimer's disease in people aged ≥ 65 years and revealed that the non-medical direct costs corresponded to 1.8 billion (including €1.1 billion attributed to informal care) (Costa et al., 2021).

Reliable data on the numerical extent of informal caregivers in Portugal is still missing. Nevertheless, a recent survey conducted by a national association (*Movimento Cuidar dos Cuidados Informais*) estimated the existence of 1.4 million caregivers, a number that is higher than a previous estimation of 800 thousand people (Eurocarers, 2021). Even though the informal caregiver status has been approved by law (Portuguese ministerial order n.º256/2020, 28th October; Law n.º 100/2019), and implemented throughout the country (Implementing Decree-Law n.º 1/2022, 10th January) these legislations and policies have not yet reflected an additional availability and/or generalized utilization of care services and support (Alves et al., 2020; OECD, 2021a; World Health Organization, 2021b).

Informal caregivers of individuals diagnosed with dementia, also referred as the "invisible patients", are at increased risk for burden and psychological morbidity (e.g., distress, anxiety, depression, burnout), social isolation, financial hardship, and a variety of other physical health complications (Alzheimer's Association, 2021; Barbosa et al., 2020; Brodaty & Donkin, 2009; Kaddour & Kishita, 2020). Particularly those experiencing significant mental and emotional strain may be at higher risk for death (Alzheimer's Association, 2021; Schulz & Beach, 1999). As suggested by a recent meta-analysis review, burden is prevalent in nearly 50% of caregivers and almost one-third of them experiences depression (Collins & Kishita, 2020). While several studies report the positive psychological aspects of caregiving, such as gaining a purpose in life, sense of meaning and personal growth or accomplishment, enjoyment, self-efficacy, companionship, and satisfaction for providing quality of life to a family member (Ribeiro et al., 2020; Yu et al., 2018), a larger number highlight the causal negative effect of caregiving on both mental and physical health (Alzheimer's Association, 2021; Bom et al., 2019), and the presence of negative emotions like resentment, sadness, fear, guilt and anticipated grief (Brodaty & Donkin, 2009; Lindeza et al., 2020). Despite the wealth of literature about the reciprocal influence that caregiving dyads have on each other's health, well-being and quality of life (Alzheimer's Association, 2021; Brodaty & Donkin, 2009), research is still required with respect to post-diagnostic support to caregivers and care-receivers (World Health Organization, 2021b).

As documented by WHO, multidisciplinary and multi-component care models for dementia may involve a range of services from within and outside the health sector (e.g., specialist medical care, rehabilitation) (World Health Organization, 2021b). According to the WHO's model of integrated dementia care, the needs and preferences of individuals living with dementia must be met, and their dignity and autonomy respected from the diagnosis to the end of life, through integrated, person-centered, culturally appropriated, affordable, community-based health, psychosocial, long-term care and support and, where appropriate, including the inputs of families and caregivers (Alzheimer's Disease International, 2022; World Health Organization, 2021b). It is for these reasons necessary to ensure that individuals with dementia and caregivers have access to evidence-based interventions conducted in community settings and in combination with adequate pharmacological treatments.

1.1.6 Post-diagnostic treatment, care, and support

People living with dementia have complex care needs and present high levels of dependency and morbidity in more advanced stages (World Health Organization, 2021b). Interventions targeting these individuals need to consider the different symptoms (e.g., neuropsychiatric symptoms/behavioral and psychological symptoms of dementia [BPSD], cognitive impairment, ADL dependency, and comorbid physical illnesses) and attend their psychological, cognitive, medical, and social needs throughout the disease course (Livingston et al., 2017).

Presently, the only approved drug treatments for dementia do not modify its underlying neuropathology or progression. Cholinesterase inhibitors (i.e., galantamine, rivastigmine and donepezil) might partly restore the deficit in acetylcholine arising as result of neuronal loss, whereas memantine might attenuate the toxic effects of glutamate released from degenerating neurons; nevertheless, these effects are not curative and only temporally mitigate some symptoms (Alzheimer's Association, 2021; Dyer et al., 2018; Livingston et al., 2020; Livingston et al., 2017). In overall, cholinesterase inhibitors have a small but clinically important effect on cognition and daily functionality in people with Alzheimer's disease from mild to severe stages, while memantine has a smaller beneficial effect on cognition in the moderate to severe stages (Livingston et al., 2020; Livingston et al., 2017). Aside from Alzheimer's disease, few other NCD subtypes have approved pharmacologic therapies for cognitive symptoms, and no specific treatment exists for frontotemporal dementia and Lewy bodies disease (Arvanitakis et al., 2019; Livingston et al., 2017).

Even though cholinesterase inhibitors are well tolerated, adverse effects, such as gastrointestinal effects (e.g., nausea, diarrhea, and vomiting), vivid dreams and leg cramps may occur (Livingston et al., 2017). Headaches and constipation have been reported as adverse effects of memantine (Arvanitakis et al., 2019). More recently, Aducanumab has received an accelerated approval pathway by the U.S. Food and Drug Administration (FDA) as the only therapy that may potentially slow the progression of Alzheimer's disease (Alzheimer's Assocation, 2021). This amyloid beta-directed antibody is the first pharmacological treatment to address the underlying biology of the disease, which is reasonably likely to mitigate the cognitive and functional declines in individuals living with early Alzheimer's disease or MCI and, therefore, allow individuals to hold on to memories longer and sustain their independence. Notwithstanding, if the sponsor (Biogen Inc, *Aduhelm*) cannot verify its clinical benefit in a post-approval trial, FDA may withdraw the approval. In turn, the European Medicines Agency (EMA) has recently recommended the refusal of the marketing authorization for *Aduhelm* in the European Union (European Medicines Agency, 2022).

As for the BPSD, to date, no drug treatment specifically targeting them has been approved by the FDA (Alzheimer's Association, 2021; Arvanitakis et al., 2019; Livingston et al., 2020). The BPSD cause substantial distress for both caregivers and individuals with dementia, negatively affecting their quality of life (Alzheimer's Association, 2021; Livingston et al., 2020; Livingston et al., 2017; Park et al., 2022). Increasing evidence advocates the need for a careful assessment of symptoms and potential multifactorial causes (e.g., personal history, unmet needs, medical episodes and comorbidities, environment, disease type and stage), to appropriately manage these syndromes (Gauthier et al., 2021; Livingston et al., 2020). Non-pharmacological approaches seem to have similar effect sizes to pharmacological therapies and, more importantly, with a lower risk of adverse events (Banerjee et al., 2021; Dyer et al., 2018). For this reason, non-pharmacological interventions may be considered as first line interventions to manage BPSD and improve patients' ability to function in everyday life.

Numerous studies have examined the potential of pharmacological and non-pharmacological treatment to prevent, delay or reverse the course of dementia. Unfortunately, most pharmaceutical approaches have met with limited clinical success (Banerjee et al., 2021; Dyer et al., 2018). Because of this, non-pharmacological therapies like physical activity or physical exercise interventions have been increasingly recognized by the scientific community (e.g., in comparison with cognitive training and rehabilitation) due to their potential to alter the trajectory of the disease course, and due to their holistic effect on other conditions that often co-occur with dementia (e.g., hypertension and type 2 diabetes mellitus) (Alanko et al., 2022; Alzheimer's Association, 2021; Blondell et al., 2014; Erickson et al., 2012; Livingston et al., 2020).

The following sections will present results from observational (or prospective) studies that assessed the longitudinal risk for dementia, MCI or cognitive decline considering levels of physical activity, leisure activities and physical exercise behaviors and, additionally, the results from structured physical exercise programs often used in clinical trials to examine whether physical exercise could be used as an effective treatment. The differences between the concepts of physical activity and physical exercise will also be addressed.

1.2 Physical Activity, Physical Exercise and NCD

1.2.1 Prevention of cognitive decline, minor and major NCD: the role of physical (in-)activity and physical exercise

Physical activity is defined as “any movement produced by skeletal muscles that results in energy expenditure exceeding the resting state” (Caspersen et al., 1985, p.126). In turn, physical exercise, is a “subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness” (Caspersen et al., 1985, p.126). A growing body of evidence has been focusing on defining threshold and optimal levels and modalities of physical activity and physical exercise that are necessary for health promotion and diseases management (e.g., minor and major NCD) (Izquierdo, Duque, et al., 2021; Izquierdo, Merchant, et al., 2021).

According to Sallis et al. (2016), physical inactivity is responsible for 3.8% of all cases of dementia worldwide. By contrast, evidence from longitudinal observational studies have shown an association between higher levels of physical activity and reduced risk of cognitive impairment and dementia (Blondell et al., 2014; Norton et al., 2014; Winblad et al., 2016).

Physical inactivity is currently considered as a pandemic, with nearly one-third of the adult population (under the age of 65) not meeting international recommendations (Cunningham et al., 2020; Fiuza-Luces et al., 2013; World Health Organization, 2018). Recently, Portugal was found to have the highest prevalence of physical inactivity (63.7%) among individuals aged 18-64 years old in a cross-sectional study including 28 European countries (Eurobarometer, 2018; Nikitara et al., 2021). Results from the 4th Wave of the *Survey of Health, Ageing and Retirement in Europe* (SHARE) database showed that the prevalence of physical inactivity among the Europeans (≥ 55 years) varied between countries, ranging from 5% in Sweden to 29% in Portugal (Gomes et al., 2017). Factors associated with inactivity included depression, increased age, physical limitations, and memory loss, among others (Gomes et al., 2017).

In parallel, and more specifically regarding physical exercise, data from the national report *Programa Nacional para a Promoção da Atividade Física* with data collected through a national health survey in 2019 (*Inquérito Nacional de Saúde)* showed that more than 73% of individuals aged 65 years and older did not exercise (at least for 10 minutes) for any day of the week (Direcção-Geral Da Saúde, 2020). These results are particularly alarming among women aged 85 years and older (91.7%) (Direcção-Geral Da Saúde, 2020), whose age group also presents the highest percentage of dementia cases (Gonçalves-Pereira et al., 2021).

A review study of systematic reviews and meta-analysis about the relationship between physical activity and cognitive decline reported a reduction of nearly 40% in the risk of cognitive decline for individuals aged ≥ 65 years that were highly physically active (Cunningham et al., 2020). According to the authors, evidence suggests a reduction in the risk of dementia ranging from 14% to 28% in healthy older adults, directly dependent of the physical activity levels and intensity. More importantly, physical activity seems to have a significant risk reduction effect (26%) on individuals aged 65 years and older for all-cause of dementia. Observations of the protective effect of physical activity were even greater when concerning Alzheimer's disease, since the relative risk reduction ranged from 32% to 42% when comparing individuals with higher vs. lower levels of physical activity (Cunningham et al., 2020). Also, based on prospective observations research designs with follow-up periods from one to 12 years, strong evidence confirmed that higher levels of physical activity are associated with a reduced risk of dementia, including Alzheimer's disease (Erickson et al., 2019).

Results from human studies have shown that during mid-life period, higher levels of physical activity are associated with greater preservation of cortical grey matter in older age (De la Rosa et al., 2020; Rovio et al., 2010; Skinner et al., 2018). Fortunately, it seems that late-onset physical exercise interventions also have a positive effect on the delay of brain aging (e.g., increasing hippocampal volume) (Erickson et al., 2019; Skinner et al., 2018).

Physical activity, and particularly physical exercise, is assumed to have a neuroprotective effect through several underlying physiologic mechanisms, such as increased cerebral blood flow, brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (IGF-1) concentrations, neurogenesis, and synaptic connections, and downregulation of neurotoxic factors (C-reactive protein, cortisol, insulin, interleukin-6) and other inflammatory cytokines, among others (Alty et al., 2020; Erickson et al., 2019; Erickson et al., 2014; Gholamnezhad et al., 2020; Kivipelto et al., 2018; Livingston et al., 2017; Skinner et al., 2018; Valenzuela et al., 2019). Also important, physical exercise has an additional indirect effect on brain health through reducing vascular disease risk (i.e., improving general cardiovascular fitness, controlling obesity, hypercholesterolemia or insulin resistance); likewise, it contributes in reducing social isolation, depression and sleep disturbance (Alty et al., 2020; Erickson et al., 2019; Erickson et al., 2014; Gholamnezhad et al., 2020; Izquierdo, Duque, et al., 2021; Kivipelto et al., 2018; Livingston et al., 2017; Skinner et al., 2018; Valenzuela et al., 2019; World Health Organization, 2019). The beneficial effect of physical activity on cognitive decline prevention seems to be mainly due to aerobic activities at moderate intensity, the most extensively used training methodology (Alty et al., 2020; De la Rosa et al., 2020; Gomes-Osman et al., 2018; Skinner et al., 2018; World Health Organization, 2019). Recent studies have shown the potential role of resistance training and mind-body exercises (e.g., tai-chi) too (Biazus-Sehn et al., 2020; Herold et al., 2019; Izquierdo, Merchant, et al., 2021).

Based on WHO guidelines for *Risk Reduction of Cognitive Decline and Dementia,* there is a strong recommendation on physical activity for adults with normal cognition to reduce the risk of cognitive decline (World Health Organization, 2019). Despite the available promising findings, further research is still needed to clarify the sex differences, the age ranges most affected, dose-response parameters, sensitive cognitive assessment methods, and brain biomarkers to better understand pathways leading to improvements in cognitive function (Alty et al., 2020; Erickson et al., 2019).

According to the ADI newest report, effective population-based risk reduction strategies require a multi-pronged approach, and there are a number of excellent initiatives around the globe (Alzheimer's Disease International, 2022). The World-Wide Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (WW-FINGERS) is the first global network of multidomain lifestyle intervention trials (i.e., dietary counselling, cognitive training, vascular and metabolic risk monitoring and physical exercise) for dementia risk reduction and prevention at different economic, geographical and cultural settings (Alzheimer's Disease International, 2022; Kivipelto et al., 2020). As highlighted by Kivipelto et al. (2020), preventive interventions should be tailored concerning the different NCD subtypes – and following the new diagnostic criteria – considering the entire continuum of disease, from at-risk asymptomatic to early-symptomatic stages, such as prodromal dementia. Fortunately, Portugal is now one of the newest additions to this network that already comprises over 45 countries across six continents (Alzheimer's Disease International, 2022).

1.2.2 After NCD diagnosis: feasibility and effects of physical activity and physical exercise

While there is supportive evidence that increased levels of general physical activity and physical exercise in cognitively healthy adults reduces the risk of cognitive impairment, all-cause dementia, vascular dementia, and Alzheimer’s disease when compared with inactive people, to date the evidence is diverse in that it may potentially slow down cognitive decline or improve cognition once MCI or dementia are established (Alty et al., 2020; de Souto Barreto et al., 2018; Erickson et al., 2019; Wahl et al., 2021; World Health Organization, 2019). Overall, low to moderate quality evidence has shown the small, but beneficial effect, of physical activity on cognition in people living with MCI, since the benefits overlap the undesirable effects. Therefore, based on the quality of evidence, a conditional recommendation was made by WHO for adults with MCI to increase their physical activity levels (World Health Organization, 2019).

Studies over the past decade have found that it is feasible to implement a physical exercise intervention in older adults with MCI, despite the early cognitive challenges (Begde et al., 2021; Ohman et al., 2014; Skinner et al., 2018). A growing body of evidence has also suggested that older adults with subjective cognitive complaints and with MCI may benefit from aerobic and/or resistance physical exercise interventions, due to their potential effect in delaying or preventing further cognitive decline into dementia (Demurtas et al., 2020; Skinner et al., 2018; Venegas-Sanabria et al., 2021; Zheng et al., 2016). For example, Suzuki et al. (2013) conducted a 6-month exercise program (bi-weekly, 90 minutes sessions) combining aerobic and muscle strength training, postural balance retraining and dual-task activities for older adults with MCI. Findings from this randomized controlled trial (RCT) showed that physical exercise benefits logical memory, maintains general cognitive function, and reduces whole brain cortical atrophy in people with MCI. Moreover, improvements of cognitive function were associated with lower total cholesterol levels and higher BDNF serum levels at baseline.

Similarly, an increasing number of studies have been investigating the role of physical exercise as a possible approach for counteracting/ managing the symptoms of dementia (Erickson et al., 2019; Skinner et al., 2018). Although results regarding the physical exercise effects on cognitive function are heterogenous (Erickson et al., 2019; Forbes et al., 2015; Gomes-Osman et al., 2018; Groot et al., 2016; Livingston et al., 2017), physical exercise interventions for people with dementia seem to be feasible and well tolerated (Forbes et al., 2015; Livingston et al., 2017; Skinner et al., 2018). Nevertheless, its therapeutic role as a co-adjuvant non-pharmacological strategy after dementia diagnosis requires further evidence (Cass, 2017; Farina et al., 2014; Li et al., 2019), particularly in what regards its effect on other outcomes rather than cognitive function, like functional capacity, physical fitness, neuropsychiatric symptomatology, and quality of life, as presented in the following subchapter.

1.2.3 Physical exercise as a co-adjuvant therapeutic approach for major NCD management

Dementia might begin decades before the stage of disease identified by subjects and their family (Livingston et al., 2017). The gradual decline of cognitive performance, along with the impaired ability to independently perform ADL, are characteristics of the disease progression that may also lead (or be exacerbated) by age-related physical function limitations (Hesseberg et al., 2016; Liu-Seifert et al., 2015). Also, individuals living with dementia may show increased declines on physical fitness abilities, namely impaired cardiorespiratory endurance, muscle strength, gait, and balance disorders (Allali et al., 2016; Burge et al., 2012; Forbes et al., 2015; Heyn et al., 2004).

As a debilitating disease, a slowing of the development of dependence in ADL functionality is critical for enhancing individuals' quality of life which, in turn, may have an impact on informal caregivers' ability to sustain their caregiving role and possibly delay the need for institutionalization (Forbes et al., 2015; Gauthier et al., 2021). Increasing evidence advocates physical exercise as a promising non-pharmacological intervention not only to improve or attenuate cognitive and functional declines, but also manage NCD-related symptoms (i.e., BPSDs), and increase quality of life.

A Cochrane review including 17 trials with a total of 1067 participants, mostly diagnosed with Alzheimer's disease, found that physical exercise may improve the ability to perform ADL; however, this meta-analysis revealed no clear evidence of benefit from physical exercise on cognitive function, neuropsychiatric symptoms, and depression (Forbes et al., 2015). These results were partially corroborated by Groot et al. (2016) that observed improvements in ADL's functionality, accompanied by positive effects of aerobic physical exercise in cognition in people with dementia, regardless of the subtype (i.e., Alzheimer's disease, vascular disease, mixed dementia, multiple infarct dementia and undefined dementia) and frequency of interventions. Despite the methodological differences and inconsistent results, encouraging results have been presented about the intrinsic benefits of physical exercise on cardiovascular health and general health status (Cass, 2017; Gomes-Osman et al., 2018).

According to Lam et al. (2018), there is a strong evidence that supports the use of regular physical exercise (60-minutes sessions, 2-3 days a week) with a combination of aerobic, resistance, balance, flexibility and functional training to improve physical functioning (i.e., lower body strength, balance, mobility, and walking endurance) in individuals diagnosed with dementia from mild to moderate stages. Park and Cohen (2019) also distinguished the benefits of various modalities of physical exercise on several functional outcomes, such as gait speed, walking endurance, balance, and muscle strength. These results were consistent with a recently published overview including 30 systematic reviews and meta-analysis (Begde et al., 2021). In overall, this review found that physical exercise, particularly MT (i.e., combining strength, balance, endurance, and flexibility), can significantly improve walking, balance, visuospatial functions, and ADL independence, which are crucially important for independent living.

Along with physical limitations and high levels of dependency in ADL, neuropsychiatric symptoms are also a strong predictor of institutionalization (Gauthier et al., 2021). Many reviews have been published examining the effect of physical exercise on specific cognitive functions and BPSDs in people with NCD. Whereas some reviews have not found a statistically significant effect of physical exercise on cognition and depression (Li et al., 2019), others found that it can reduce global cognitive decline (Du et al., 2018; Jia et al., 2019; Venegas-Sanabria et al., 2021), particularly on working memory, and diminish behavioral problems (Law et al., 2020). These conflicting results might be due to the inclusion criteria of reviews, such as types and stages of disease, use of different assessment tools, types of physical exercise intervention, among other factors (Du et al., 2018; Hernandez et al., 2015; Law et al., 2020; Lewis et al., 2020; Li et al., 2019; Park & Cohen, 2019). Notwithstanding, Hoffmann et al. (2016) showed that moderate-to-high intensity aerobic physical exercise (ADEX intervention) may inhibit or delay the emergence of more severe neuropsychiatric symptoms in individuals with Alzheimer’s disease. Sobol et al.

(2018) found out that improvements in peak oxygen uptake (i.e., VO_2peak) after the 16-week ADEX intervention appeared to be associated with changes in cognition and BPSDs. Likewise, Roitto et al. (2018) identified that physical exercise significantly modified the effect of neuropsychiatric symptoms on the risk of falling in community-dwelling individuals with Alzheimer's disease. In brief, although these studies' results and methodologies are heterogenous, the overall picture indicates a potential positive effect of physical exercise in neuropsychiatric symptoms (Law et al., 2020; Matura et al., 2016; Skinner et al., 2018), principally in alleviating depressive symptomatology (Forbes et al., 2015; Li et al., 2019; Morris et al., 2017). Specifically, MT might positively affect aberrant motor behavior, apathy, agitation and eating disorders (de Souto Barreto et al., 2015), which consequently may have an impact on well-being.

As stated by Dimities et al. (2021), possibly due to the indirect effects on cognitive function, neuropsychiatric symptomatology, and overall ADL functionality, physical exercise may constitute a promising intervention to improve well-being and quality of life of individuals living with major NCD. Ojagbemi and Akin-Ojagbemi (2019) also highlighted the importance of physical exercise in improving social interaction, interaction capacity, sense of well-being and of aesthetics, and bodily well-being; however, similarly to other studies (Farina et al., 2021; Forbes et al., 2015; Lamb, Mistry, et al., 2018; Lamb, Sheehan, et al., 2018; Marquez et al., 2020), these authors did not found a significant difference in the quality of life of individuals with NCD who were participating in physical exercise interventions, comparing to controls.

Even though there is a theoretical support that justifies the possible benefit of physical exercise in improving quality of life in individuals with NCD, empirical evidence is yet inconclusive, partially due to the small number of studies and inconsistency in outcomes measures (e.g., use of generalized quality of life measures *vs*. disease-specific outcomes), insufficient sample sizes, diversity of type and stages of disease, and wide ranging training methodologies (Dimities et al., 2021; Marquez et al., 2020; Ojagbemi & Akin-Ojagbemi, 2019). Above all, as summarized by Lewis et al. (2020), there is no evidence that physical exercise is detrimental for individuals living with dementia, and the general consensus is that physical exercise interventions can be recommended to improve general physical and mental health. It’s clear, though, that the recommendation “one size fits all” may not be optimal (Lewis et al., 2020), and for this reason, the physical exercise recommendations for older populations defined by the American College of Sports Medicine (ACSM) (American College of Sports Medicine, 2017, 2021) need to be considered when concerning individuals with major NCD.

Regardless of the target outcome, adherence to physical exercise interventions is essential for obtaining a meaningful effect (van der Wardt et al., 2017), whether it is a MT intervention or not. van Alphen, Volkers, et al. (2016) showed that community-dwelling and institutionalized individuals with dementia are sedentary for most of the day, and the small amount of physical activity they perform tends to be of lower intensity when comparing to their healthy peers. In addition to practical support strategies, such as group-based interventions and inclusion of a learning or adaptation period (van der Wardt et al., 2017), other review studies (van Alphen, Hortobágyi, et al., 2016) have also identified intra- and interpersonal factors, as well as community factors, that might support physical exercise engagement in people with dementia (i.e., barriers, motivators and facilitators).

Another topic that remains unclear regards the involvement of caregivers, particularly when planning community-based interventions. Previous studies confirmed their decisive role in providing transportation and guaranteeing care-receivers access and motivation, which may potentially influence the impact of exercise interventions (American College of Sports Medicine, 2021; Di Lorito, Bosco, Booth, et al., 2020; van der Wardt et al., 2017; van der Wardt et al., 2020). Unfortunately, caregivers are often disregarded for participation and examined only secondarily in this type of physical exercise programs designed for individuals with NCD (Doyle et al., 2020). Particularly concerning the national context, individuals with NCD and their caregivers often struggle to have access to appropriate services (Balsinha et al., 2022; Gonçalves-Pereira et al., 2019).

In sum, findings confirm the need for individualized, person-centered, and tailored approaches to support individuals with major NCD adherence to physical exercise (Di Lorito, Bosco, Pollock, et al., 2020; van Alphen, Hortobágyi, et al., 2016; van der Wardt et al., 2017; van der Wardt et al., 2020). More importantly, MT seems to be appropriate for vulnerable populations, including those with major NCD (American College of Sports Medicine, 2021; Izquierdo, Duque, et al., 2021); MT is also associated with high levels of satisfaction (Cadore et al., 2014; Carvalho et al., 2009), which may increase the success rate of these type of interventions and promote individuals' compliance/ engagement. Despite MT promising reported impact, several questions need to be answered about the effectiveness and operationalization of an MT intervention for individuals with major NCD, as we will next summarize.

1.3 Multicomponent Training for Individuals with Major NCD

1.3.1 Definition, characteristics, and relevance to individuals with major NCD

Multicomponent training can be defined as a combination of “at least the three modalities of strength/resistance training, aerobic/cardiovascular endurance training, and balance/stability training, and may or may not have included flexibility exercises” (Baker et al., 2007, 376). These physical fitness components might be combined into each session, and/or equally distributed throughout the entire duration of the program.

Current position statements and consensus guidelines for physical activity and sedentary behavior from the WHO (Bull et al., 2020) recommend the integration of MT activities, via a combination of structured group/class settings and incidental activities (lifestyle-integrated that can be done at home), at least three days a week in order to enhance functional capacity, prevent osteoporosis and falls for all older adults and not only those with poor mobility.

Consistent evidence has demonstrated the MT’s important effect in reducing the risk of fall-related injuries by nearly 32%-40%, including severe falls that result in head trauma, bone fracture, or any other injury requiring medical care or admission to hospital (American College of Sports Medicine, 2021; U.S. Department of Health and Human Services, 2018). According to the 2021 ACSM guidelines on physical exercise prescription for older adults, evidence suggests that MT, when compared with single-component training, is associated with greater benefits on physical function. In particular, those experiencing frequent falls or with mobility limitations, should perform 2-3 days per week neuromotor physical exercises, combining balance, agility and proprioceptive training, to effectively reduce and prevent the occurrence of falls (American College of Sports Medicine, 2021).

MT as a training methodology has been gaining relevance in the scientific community and recommended to older populations for more than 10 years

(Nelson et al., 2007; U.S. Department of Health and Human Services, 2018; World Health Organization, 2010), especially for those with poor mobility. This is mainly due to its holistic benefit in the different physical fitness abilities of older adults that are necessary to maintain or improve their ability to independently perform ADL (Cadore et al., 2019; Valenzuela et al., 2019).

According to the recent *International Exercise Recommendations in Older Adults (ICFSR): Expert Consensus Guidelines* the "exercise prescriptive elements that best address the underlying contributors to dementia (sarcopenia, low aerobic capacity, hypertension, diabetes, diabetes, anorexia, cerebrovascular pathology, inflammation, etc.) offer the best basis on which to prescribe exercise at this point in time for dementia itself" (Izquierdo et al., 2021, p. 842-843). Thereby, as highlighted by Izquierdo, Duque, et al. (2021), evidence-based physical exercise modalities that holistically address frailty and sarcopenia, polypharmacy, malnutrition, falls, osteoporosis, cardiometabolic disease or depression, should be recommended to individuals with an established diagnose of dementia.

Even though the link between dementia, sarcopenia, and frailty still need further research, studies undertaken up until now indicate that people with dementia may present an increased prevalence of frailty and sarcopenia (Pacifico et al., 2020; Waite et al., 2021), two important geriatric syndromes associated with many adverse outcomes, including disability, falls, and mortality (Izquierdo, Duque, et al., 2021). The association of sarcopenia and frailty with poorer health-related outcomes, their potentially reversible nature, and the possible relationship with dementia, which are all precursors of disability, strengthens the need to monitor these syndromes and prevent their progression (Cadore et al., 2019; Izquierdo, Merchant, et al., 2021; Livingston et al., 2020; Waite et al., 2021). Fortunately, increasing data suggest that MT interventions might help to mitigate the trajectory of frailty and disability in older adults with NCD (Begde et al., 2021; Casas-Herrero et al., 2022; Lam et al., 2018).

A previous study revealed that frail individuals with dementia who were submitted to an 8-weeks moderate-intensity MT intervention showed improvements in muscle strength, balance, and gait ability (Cadore et al., 2014). Indeed, many studies have shown that MT interventions are more effective in improving most, if not all, of the frailty hallmarks, such as poor balance, reduced muscle strength, poor gait ability, and increased incidence of falls (Cadore et al., 2014; Cadore et al., 2019; Izquierdo, Merchant, et al., 2021). For this reason, MT should be prescribed for most vulnerable populations, including those with cognitive impairment or dementia to counteract the physical consequences of frailty and sarcopenia (Izquierdo, Merchant, et al., 2021).

The accumulated evidence from ACSM guidelines for older populations throughout the years (American College of Sports Medicine, 2017; Chodzko-Zajko et al., 2009; U.S. Department of Health and Human Services, 2018), along with the inconsistent (but promising) evidence from systematic reviews and meta-analytic studies regarding the multiple benefits of MT (Begde et al., 2021; Hernandez et al., 2015; Heyn et al., 2004; Kirk-Sanchez & McGough, 2014; Lam et al., 2018; Skinner et al., 2018), corroborate the usage of this training methodology when the purpose is to improve physical fitness, functional capacity and cognitive function of individuals living with major NCD.

It is worth highlighting that the concepts of multimodal and MT interventions are often used interchangeably. Multimodal interventions, i.e., interventions combining physical exercise training with other interventions (such as cognitive stimulation or ADL training) must be carefully compared with those only offering a physical exercise program given the difficulties to detach the effects of physical exercise from the rest of interventions (Baker et al., 2007; Begde et al., 2021; Lewis et al., 2020). Therefore, it is necessary to systematize the existing evidence on the operationalization of MT interventions for individuals with major NCD and explore the potential benefits of this well-promising training methodology on multiple domains [3]. Other questions also need to be answered, such as: training intensity progression and control, evaluation methods, and use of music. And last, but not least, the selection of adequate settings to implement the MT intervention, the involvement of informal caregivers and partner entities,

[3] Considering the MT definition of Baker and colleagues (2007).

and the participants’ recruitment are also determinant aspects for implementing a community-based physical exercise intervention.

PART II – Objectives

Chapter 2. Objectives of this Thesis

The previous chapter presented the theoretical framework highlighting the main topics explored in the present thesis. Accordingly, several objectives were defined, as presented in the following subsections.

2.1 Primary and Secondary Objectives

The primary purpose of the present thesis was to investigate the contribution of a 6-month MT intervention on the physical and cognitive function of individuals diagnosed with major NCD. Complementarily, this thesis encompasses the following secondary objectives:

- Examine the effects of MT on individuals' functional and psychosocial outcomes (e.g., ability to independently perform ADL, neuropsychiatric symptomatology, and quality of life).
- Analyze the association between health-related physical indicators and quality of life of individuals with NCD.
- Explore the factors that influence individuals with NCD adherence to a community-based physical exercise program.

This thesis includes one systematic review and meta-analysis and five original studies that address these objectives. The systematic review and meta-analysis were conducted to synthetize the existing evidence about the effects of MT on physical fitness, cognition, and ability to function independently in ADL, and to identify moderation patterns of those effects regarding FITT variables (*chapter 4*). The original studies report a 6-month MT intervention that was designed and implemented in multicentered settings from September 2018 to March 2020, within a project entitled "Body & Brain", which protocol can be consulted elsewhere (Carvalho et al., 2021).

Original study I (chapter 5) examined the effects of the “Body & Brain” community-based physical exercise program on functional capacity (e.g., lower body function, mobility, and gait speed) and ADL independence in older adults diagnosed with NCD. In turn, the *original study II* (*chapter 5*) explored the contribution of this intervention on cognitive function, neuropsychiatric symptoms, and quality of life.

Subsequently, a cross-sectional study was conducted to better understand the association between health-related physical indicators and quality of life (*original study III: chapter 6*), considering the relation between functional capacity, frailty status, physical disability, and dependency.

Additionally, a qualitative study was conducted to analyze the perception of informal caregivers about the barriers, motivators, and facilitators towards the participation of care-receivers in a physical exercise program (*original study IV: chapter 7*).

Finally, a qualitative study was conducted to explore the views of caregivers of people with NCD about taking part in physical exercise sessions with their care-receivers. Complementarily, this study aimed to explore the subjective impact of the program on those caregivers who have physical exercised together with their care-receivers (*original study V: chapter 7*). **Table 2** provides a schematic rational from the topics of the chapters included in this thesis.

Table 2. Representation of the rational from the topic to the chapters of this research work

Topic	Research question	Aim	Sample	Outcomes	Design	Data Analysis	Publications	Dissertation Chapter†
MT intervention for individuals with NCD	What are the effects of MT intervention in individuals with NCD?	To determine MT effectiveness in improving physical fitness, cognition, and ADL's functionality. To identify moderation patterns of those effects regarding FITT training variables.	6 studies, including 489 participants diagnosed with major NCD	ADL's functionality Cognitive Function Agility	Systematic review with meta-analysis	Random-Effect Model	Systematic Review and Meta-analysis	4
Effectiveness of a 6-month MT intervention on physical and cognitive functions	What are the effects on functional capacity and ADL functionality?	To examine the contribution of a 6-month MT intervention on the functional capacity (e.g., lower extremity function, mobility, and gait speed) in older adults living with NCD, and on their ability to independently perform ADL.	43 individuals with NCD (30 women) were allocated to a physical exercise group (N: 23; mean 75.09, SD=5.54 years) or a control group (N:20; mean 81.90, SD=1.33 years)	SPPB TUG 6-meter Walk Test BI	Quasi-experimental controlled trial	Linear Mixed-effects Models	Original study I	5
	What are the effects on cognitive function, neuropsychiatric symptoms, and quality of life?	To explore the effects of a 6-month MT intervention on the cognitive function, neuropsychiatric symptoms, and quality of life of people with major NCD.	36 individuals with major NCD (25 women) were allocated to a physical exercise group (N: 18; mean 74.33, SD=5.87 years) or a control group (N:18; mean 81.83, SD=6.18 years)	ADAS-Cog NPI QoL-AD	Quasi-experimental controlled trial	Linear Mixed-effects Models	Original study II	

Determinants of quality of life of individuals with NCD	What is the association between physical health-related indicators and quality of life of individuals with NCD?	To identify the association between health-related physical indicators – sarcopenia-related factors, physical fitness, independence in ADL and habitual physical activity - with self-rated quality of life in individuals with NCD.	115 individuals with NCD (mean 78.22, SD=7.48 years; 74.8% female)	QoL-AD DXA Handgrip strength SPPB 6-meter Walk Test SFT One Leg Balance Test BI Modified Habitual Physical Activity Questionnaire	Cross-sectional	Multivariable Linear Regression Model	Original study III	6
Adherence to a community-based physical exercise program	What are the barriers, motivators, and facilitators to the participation of individuals with NCD in a physical exercise program?	To explore the perception that informal caregivers have on the contributing factors for (non)adherence to a group-based physical exercise program for individuals with NCD living in the community.	20 informal caregivers (13 men; mean 67.5, SD=13.94 years; age range: 37-86)	Semi-structured interviews	Exploratory Qualitative	Braun and Clarke's Thematic Analysis, under the socio-ecological framework	Original study IV	7

	Should caregivers be involved in physical exercise interventions to their care-receivers with NCD?	To explore the views of caregivers of individuals with NCD about taking part in a community-based physical exercise intervention with their care-receivers; To explore the subjective impact of the physical exercise program in those caregivers who have physical exercised together with their care-receivers.	20 informal caregivers (13 men; mean 67.5 SD=13.94 years old; age range: 37-86), of whom ten (mean age 72.9 years; range 59-83 years; 2 female) took part of the physical exercise sessions with care-receivers.	Semi-structured interviews	Exploratory Qualitative	Braun and Clarke's Thematic Analysis guideline, using and inductive approach	Original study V	

ADAS-COG - Alzheimer's Disease Assessment Scale – Cognitive; BI - Barthel Index; CG – Control group; DXA - Dual energy X-ray Absorptiometry; EG – Experimental Group; MMSE - Mini Mental State Examination; NCD - Neurocognitive disorder; NPI - Neuropsychiatric Inventory; QoL-AD - Quality of Life – Alzheimer's Disease; SFT - Senior Fitness Test; SPPB - Short Physical Performance Battery; TUG - Timed-Up and Go Test.

† Published chapters are entirely reproduced on this thesis with the permission of each journal (**Appendix 2**).

PART II – Empirical Work

Chapter 3. General Description

This chapter provides a general description of the thesis methodology, namely study design and setting, sample recruitment, eligibility criteria and interventions offered to experimental and control groups. Ethical procedures are also depicted. In addition, the chapter includes a description of the outcome measures and data collection procedures. Information on general sample characteristics is also presented. Finally, a COVID-19 contingency plan is presented to explain the impacts on the ”Body & Brain” project and the required methodological adaptations.

3.1 Design and Setting

The present thesis is nested in the “Body & Brain” project, a two-arm quasi-experimental controlled trial with a parallel design, carried out in multicentered settings in the Oporto Metropolitan Area – Portugal, and funded by the Portuguese Foundation for Science and Technology (Fundação para a Ciência e a Tecnologia, POCI-01-0145-FEDER-031808).

The ”Body & Bran” project was conducted from September 2018 to March 2022, and retrospectively registered in the US National Institute of Health clinical trials registry - ClinicalTrials.gov (Identifier Number: NCT04095962) in September 2019 (**Appendix 3**). It offered eligible participants the opportunity to take part of a community-based MT program – experimental group (EG), or monthly social activity sessions – control group (CG), according to their wish and readiness to join one of the groups. Additional information on this study protocol can be found elsewhere (Carvalho et al., 2021), as well as results from a previous pilot experience (Borges-Machado et al., 2019).

In total, the “Body & Brain” project was conducted in collaboration with 17 entities including: nursing homes and daycare centers, municipalities, a university sports hall, a psychiatric hospital with a specific unit devoted to dementia care, and a healthcare center. As presented in **Figure 1,** the project was carried out in two intervention cycles: from September 2018 to May 2019, and between August 2019 and March 2020. In other words, recruitment process occurred in September 2018 and August/ September 2019. Baseline evaluations were conducted during October 2018 and September/ October 2019, and the post-intervention evaluations were performed immediately after the 6-month period MT intervention. For further details on evaluation measurements please see topic *3.2.2 Outcome measures*. Considering both intervention cycles, there were seven groups receiving the MT program (EG), and eight groups participating in the monthly social activity sessions (CG).

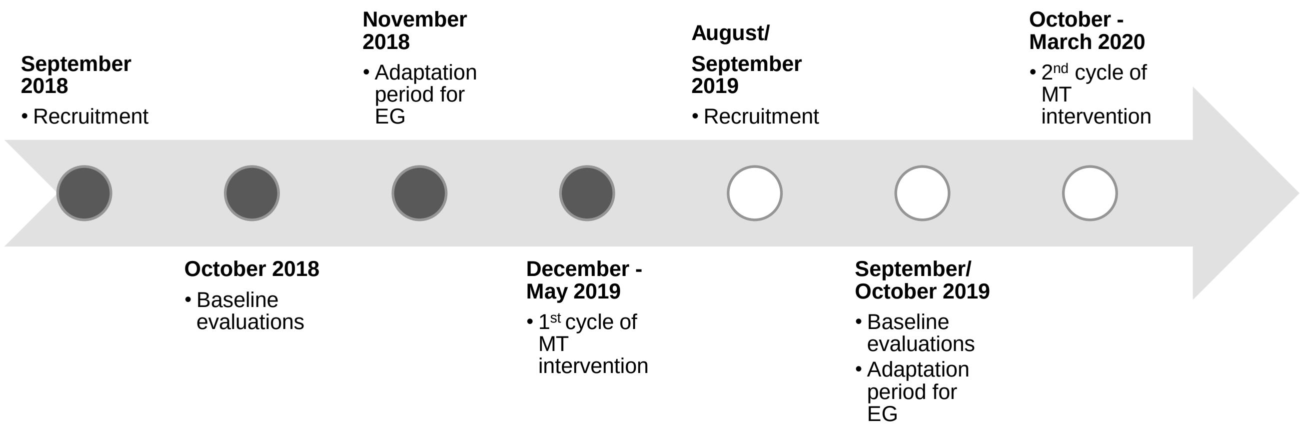


Figure 1. Project timeline

3.1.1 <u>Procedures</u>

3.1.1.1Sample recruitment

One hundred and eighty-three individuals were signalized at multicentered settings for the two intervention cycles. Individuals were recruited from public and private institutions dedicated to older adults (e.g., day care centers, nursing homes, local community centers), hospital centers and clinics (i.e., outpatients accompanied by psychiatrists or neurologists), Alzheimer's and caregivers' associations, municipalities, local journals, and social media.

Advertisements were made via phone calls, emails, informative flyers and presential and online meetings (**Appendix 4**). To motivate and clarify concerns about the physical exercise sessions, short informative talks were provided to exemplify simple exercises and illustrate a typical session of MT intervention.

3.1.1.2 Eligibility criteria

The eligible subjects pool was restricted to individuals with the following characteristics:

i) age ≥ 60 years;

ii) clinically diagnosed with major NCD according to *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR or DSM-5) (American Psychiatric Association, 2013), or with dementia according to the ICD-10 (World Health Organization, 2016), or the *National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association* (NINCDS-ADRDA) (McKhann et al., 1984), by a physician for at least 6 months;

iii) capacity to walk independently without a human assistance or assistive device at indoor environments (e.g., individuals who were afraid to walk without a stick or a crutch outdoors [only] were considered as valid).

Individuals were excluded if the following criteria were present:

i) diagnosed with any condition or disorder in which physical exercise was contraindicated, such as unstable or ongoing cardiovascular and/or respiratory and/or musculoskeletal condition;

ii) recent hospitalization (e.g., previous month to recruitment) and/or in recovering from surgery or rehabilitation;

iii) presenting an advanced stage of major NCD (e.g., ≤ 10 points on MMSE) that could affect physical performance in the physical exercise training sessions or testing procedures.

3.1.2 Interventions

Experimental Group: MT program

The physical exercise sessions were conducted twice a week for 6-months, took about 60-minutes each and occurred during the late morning or early afternoon periods. Following the ACSM physical exercise guidelines for older adults (American College of Sports Medicine, 2017, 2021), and the recently published orientations by the WHO (Bull et al., 2020), the sessions were subdivided in three main parts (please see **Table 3**), specifically: 10 minutes for warm-up (i.e., general activation, joint mobilization and stretching), 35-45 minutes dedicated to specific training (i.e., balance and coordination, muscle strength, and aerobic endurance), and the final five minutes to cool-down exercises (i.e., slow walking, mobility and stretching exercises for the main worked muscle groups and breathing exercises).

Table 3. "Body & Brain" project MT intervention plan

Warm-up	Balance & Coordination		Muscle Strength		Aerobic Endurance	Cool down
E.g., slow walk, mobility physical exercises for the shoulders, trunk, hip, and ankles as rotations, flexion/extension, and adduction/abduction	E.g., one leg stand, semi-tandem stand, tandem walk, sideways walk, heel-to-toe stands and walk, step over objects as cones, hoops and huddlers, physical exercises with balance pads, shift weight from foot to foot, turning and changing direction		E.g., biceps arm curl, triceps extension, adapted planks, seated row, chest press, squats, knee extension, hip extension, toe raises, standing leg curl		E.g., stationary marching, walking, simple step-based choreographic movements - physical exercises will start with only lower limbs and as needed will include upper limbs	E.g., back and chest stretch, quadriceps and hamstrings stretch, diaphragmatic breathing
1st & 2nd months						
10 min	15 min	2-3 exercises	15 min	4 exercises	10 min	5 min
	Static and dynamic balance		2 sets 10-12 repetitions		60-65% HRmax	
3rd month						
10 min	15 min	2-3 exercises	15 min	4-6 exercises	15 min	5 min
	Dynamic balance and coordination		2 sets 10-12 repetitions		65-75% HRmax	
4th month						
10 min	10 min	2-3 exercises	15 min	4-6 exercises	20 min	5 min
			2 sets 8-10 repetitions		65-75% HRmax	
5th and 6th months						
10 min	10 min	2-3 exercises	15 min	4-6 exercises	20 min	5 min
			2 sets 8-10 repetitions		75-80% HRmax	

HRmax-maximum heart rate; min-minutes.
Note: Table content was adapted from "Body & Brain" study protocol, published elsewhere (Carvalho et al., 2021)

Simple and functional exercises were preferred, and new exercises were introduced as a progression of previous well-known ones. In addition, to maintain a routine and to promote individuals' success in performing the physical exercises, within each group, both weekly sessions had the exact same plan. Whenever possible, music accompanied sessions to promote appropriate intensity, social interaction, and enthusiasm (van der Wardt et al., 2017), particularly during aerobic endurance.

The sports equipment encompassed chairs, ground markers, strings, elastic resistance bands, dumbbells, hurdles, balance pads, agility ladders, balls, and steps. Heart rate monitors were used to control intensity (Tedesco et al., 2019).

The MT program was implemented by professionals specialized in physical exercise that prior to the program implementation received specific training concerning NCD clinical features and progression, communication strategies, challenging behavioral and psychological symptoms, and safety issues (Laventure & Aherne, 2010). Throughout the intervention, each one of these professionals conducted all sessions within the same group. Whenever possible, another specialized trainer accompanied the sessions and provided support to participants during exercises performance.

Although the “Body & Brain” project was not a dyadic intervention, caregivers were invited to participate in this MT program as class members, according to their availability and willingness. In other words, this physical exercise program was designed to individuals with NCD, but caregivers could perform the proposed activities by the professionals or assist their care-receivers if necessary. Prior to the intervention, caregivers decided whether they wanted or not to participate, and those who were unavailable or did not want to take part in the physical exercise sessions were invited to attend in specific recreational activities (i.e., festive gatherings), and received regular telephone contacts to clarify any doubts about the care-receiver’s participation.

Group-sessions comprised five to eight participants in cases where there were only individuals with NCD, or 10 to 12 participants if caregivers were also participating in the physical exercise sessions (i.e., five to six caregiving dyads).

Control Group: Social activity

Although no specific physical exercise intervention was conducted in the CG, considering ethical aspects and motivation to participate in the study, participants received monthly sessions regarding physical activity and other health-related topics (e.g., healthy eating habits and lifestyle, falls prevention, breathing and relaxation activities) information as a complement to standard care. These sessions took about 60-minutes each, and were conducted by specialized professionals, who were not responsible for the implementation of the MT program but were aware of the existence of different interventions for EG and CG.

Group-sessions involved five to 12 participants, and only included individuals with major NCD. Most of the CGs included participants from daycare centers, and, for this reason, informal caregivers were frequently unavailable to participate in these sessions. In parallel, individuals with NCD and/or their main caregiver/significant person were contacted regularly via phone calls to ensure retention and compliance (i.e., chat-talk unrelated with the intervention). These telephone contacts were not scheduled in advance.

3.2 Methodology

3.2.1 Ethics

The “Body & Brain” project was approved by the Ethical Committee of the Faculty of Sports of the University of Porto (CEFADE22.2018), and by the Institutional Ethical Boards of three organizations (two public hospitals and a private institution of social solidarity) that have collaborated with the project, as presented in **Appendix 5**. In full compliance with the Helsinki Declaration, individuals with NCD and their main caregivers received a complete explanation of the study purposes, risks, and procedures. Following the best ethical procedures, and complying with the specific legal requirements associated (Diário da República, 2018), informed consent was obtained from all participants and their legal representative/ proxy decision-maker/ significant person or assigned main caregiver (**Appendix 6**).

3.2.2 Outcome measures

Data was collected at baseline and immediately after the 6-month MT intervention, as presented on **Table 4**. Evaluations were conducted by specialized and well-trained researchers, who were not responsible to implement the MT program or the social activity sessions, and were not masked to group assignment. The same evaluator was responsible to perform the same procedures along the different assessment periods.

Additionally, a cutoff of 70% of the attendance rate was considered, to determine the valid participants among the experimental group (Di Lorito, Bosco, Booth, et al., 2020). The attendance rate was calculated considering the total number of attended sessions through the total offered.

Table 4. Description of methods and/or instruments to evaluate individuals with NCD and/or their caregivers/significant person

	Domain	Measure	Data from	
			Individuals with NCD	Caregiver/significant person
Screening[a]	Anamnesis (sociodemographic and general clinical data)	Participants' sociodemographic information (age, sex, marital status, education, and living situation) general clinical data, and pharmacological treatment was gathered via a screening questionnaire.	X	X
Primary[b] **and Secondary**[b]	Cognitive Function	*Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog)* (Nogueira et al., 2018; Rosen et al., 1984)	X	
		Mini Mental State Examination (MMSE) (Folstein et al., 1975; Santana et al., 2016)	X	
	Lower Body Function	*Short Physical Performance Battery (SPBB)* (Guralnik et al., 1994)	X	
	Physical Fitness	*Senior Fitness Test (SFT)* (Rikli & Jones, 2012)	X	
		One Leg Balance Test (Vellas et al., 1997)	X	
	Mobility	*Timed-Up and Go Test (TUG)* (Podsiadlo & Richardson, 1991)	X	
	Gait Speed	*6-Meter Walk Test* (Blankevoort et al., 2013)	X	
	Handgrip strength	*Hand Dynamometer* (Mendes et al., 2017)	X	
	Total Body Lean Mass	*Dual energy X-ray Absorptiometry (DXA)* (Shepherd et al., 2017)	X	
	Appendicular Skeletal Mass Index			
	Anthropometry	*Height (Direcção-Geral Da Saúde, 2013)*	X	

		Weight *Body Mass Index (BMI)* *(Direcção-Geral Da Saúde, 2013)*	X	
		Waist and Hip circumferences (Direcção-Geral Da Saúde, 2013)	X	
	ADL's functionality	*Barthel Index (BI)* (Mahoney & Barthel, 1965; Sequeira, 2007)		X
	Quality of life	*Quality of Life – Alzheimer's Disease (QoL-AD)* (Barrios et al., 2013; Logsdon et al., 2002)	X	X
	Neuropsychiatric symptoms	*Neuropsychiatric Inventory (NPI)* (Cummings et al., 1994; Ferreira et al., 2015)		X
Confounders[b]	Physical activity levels	*Modified Habitual Physical Activity Questionnaire (Baecke)* (Almeida & Ribeiro, 2014; Baecke et al., 1982)	X	
Qualitative[c]	Barriers, motivators, and facilitators	The semi-structured interview guideline was developed based on similar studies (Karuncharernpanit et al., 2016; Lamb, Mistry, et al., 2018; Suttanon et al., 2012; Yu & Swartwood, 2012), and subdivided and two sections. The first part covered the barriers, motivators, and facilitators toward the participation of care-receivers with NCD in a physical exercise program. In what concerns the second part, questions aimed to explore the caregivers' point-of-view about taking part in a community-based physical exercise program designed to their care-receivers with NCD. In addition, those who took part in the physical exercise sessions with their care-receivers were complimentarily invited to freely talk about the impact this intervention had in their lives.		X
	Caregivers' inclusion			X

a – only on baseline evaluations; b – at baseline and after 6-month intervention; c – only after 6-month intervention.

Evaluations were conducted in three different in-person appointments (in separate days), and thelephone interview. At the first appointment, sociodemographic and general clinical data were gathered, and all physical domain tests were performed (i.e., lower body function, physical fitness, mobility, gait speed, and handgrip strength). On the second appointment, cognitive tests and quality of life were evaluated. Antropometry and body composition tests were performed at the third evaluation moment (at the sports university facility). Caregivers' questionnaires referring to care-receivers' quality of life, neuropsychiatric symptoms and daily functionality were obtained subsequently via scheduled meeting and/or phone interview.

The qualitative semi-structured interviews were performed by a trained qualitative research assistant who was not involved in the "Body & Brain" project, and took place between April and May 2020.

3.3 General Sample Characteristics

One hundred and eighty-three individuals were identified as potentially eligible participants for the “Body & Brain” project from September 2018 to September 2019. From the 83 individuals signalized between August and September 2019, 30 persons participated in the 1st cycle of intervention and expressed their interest to further continue in the physical exercise program: however, only 26 enrolled again in the program. Overall, 65 individuals were excluded after eligibility assessment. Reasons for exclusion are presented in **Figure 2** and **Figure 3**.

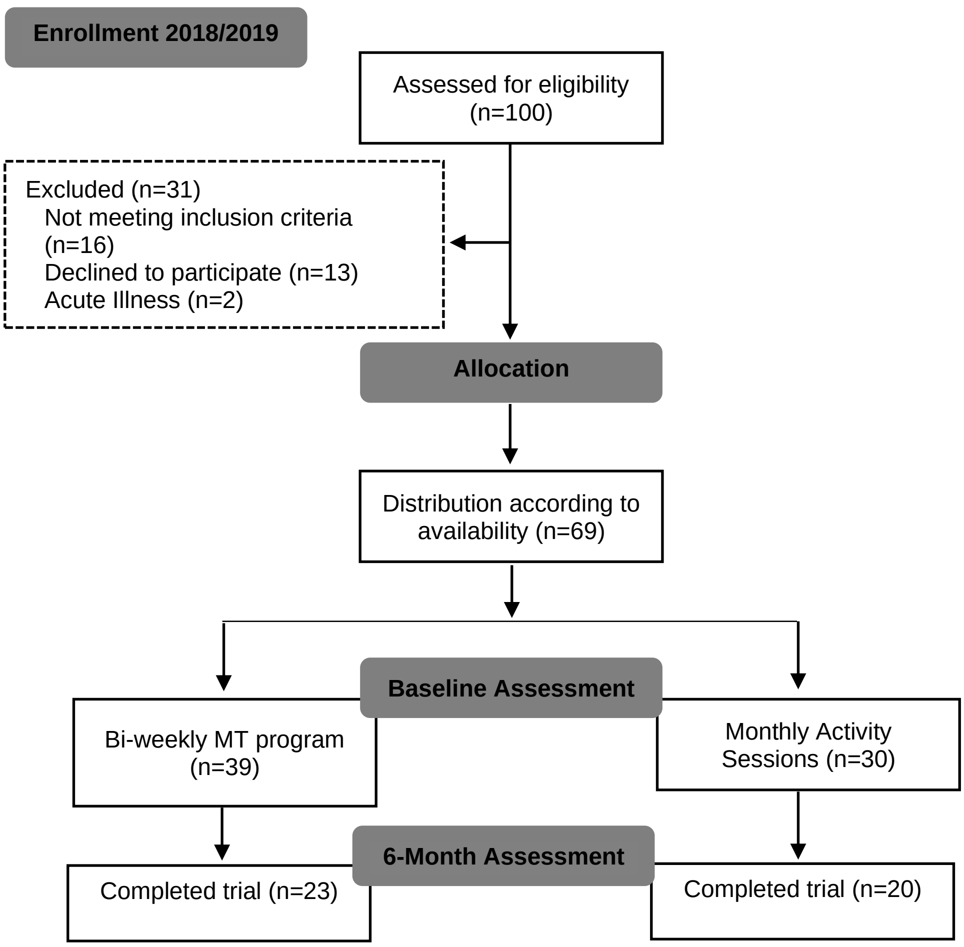


Figure 2. First cycle intervention of “Body & Brain” flow diagram

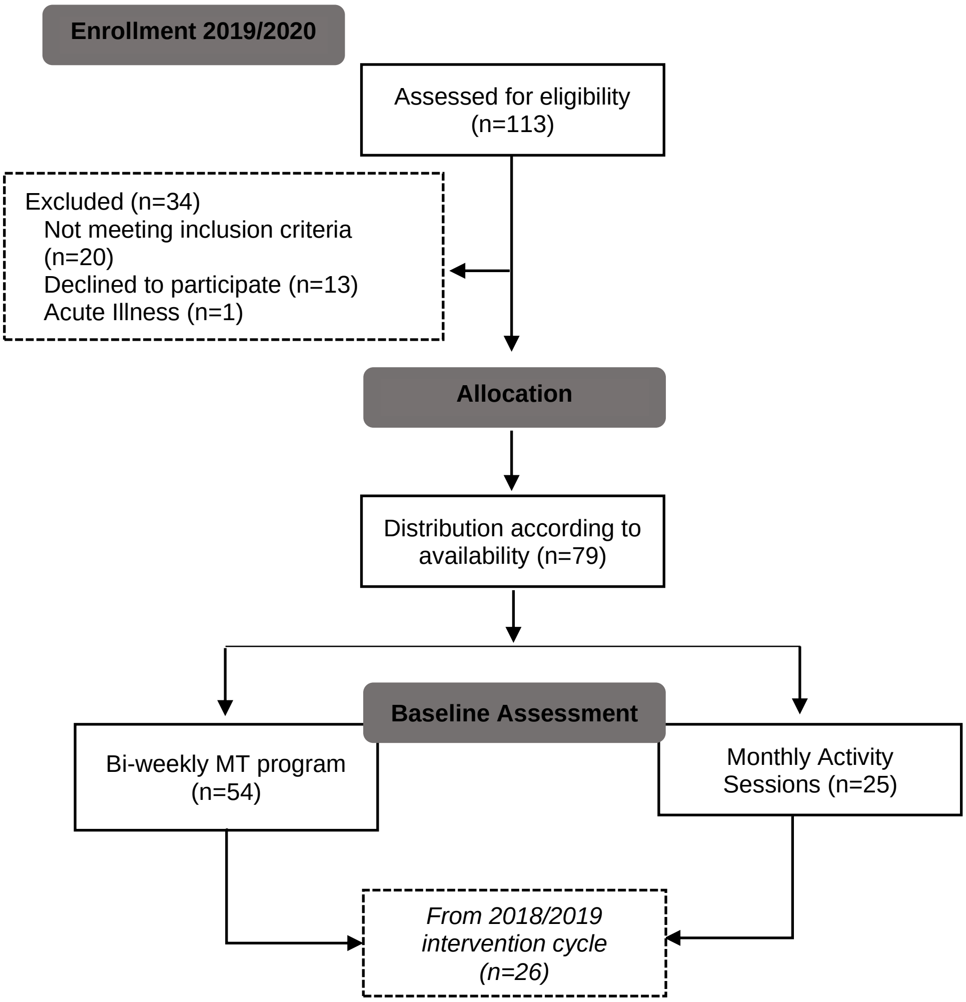


Figure 3. Second cycle intervention of “Body & Brain” flow diagram

Sixty-nine older adults (mean 79.50 years old (SD=6.73), 72.5% female) were included in the 1st cycle of intervention and distributed between the EG and CG. From those, 26 participants were lost to follow-up (n=9) or discontinued the intervention (n=17), which translates into a dropout rate of 38%. Forty-three individuals diagnosed with NCD (mean 78.26 years old (SD=6.68), 69.8% female) have completed the intervention, respectively, 23 in the EG and 20 in the CG. In what regards the 2nd cycle of intervention, 79 participants were considered as eligible and distributed between the EG and CG according to their availability and preferences to adhere one of the groups. Of those, 54 participants received the MT program (mean 76.04 years old (SD=7.08), 75.9%

female), and 25 individuals with NCD (mean 78.52 years old (SD=9.14), 72.0% female) received the monthly social activity sessions along with usual care.

In short, 69 older adults completed baseline evaluations from the 1st cycle, and 53 new participants from the 2nd cycle. Participants' characteristics are described in **Table 5**. So, the "Body & Brain" project sample comprised 122 individuals with a mean age of 78.26 years old (SD=7.60, age range: 61-94 years), of which 91 were female (74.6%). Most of them were married (47.5%) and had a low to medium education (67%), i.e., these participants studied during an average of 5.94 years (SD=3.68). Nearly 35% of the individuals with NCD lived with their spouse, or with other family member (i.e., children) (32.8%). On average, participants were prescribed with 7.51 (SD=3.23) different medicines and, in addition to NCD-related pharmacological treatments, these individuals were taking anti-depressants (72.9%), hypnotics, sedatives or anxiolytics (43.6%), and anti-psychotics (28.2%). Most participants received a clinical diagnosis of major NCD or dementia (91.5%), and the underlying subtype was mostly unspecified (38.3%), or due to Alzheimer's disease (35.5%) or vascular disease (9.3%).

At baseline, participants presented a mean value on SPPB of 7.38 (SD=3.01) points, indicative of a pre-frail status. In turn, data on TUG (mean 15.62, SD=8.40 seconds) is indicative of frailty and increased risk of falls. Overall, comparing SFT results with the normative functional fitness standards for the Portuguese older adults[4] established for women and men by age group, it is possible to verify that the individuals included in our sample presented a fitness level of 10-25% of the population, which reveals their low of physical fitness levels. Nevertheless, baseline values on BI (mean 86.31, SD = 15.23 points) are indicative that individuals were relatively independent ability to perform ADL and presented a moderate cognitive impairment according to total scores on MMSE (mean 18.28, SD = 5.88 points).

[4]As published in: Marques, E. A., Baptista, F., Santos, R., Vale, S., Santos, D. A., Silva, A. M., Mota, J., & Sardinha, L. B. (2014). Normative functional fitness standards and trends of Portuguese older adults: cross-cultural comparisons. *J Aging Phys Act*, *22*(1), 126-137. https://doi.org/10.1123/japa.2012-0203

Lastly, it is important to highlight that this sample includes the total number of eligible participants included on both cycles of intervention, since September 2018, whether on EG or CG. According to the different purposes of the following studies, data was analyzed considering different subgroups of the whole sample.

Table 5. Baseline characteristics

Domain	Measure	Total (n=122)
Sociodemographic and general clinical data	Age (years), mean (SD)*	78.26 (7.60)
	Age, range	61-94
	Sex (female), n (%)	91 (74.6%)
	Civil Status, n (%)	
	Married or civil union	58 (47.5%)
	Widow	52 (42.6%)
	Divorced or separated	11 (9.0%)
	Single	1 (0.8%)
	Year of Formal Education, mean (SD)[a]	5.94 (3.68)
	Education levels, n (%)[a]	
	Low (0-3 years)	27 (23.5%)
	Medium (4-6 years)	50 (43.5%)
	High (7-12 years)	31 (27.0%)
	University (13-17 years)	7 (6.1%)
	Living Situation, n (%)	
	Spouse	43 (35.2%)
	With other family member	40 (32.8%)
	Nursing home	30 (24.6%)
	Alone	9 (7.4%)
	Number of Medications and Supplements, mean (SD)[b]	7.51 (3.23)
	NCD-Related Medications, n (%)[b]	
	Any specific	29 (24.6%)
	Only memantine	28 (23.0%)
	Only cholinesterase inhibitors	27 (22.1%)
	Combined cholinesterase inhibitors and memantine	34 (27.9%)
	Antiparkinsonian	5 (4.1%)
	Other supplements for cognition	11 (9.0%)
	Number of Comorbidities, mean (SD)[c]	3.31 (1.93)
	Chronic Health Conditions, n (%)[c]	
	Hypertension	77 (64.7%)
	Dyslipidemia	75 (63.0%)
	Diabetes mellitus	33 (27.7%)

	Fallers in Past 12 months, n (%)[d]	48 (42.5%)
	Disease Duration (years), mean (SD)[e]	2.83 (2.24)
	Diagnosis, n (%)[f]	
	Mild NCD or Mild Cognitive Impairment	10 (8.5%)
	Major NCD or Dementia	107 (91.5%)
	Unspecified	41 (38.3%)
	Alzheimer's disease	38 (35.5%)
	Vascular disease	10 (9.3%)
	Multiple etiologies	8 (7.5%)
	Frontotemporal lobar degeneration	3 (2.8%)
	Lewy bodies disease	3 (2.8%)
	Parkinson's disease	3 (2.8%)
	Korsakoff syndrome	1 (0.9%)
Cognitive function	MMSE, mean (SD)[g]	18.28 (5.88)
	ADAS-Cog, mean (SD)[c]	34.45 (13.63)
Quality of life	QoL-AD, mean (SD)[f]	30.83 (4.46)
Neuropsychiatric symptoms	NPI, mean (SD)[h]	14.41 (11.26)
ADL's functionality	BI, mean (SD)[b]	86.31 (15.23)
Body composition and anthropometry	Total Body Lean Mass (kg), mean (SD)[i]	37.82 (65.50)
	ASMI (kg/ m^2), mean (SD)[j]	6.37 (0.85)
	BMI (kg/ m^2), mean (SD)[j]	27.62 (4.33)
Lower body function	SPPB, mean (SD)[l]	7.83 (3.01)
Gait speed	6-Meter Walk Test (m/s), mean (SD)[l]	0.72 (0.23)
Handgrip strength	Handgrip strength (kgf), mean (SD)[a]	19.31 (6.76)
Mobility	TUG (sec), mean (SD)[l]	15.62 (8.40)
SFT	Upper-body strength (reps), mean (SD)[m]	9.63 (3.83)
	Lower-body strength (reps), mean (SD)[f]	9.97 (3.85)
	Upper-body flexibility (cm), mean (SD)[f]	-29.70 (15.34)
	Lower-body flexibility (cm), mean (SD)[c]	-19.69 (12.38)
	Agility/dynamic balance (sec), mean (SD)[c]	12.96 (7.17)
	Cardiorespiratory capacity (reps), mean (SD)[b]	48.89 (19.17)
Balance	Balance (sec), mean (SD)[l]	3.59 (5.71)
Physical activity levels	Modified Baecke, mean (SD)[j]	3.30 (0.92)

a – seven missing cases; b – four missing cases; c – three missing cases; d – nine missing cases; e – eighteen missing cases; f – five missing cases; g – one missing case; h – six missing cases; i – twenty-one missing cases; j – twenty-two missing cases; l – two missing cases; m – eight missing cases.

As for caregivers, 20 (mean 65.50 years old (SD=13.94), 35% female) were interviewed. Of those, ten were active-participating caregivers (mean age 72.9 years; range 59-83 years; 2 female) and took part in the exercise sessions, whereas the other ten were social-participating caregivers (mean age 62.0 years; range 37-86 years; 5 female).

3.4 COVID-19 Contingency Plan

Due to the coronavirus pandemic, the 2nd cycle of intervention of the "Body & Brain" project had to be interrupted on March 6th and, afterwards, the country declared a state of emergency. For this reason, data is missing on follow-up evaluations, dropout, and attendance rates. A contingency plan for the project was developed, assuring regular telephone contacts with participants to find out about their overall status and needs.

As result, three months after home confinement (June 2020), a telephone-based evaluation was conducted to investigate the impact of home COVID-19 pandemic on care provision of individuals with NCD through informal caregivers' perspective. As suggested by our study findings, the coronavirus pandemic had significantly increased caregiving subjective burden and decreased well-being, potentially due to worsening of physical and cognitive functions of people living with NCD (Barros et al., 2020; Borges-Machado et al., 2020).

Subsequently, efforts were made to adjust and adapt the in-person program and assessments to a virtual intervention, guaranteeing the participants' safety. Participants were conveniently recruited in September 2020 from two partner entities (i.e., one nursing home and one day-care centre specialized in dementia) and following the same eligibility criteria as in the in-person "Body & Brain" project (Borges-Machado et al., 2021; Carvalho et al., 2021).

In brief, although the methodological adaptation of the MT program (4-month, twice a week on 35-minute sessions) and of an evaluation protocol carried out remotely through videoconference and/or telephone need further investigation to examine its feasibility and effects, it was perceived as an important strategy to counteract NCD progression that was particularly emphasized due to social isolation and home confinement (Borges-Machado et al., 2021). It was also a way to provide some sort of support to those older adults who found themselves confined under a particularly stressful and demanding situation.

PART III – Results

Chapter 4. Systematic Review and Meta-analysis on Multicomponent Training Physical Exercise Interventions

The present chapter includes one published paper.

4.1 *Systematic Review* – Effectiveness of multicomponent exercise interventions in older adults with dementia: a meta-analysis

Citation: Borges-Machado F, Lima N, Farinatti P, Poton R, Ribeiro O, Carvalho J. (2021) Effectiveness of multicomponent physical exercise interventions in older adults with dementia: a meta-analysis. *The Gerontologist*. 61(8): e449-e462. doi: 10.1093/geront/gnaa091.

ABSTRACT

Background and Objectives: Multicomponent training (MT) combines aerobic, strength, postural, and balance exercises, and may be a promising intervention strategy for dementia. This meta-analysis study aims to systematize evidence concerning the effectiveness of MT in physical fitness, cognition, and functionality on activities of daily living (ADL) in older adults with dementia, and to identify moderation patterns regarding training variables.

Research Design and Methods: Four databases were systematically searched to locate potential trials through March 2019. A total of 2.312 records were identified and a final set of 17 manuscripts reviewed; of these, 6 satisfied all eligibility criteria.

Results: Samples sizes ranged from 27 to 170 participants; MT programs lasted between 4 weeks up to 12 months, took place from a daily basis to twice a week, and sessions ranged from 30-60 min. The TESTEX scale was used to analyze the methodological quality, and the funnel plots to assess risk of bias. This meta-analysis revealed that MT interventions benefit older adults with dementia regarding ADL performance (ES= 0.313 [0.16 to 0.46]; $p<0.01$), but the evidence was not sufficiently robust to determine the effectiveness of MT on cognitive function and physical fitness, particularly, on agility.

Discussion and Implications: MT may be an important non-pharmacological strategy to enhance ADL functionality on older adults with dementia. Findings suggest that long-term interventions are more prevailing than high frequency and longer duration exercise sessions. Further evidence is needed for acknowledging its benefits in specific cognitive abilities and physical fitness. This meta-analysis is registered in PROSPERO (no. CRD42020141545).

Keywords: Cognition, exercise/physical activity, function/mobility, intervention, neurocognitive disorder.

INTRODUCTION

Dementia or neurocognitive disorder are umbrella terms used to describe a set of diseases that progressively affect the brain and several cognitive functions (American Psychiatric Association, 2013; WHO, 2017). In 2012, the World Health Organization (WHO) placed this condition as a global public heath priority (Alzheimer's Disease International, 2018). Approximately 5% of the world’s elderly population (roughly 47 million people) was affected by dementia in 2015, and estimations predict a total of 75 million in 2030 and 132 million by 2050 (WHO, 2017).

Globally, dementia represents one of the major causes of disability and dependence among older adults (WHO, 2017, 2018, 2019). The *Lancet Commission on Dementia Prevention, Intervention and Care* (2017) has recently emphasized that effective interventions to delay or prevent dementia cases should address multiple reversible risk factors like physical inactivity, depression, metabolic and cardiovascular disease (diabetes, hypertension, and obesity), hearing loss, smoking, social isolation, and poor education (Livingston et al., 2017).

Physical inactivity accounts for 3.8% of cases of dementia worldwide (Sallis et al., 2016) and is the highest (out of 7 potentially modifiable) population-attributable risk factors (Norton, Matthews, Barnes, Yaffe, & Brayne, 2014) – between diabetes mellitus, midlife hypertension and obesity, depression, smoking and low educational attainment. It is estimated that around 3 million cases of Alzheimer’s Disease (AD), the most common dementia type, could be avoided with a 10-25% shift in modifiable risk factors (Blondell, Hammersley-Mather, & Veerman, 2014; Erickson, Weinstein, & Lopez, 2012). Blondell et al. (2014) emphasized that higher levels of physical activity were associated with an 18% reduction in the risk of dementia.

Physical activity is defined as any corporal movement produced by skeletal muscles contraction, resulting in energy expenditure. Exercises refer to planned, structured and systematic physical activity, with the purpose to maintain or improve at least one of the physical components of physical fitness

– aerobics, strength, flexibility, or coordination/balance (American College of Sports Medicine, 2017; Caspersen, Powell, & Christenson, 1985). Physical activity, and particularly exercise, might have a significative impact to improve cognition and/or prevent dementia (Erickson et al., 2019; Quaglio, Brand, & Dario, 2016; Winblad et al., 2016).

The accumulated evidence acknowledges the benefits of exercise as a preventive measure against dementia (Alty, Farrow, & Lawler, 2020; Gomes-Osman et al., 2018; Livingston et al., 2017; WHO, 2019) particularly AD (Norton et al., 2014; Radak et al., 2010). However, prior reviews suggest that the dose-response relationship of interventions to induce those benefits remains undefined (Cass, 2017; Kivipelto, Mangialasche, & Ngandu, 2018; Skinner, Ellis, & Pa, 2018).

Regular exercise appears to benefit individuals diagnosed with dementia due to its potential influence on treating the symptoms or delaying its progression, in addition to its intrinsic benefits upon physical fitness, cardiovascular health, and individual wellness (Almeida, Gomes da Silva, & Marques, 2019; Cass, 2017; Skinner et al., 2018; Smith et al., 2010). In fact, there is strong evidence that different modalities of exercise (e.g., aerobics, balance, strength training, or a combination of these) may help to delay functional and cognitive decline, minimize the risk of falls, manage neuropsychiatric symptoms, and improve ADL independence and quality of life in older individuals with cognitive impairment (American College of Sports Medicine, 2017; Forbes, Forbes, Blake, Thiessen, & Forbes, 2015).

Forbes et al. (2015) and Skinner et al. (2018) reinforced the need to identify the best combination of training variables (frequency, intensity, type, and time – or *FITT*) appropriated to a specific type/severity of disease and considering the right target outcome. In fact, the therapeutic role of exercise as a non-pharmacological adjuvant treatment of patients diagnosed with dementia needs further evidence (Livingston et al., 2017).

This meta-analysis focuses on a specific training methodology entitled Multicomponent Training (MT). It has been suggested that MT combining aerobic, strength, postural, and balance exercises (Baker, Atlantis, & Singh, 2007) can improve functional and cognitive performances in healthy older adults (Baker et al., 2007; Carvalho, Marques, & Mota, 2009; Toraman, Erman, & Agyar, 2004), and seems to be a feasible intervention for older adults with dementia (Borges-Machado et al., 2019; Kirk-Sanchez & McGough, 2014; Sampaio et al., 2020; Sampaio, Marques, Mota, & Carvalho, 2016; Smith et al., 2010). These components must be combined during each exercise session and distributed over time along training planning. Despite multimodal methodologies have been presented as feasible – and to provide a maximum benefit on several dimensions for individuals with dementia (Burton et al., 2015; Hernandez et al., 2015; Lam et al., 2018) –, the existent systematic reviews and meta-analytical studies regarding efficacy of exercise for people with dementia do not focus on this specific training methodology (Blankevoort et al., 2010; Farina, Rusted, & Tabet, 2014; Forbes et al., 2015; Gomes-Osman et al., 2018; Groot et al., 2016; Heyn, Abreu, & Ottenbacher, 2004; Lam et al., 2018; Pitkala, Savikko, Poysti, Strandberg, & Laakkonen, 2013; Smith et al., 2010).

In short, stronger evidence is warranted to confirm the role of MT in the improvement of cognitive function, ADL functionality, and physical fitness of older adults with dementia. Moreover, we could not find prior studies investigating the role of FITT components within MT as moderators of changes in cognitive and functional conditions.

To address this gap in the literature, the present meta-analysis includes controlled trials of MT interventions for older adults diagnosed with dementia considering the two following objectives: (1) to determine MT effectiveness to improve physical fitness, cognition, and ADL functionality; (2) to identify moderation patterns of those effects in regard to FITT training variables.

METHODS

This meta-analysis is consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Moher et al., 2015), and was registered in the International Prospective Register of Systematic Reviews (registration no. CRD42020141545) – available on request. PRISMA checklist can be consulted in Supplementary Table 1.

Study inclusion criteria

The systematic review included studies published in English meeting the following criteria: (a) controlled trials (randomized or not); (b) exercise interventions conducted with older adults clinically diagnosed with dementia (from mild to severe stages); (c) Studies performed with humans, with a mean age 65+ years old; (d) interventions applying exclusively MT; (e) peer-reviewed studies. In brief, only trials investigating the effect of MT *vs.* non-exercise control groups on physical fitness, cognitive function, or ADL functionality were included. There was no restriction on intensity, frequency, and duration of exercise programs. Studies exclusively performed with participants diagnosed with Parkinson's disease, Huntington's disease or other rare forms of dementia were excluded, since these patients tend to exhibit significant motor/functional limitations.

Literature search strategy

Potential trials were identified through an electronic literature search using PubMed, Web of Science, SCOPUS (including Embase), and SportDiscus databases. The first two authors (F. Borges-Machado and N. Silva) systematically searched the databases to locate potential trials through March 2019. A Boolean search strategy using the following combination of medical subject heading (MeSH) descriptors and their synonyms was applied: "exercise," "motor activity," "circuit-based," "dementia," "neurocognitive (disorder/disease)," "cognition," "executive function," "activities of daily living," "functional (independence/ performance/ autonomy)," "physical (fitness/ conditioning) ," as presented on Supplementary Table 2.

Study Selection

The same two authors (F. Borges-Machado and N. Silva) further screened all potential reports using a multi-stage review process: (a) by title only; (b) by title and abstract; and (c) finally by full-text review. This process was completed using a spreadsheet program from Microsoft. After a detailed review of the articles, F. Borges-Machado conducted manual searches in order to identify additional studies that met the inclusion criteria by consulting the references list of the included studies. Any disagreements regarding potential inclusion or exclusion of studies were resolved by discussion between the authors to achieve consensus. Inter-rater reliability regarding study selection was assessed by means of Cohen's kappa, reporting a substantial agreement k= 0.742 (p < 0.002); 95% IC [0.41 to 1.08].

Data Extraction, Quality Assessment and Study Outcomes

Data from studies were extracted independently by one author (F. Borges-Machado) according to the following categories: (a) study identification - authors, publication year, country, study design; (b) sample characteristics - size, sex proportion and age, type of dementia, clinical dementia diagnosis criteria, scores in the Mini-Mental State Examination (MMSE) and/or Clinical Dementia Rating (CDR); (c) ADL functionality (basic and instrumental activities of daily living measured through validated questionnaires), cognitive function, and physical fitness (gait speed, agility, balance, upper and lower body strength, flexibility, cardiorespiratory capacity and motor hand function) outcomes with level of significance; (d) control group treatment; and (e) exercise intervention – FITT variables, intensity monitoring, supervision, design setting. Corresponding authors were contacted to request additional data/ information when required.

As presented on Supplementary Table 3, study quality was assessed by means of the TESTEX Scale (Smart et al., 2015), a 12-point checklist with higher scores (maximum 15 points) indicating better study quality.

Effect Size Estimate

The *Hedge's g* effect size was used to quantify alterations on cognition, ADL functionality and physical fitness (agility) from multicomponent interventions, defined as corrected standardized mean difference (SMD) between two groups based on the pooled, weighted standard deviation (SD; Durlak, 2009).

Initially the paired difference *(mean experimental group – mean control group)* and paired difference standard deviation *(experimental* SD^2 + *control* SD^2 *– 2 x intertrial correlation x experimental SD x control SD)*$^{1/2}$ were calculated. Subsequently, we determined the standardized mean difference *(paired difference x (2 – 2 x intertrial correlation))*$^{1/2}$ *÷ paired difference SE)* and the standardized mean difference SE (standard error) *((1/n + standardized mean difference*^{2} *÷ (2 x n))*$^{1/2}$ *x (2 – 2 x correlation factor))*$^{1/2}$.

Thus, the correction factor obtained by the equation *1 – {3 ÷ [4 x (total n –2) –1]* was multiplied by the standardized mean difference to estimate the *Hegde's g* (Borenstein, Hedges, & Higgins, 2009). When studies reported only the SE value, the SD was calculated by multiplication of SE by the square root of the sample n. The inter-study correlation factor (correlation between data from experimental and control groups) was not provided by any of the studies, therefore the value a SMD of 0.5 was considered across studies. A positive value of *Hedge's g* ES indicate that the experimental group was superior on a positively oriented outcome measure (ADL functionality, physical fitness or cognition), when comparing to the control group (Durlak, 2009).

Sensitivity analysis were performed to confirm if the calculated effect sizes of the included studies were dependent of each other (Becker, 1988; Card, 2011).

The *Cochran Q* was calculated to analyze whether the individual studies' treatment effects are farther away from the common effect, beyond what is expected by chance, i.e., to verify if the homogeneity of the observed effect sizes were significant. The *Cochran Q* was converted to a standardized homogeneity measure (I^2 statistic) and to the correspondent confidence interval (95% CI) to evaluate how much heterogeneity was present on the included sample – ranging from 0 to 100%, representing to total of variation across studies – with values of 25, 50 and 75% corresponding to low, moderate and high heterogeneity (Higgins, Thompson, Deeks, & Altman, 2003). As the I^2

approaches 100% and CI do not include 0% the hypothesis of homogeneity is rejected and is more probable that heterogeneity has occurred.

Statistical Analysis

The meta-analysis and meta-regressions were executed through the *Comprehensive Meta Analysis* program (version 2.2, Biostat^{TM} Inc. Englewood, NJ, USA). The random-effect model was applied based on the possibility of the samples presenting unknown particularities that could interfere with the true effect of the intervention. Differences between variables of the subgroup were tested trough Q test based on ANOVA, namely: age (years), % women, BMI, total intervention duration (weeks), weekly frequency, session duration (min), TESTEX Scale, Journal Impact Factor. The risk of bias across studies was analyzed through funnel plots with effect sizes (*x*-axis) versus the standardized mean difference to each group of study (*y*-axis). Additionally, the non-parametric “trim and fill” method of Duval and Tweedie’s was also used to test and correct potential publication biases (Hoffman, 2019).

RESULTS

Study Selection and Quality Assessment

A total of 2.312 records were retained after removing duplicates. Of these, 2.295 trials were excluded based on titles and abstracts. The reasons were: samples not composed by human individuals with dementia (k = 1.805); interventions without exercise (medication, genetics, behavioral strategies, etc.), multimodal (k = 414), or trials that did not apply MT or did not report the presently investigated outcomes (k = 86). Of the 17 manuscripts retained for full-text review, only five satisfied all inclusion and exclusion criteria and were included in the meta-analysis. For the qualitative analysis, however, six studies were considered. Figure 1 presents the *PRISMA* literature review flowchart.

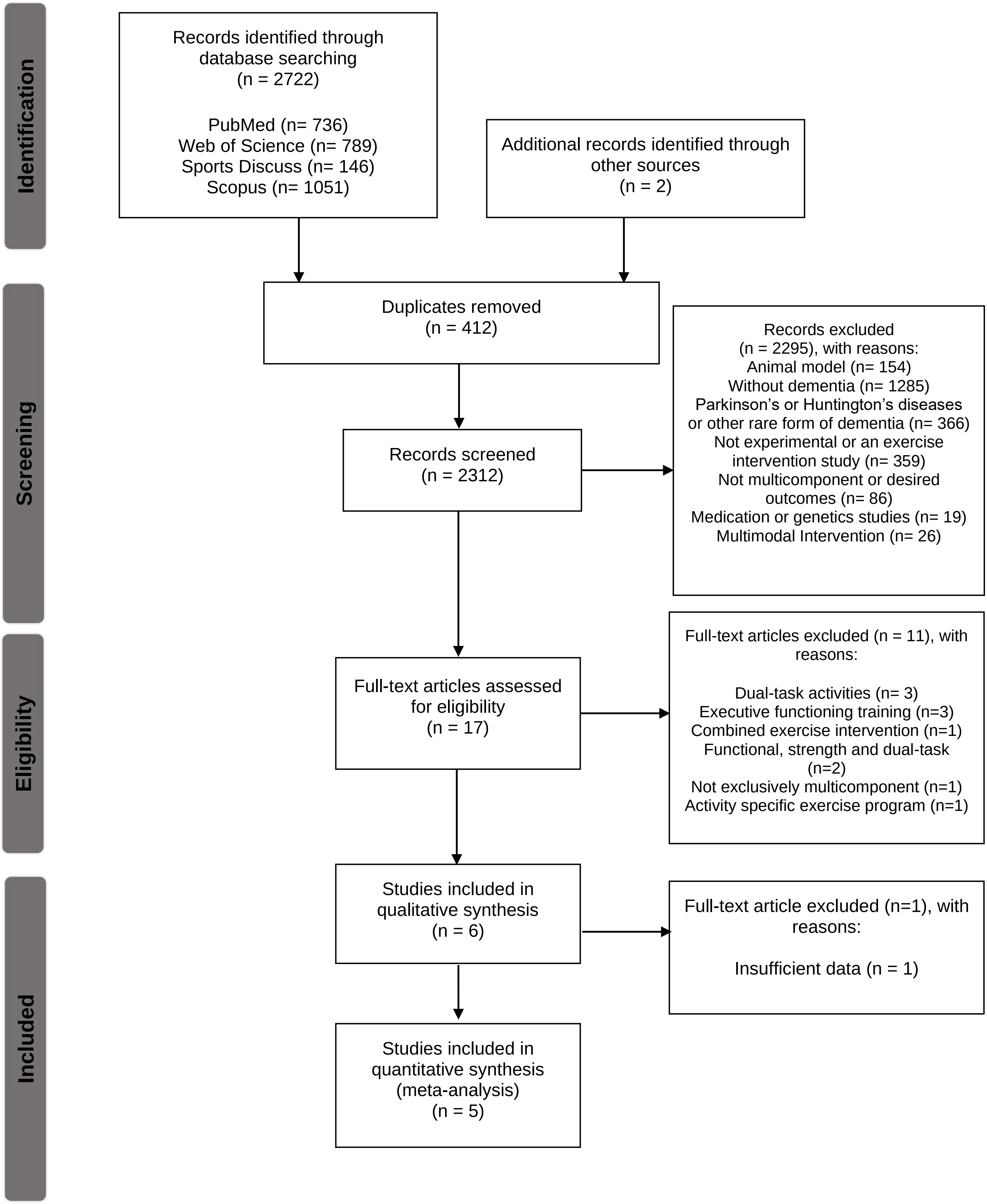


Figure 1. PRISMA flow chart diagram showing the articles screened and included in the meta-analysis study (n = 5)

Sample and Study Characteristics

Six controlled trials (Barreto et al., 2017; Burge et al., 2016; Rolland et al., 2007; Sampaio et al., 2016; Steinberg, Leoutsakos, Podewils, & Lyketsos, 2009; Vreugdenhil, Cannell, Davies, & Razay, 2012) were included in qualitative analysis. Of these, one was a non-randomized trial (Sampaio et al., 2016) and two were pilot studies (Barreto et al., 2017; Steinberg et al., 2009). As presented in Table 1, sample sizes across the studies ranged from 27 (Steinberg et al., 2009) to 160 (Burge et al., 2016) participants clinically diagnosed with dementia (n=489), with a mean age of 80.9 years old [age range: 51-93], 67.48% (n=330) were female and presented a *Mini-Mental Status Examination* mean score of 15.03 ± 5.69 points, or 81% of participants had a total score lower than 20 points.

Table 1. Summary of the included studies characteristics

Authors (publication year)	Country	Study Design	Sample Characteristics						Primary and Secondary Outcomes			Control Group
			N [a]	IG *% female; Mean (SD or range)*	CG *% female; Mean age (SD or range)*	Type of dementia	Clinical Dementia criteria	Stage of dementia (MMSE or CDR score) [b]	Physical Fitness	ADL Functionality	Cognitive Function	
Barreto et al. (2017)	France	Pilot Randomized Controlled Trial	97	93.2% 88.3(5.1)	76.6% 86.9(5.8)	AD, VaD, MD	DSM-IV	MMSE ≤ 20 IG: 11.4(6.2) CG: 10.8(5.5)	Time vs. Group baseline & 6mo: SPPB (p=0.22) Gait Speed (p=0.30)	IG vs.CG 3 & 6mo, respectively: ADCS-ADL-sev (p<0.001) ADCS-ADL-sev (p=0.23) Time vs. Group baseline & 6mo: ADCS-ADL-sev (p=0.19)	Time vs. Group baseline & 6mo: MMSE (p=0.43)	Social Activity Group (2 x week, 60 min, 24-week)
Burge et al. (2016)	Switzerland and Belgium	Multisite Randomized Controlled Trial	170	48.7% 81.7(7.7)	53.7% 81.1(7.7)	AD, VaD, MD, LbD, FtD, SD	ICD-10	CDR = 3 IG: 32.1% CG: 34.1% MMSE ≤ 20 IG: 84.2% CG: 78.1%	N/A	Time vs. Group baseline & 2wk follow-up: BI (p=0.001) FIM (p=0.002)	N/A	Social Group (videos or other activities)

Rolland et al. (2007)	France	Randomized Controlled Trial	134	71.7% 82.8(7.8)	79.1% 83.1(7.0)	AD	NINCDS-ADRDA	MMSE ≤ 25 IG: 9.7(6.8) CG: 7.9(6.4)	IG vs.CG baseline & 6mo: Walk speed Test (*p*=0.01) Get-up-and-go Test (*p*=0.68) One-leg Balance Test (*p*=0.47) IG vs.CG after 12mo: Walk speed Test (p=0.002) Get-up-and-go Test (*p*=0.31) One-leg Balance Test (*p*=0.34)	IG vs.CG baseline & 6mo: KATZ-ADL (*p*=0.51) IG vs.CG after 12mo: KATZ-ADL (*p*=0.02)	N/A	Routine medical care
Sampaio et al. (2016)	Portugal	Non-randomized Controlled Trial	37	78.9% 84.8(5.9)	72.2% 83.3(5.3)	AD	Not reported	CDR IG: 1.68(0.48) CG: 1.67(0.49) MMSE IG: 14.9 (6.0) CG: 16.1 (4.2)	Time vs. Group baseline & 6mo: Chair Stand Test (*p*<0.001) Arm Curl Test (*p*<0.001) Chair Sit-and-Reach Test (*p*<0.001) Back Scratch Test (*p*=0.022) 8-Foot Up and Go Test (*p*=0.029) 2-min Step Test (*p*<0.001)	N/A	Time vs. Group baseline & 6mo: MMSE (p=0.008)	Routine medical care
Steinberg et al. (2009)	United States	Pilot Randomized Controlled Trial	27	71.4% 76.5(3.9)	69.2% 74.0(8.1)	AD	NINCDS-ADRDA	MMSE IG: 20.1(5.1) CG: 15.5(5.4)	Time vs. Group baseline & 12wk: Jebsen Total Time Test (*p*=0.04) Walking Speed Test (*p*=0.77) 5 Chair Sit to Stand Test (*p*=0.22)	N/A	Time vs. Group baseline & 12wk: BNT (*p*=0.26) HVLT (*p*=0.19)	Home safety assessment

Vreugdenhil et al. (2012)	Australia	Randomized Controlled Trial	40	45% 73.5(51-83)	75% 74.7(58-89)	UD, AD	DSM-IV NINCDS-ADRDA	MMSE IG: 22.9(5.0) CG: 21.0(6.3)	Time vs. Group baseline & 4mo: Functional Reach (*p*=0.032) TUG (*p*=0.004) Sit-to-stand (*p*<0.001)	Time vs. Group baseline & 4mo: BI (*p*=0.047) IADL (*p*=0.007)	Time vs. Group baseline & 4mo: MMSE (*p*=0.001) ADAS-Cog (*p*=0.001)	Usual Treatment

AD - Alzheimer's Disease; ADAS-Cog - Alzheimer's Disease Cognitive Scale – Cognitive Subscale; ADCS-ADL-sev - Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory for Severe Alzheimer's Disease; BI - Barthel Index of Activities of Daily Living; BNT - Boston Naming Test; CDR - Clinical Dementia Rating; CG - Control Group; DSM-IV - Diagnostic and Statistical Manual of Mental Disorders 4th Edition; FIM - Functional Independence Measure; FtD – Frontotemporal Dementia; HVLT - Hopkins Verbal Learning Test; IADL - Instrumental Activities of Daily Living; ICD-10 - International Classification of Diseases 10th Revision; IG - Intervention Group; JTT - Jebsen Total Time; KATZ-ADL- Katz Index of ADLs; LbD – Lewy-Body Dementia; MD - Mixed Dementia; MMSE - Mini Mental State Examination; mo - months; N/A – Not Applicable; NINCDS-ADRDA - National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; SD – Subcortical Dementia; SFT - Senior Fitness Test; SPPB - Short Physical Performance Battery; TUG - Timed Up and Go Test; UD - Undefined Dementia; VaD - Vascular Disease; wk - weeks; YPAS - Yale Physical Activity Survey.
a - sample size at baseline; b - Mean (SD) or percentage

Dropouts, Adherence and Adverse Events

The greatest attrition rate occurred in the study conducted by Rolland et al. (2007), specifically among controls (19%). Sampaio et al. (2016) reported an attrition rate of 18.9% - 7 out of 37 participants dropout in both groups from initial to final assessments. Barreto et al. (2017) reported a dropout rate of 6.2% and 12.4% after 3 and 6 months of intervention, respectively. In Burge et al.'s study (2017), 10 out of 170 participants failed to finish the MT intervention, representing an attrition rate of 5.88%. Vreugdenhil et al. (2012) evaluated 27 participants at baseline, all of whom completed the final evaluations. Steinberg et al. (2009) did not report information on the attrition rate.

Regarding the mean adherence to MT interventions, three studies reported rates around 70-80% (Barreto et al., 2017; Sampaio et al., 2016; Steinberg et al., 2009). In the study conducted by Burge et al. (2016), participants in experimental and control groups were present in 13 out of 20 sessions. Similarly, in Rolland et al.'s (2007) study, most participants had low adherence (participated in less than 30 sessions). Vreugdenhill et al. (2012) did not report the adherence levels to their MT intervention.

Three studies addressed potential adverse events of MT interventions for older adults with dementia (Barreto et al., 2017; Rolland et al., 2007; Steinberg et al., 2009), including mortality, hospitalizations, fractures, falls, and other non-serious and serious events. Barreto et al. (2017) found greater occurrence of falls in the control group, and Rolland et al. (2007) reported higher hospitalization rates among patients that exercised. Although Steinberg et al. (2009) reported serious adverse events in individuals assigned to the intervention group, none of them was due to the MT intervention.

Design of the Interventions

Routine medical care (Rolland et al., 2007; Sampaio et al., 2016; Vreugdenhil et al., 2012) or other specific health-related care (Steinberg et al., 2009) were the most frequent intervention offered to control groups. Two studies offered social activities for the control groups. Barreto et al. (2017) proposed 1-h sessions of arts and crafts or therapeutic music, twice a week for 24 weeks. In Burge et al.'s study (2016), patients watched videos or played social games five times a week during 30 min.

The length of exercise interventions (described on Table 2) was between 4 weeks and 12 months, twice a week (Barreto et al., 2017; Rolland et al., 2007; Sampaio et al., 2016), five times a week (Burge et al., 2016), or in a daily basis (Steinberg et al., 2009; Vreugdenhil et al., 2012). The duration of exercise sessions ranged from 30 to 60 min (51.3 ± 12.4 min). Vreugdenhill et al.'s (2012) intervention consisted of 10 simple exercises in addition to at least 30 min of brisk walking. Participants in Steinberg et al.'s (2009) study were instructed to achieve daily specific scores in three physical components. Older adults with AD accrued points for each activity totally or partially completed (as registered on diaries by their cares), considering the pre-defined weekly goals for aerobics (6 points) and strength/balance (4 points each). These were the only studies where caregivers were included in the implementation of the exercise interventions (Steinberg et al., 2009; Vreugdenhil et al., 2012).

Considering the size of exercise groups, Barreto et al. (2017) did not report any information. According to Rolland et al. (2007), each group was formed of 2 to 7 participants (mean 5.2), based on their baseline physical abilities, cognitive function, behavior disturbances and affinity. Burge et al. (2016) formed groups of at most 4 participants, and on Sampaio et al.'s (2016) study each exercise group consisted of 4 to 7 individuals with dementia.

In three studies, music accompanied the exercise sessions (Burge et al., 2016; Rolland et al., 2007; Sampaio et al., 2016).

Table 2. Multicomponent exercise programs description

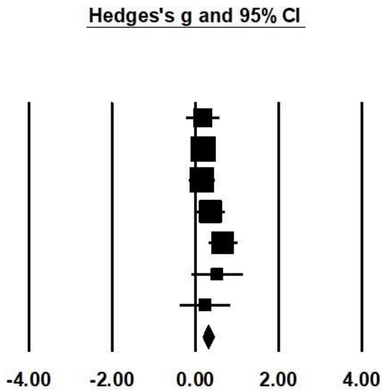
Study	Intensity (min/sess)	Frequency (sess/wk)	Duration	Exercise Protocol	Exercise intensity	Design Setting	Supervision
Barreto et al. (2017)	60	2	24wk 48 sess	Warm-up 10 min Coordination/ balance 10 min Strength 10-15 min Aerobics 20 min Cool-down 5-10 min	Moderate [a]	7 NH	Exercise Instructors
Burge et al. (2016)	30	5	4wk 20 sess	Rolland et al. (2007) exercise protocol: Strength, flexibility, walking and balance training	Moderate [b]	5 Acute psychiatric settings	Occupational, Physical or Psychomotor Therapists
Rolland et al. (2007)	60	2	12mo 88 sess	Inside circular walking trail created and adapted to each exercise group After warm-up and stretching individuals were motivated to walk (at least during half of the session) Strength, flexibility and balance exercises intercepted on pre-determined stations along the trail	Moderate [b]	5 NH	Occupational Therapist
Sampaio et al. (2016)	45-55	2	6mo 48 sess	Warm-up 5-10 min Specific training (Aerobics 15 min & Strength, Coordination/ Balance 15-20 min) Cool-down (flexibility & respiratory exercises) 5-min	Moderate [c]	9 NH	Exercise Instructors
Steinberg et al. (2009)	Points for each aerobic, strength and balance completed activities Weekly goals: 6 aerobic points, 4 strength and balance points	Daily, reported on weekly diaries	12wk	Aerobics (brisk walking) Strength training (with resistive brands and ankle weights) Balance & flexibility training (tandem walks, chair sit to stands, forward and backward walks, change of gravity center)	Moderate [b]	Home-based exercise program	Caregivers & Exercise Physiologist
Vreugdenhil et al. (2012)	At least 30 min of brisk walking and 10 simple exercises	Daily	4mo	Home Support Exercise Program: 10 simple exercises for upper and lower body strength, balance training; & at least 30 min of endurance (brisk walking)	Not monitored [d]	Home-based exercise program	Caregivers

min - minutes; mo - months; NH – Nursing Home; sess - sessions; wk - week; a - any objective measure used; b - contacted by e-mail for details, but no response received; c - Borg Scale of Perceived Exertion; d - Quote: “increased difficulty on exercises over time”; exercise intensity wasn’t objectively monitored

Major Outcomes

The statistical analysis was conducted with 16 trials, identified through the 5 studies included in the meta-analysis. Meta-analysis was performed regarding ADL functionality, cognition and agility, as data was not sufficient to proceed to further analysis regarding other physical fitness components. The effects sizes of MT are represented on Figures 2-4, respectively. In overall, this analysis revealed a positive impact of MT exercise on ADL functionality with an ES of 0.313 (0.16 to 0.46; $p<0.01$). Regarding cognition (ES= 0.29 [-0.00 to 0.59]; $p=0.05$) and agility (ES= 0.153 [-0.052 to 0.356]; $p=0.14$), results showed that MT intervention did not promote modification on these outcomes. The I^2 statistic revealed low heterogeneity for the studies that investigated ADL ($I^2=8.1$; $p<0.01$), cognition ($I^2=7.8$; $p=0.35$), and agility ($I^2=0.0$; $p=0.48$).

Study name	Statistics for each study			
	Hedges's g	Lower limit	Upper limit	p-Value
Barreto et al. (2017)	0.179	-0.229	0.588	0.390
Burge et al. (2016)_Trial 1	0.186	-0.123	0.495	0.238
Burge et al. (2016)_Trial 2	0.156	-0.153	0.465	0.323
Rolland et al. (2007)_Trial 1	0.367	0.027	0.706	0.034
Rolland et al. (2007)_Trial 2	0.660	0.314	1.006	0.000
Vreugdenhil et al. (2012)_Trial 1	0.527	-0.092	1.145	0.095
Vreugdenhil et al. (2012)_Trial 2	0.232	-0.378	0.841	0.456
	0.313	0.163	0.463	0.000



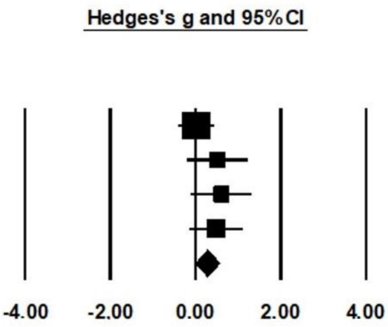
g= 0.313 (0.163 to 0.463), p< 0.01;

Q= 6.533, df= 6; I^2= 8.1%, p< 0.01

Barreto et al. (2017):ADCS-ADL-sev_6months; Burge et al. (2026):BI_2week_Trial 1; Burge et al. (2026):FIM_2week_Trial 2; Rolland et al. (2007):KATZ-ADL_6months_Trial 1; Rolland et al. (2007):KATZ-ADL_12months_Trial 2;

Figure 2. Effect of MT exercise interventions on ADL's

Study name	Hedges's g	Lower limit	Upper limit	p-Value
Barreto et al. (2017)	0.013	-0.395	0.421	0.950
Sampaio et al. (2016)_Trial 1	0.511	-0.197	1.220	0.157
Sampaio et al. (2016)_Trial 2	0.606	-0.107	1.319	0.096
Vreugdenhil et al. (2012)	0.479	-0.138	1.095	0.128
	0.295	-0.003	0.592	0.050

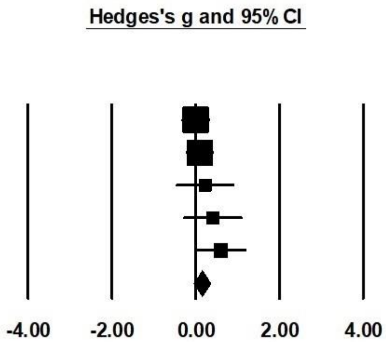


Q= 3.256, df= 3; I^2= 7.8%, p= 0.35

Barreto et al. (2017):MMSE _6months; Sampaio et al. (2016):MMSE_3months_Trial 1; Sampaio et al. (2016):MMSE_6months_Trial 2; Vreugdenhil et al. (2012):MMSE_4months

Figure 3. Effect of MT exercise interventions on cognition

Study name	Hedges's g	Lower limit	Upper limit	p-Value
Rolland et al. (2007) _Trial 1	0.000	-0.337	0.337	1.000
Rolland et al. (2007)_ Trial 2	0.097	-0.240	0.434	0.571
Sampaio et al. (2016)_ Trial 1	0.227	-0.472	0.926	0.524
Sampaio et al. (2016)_ Trial 2	0.412	-0.292	1.116	0.251
Vreugdenhil et al. (2012)	0.600	-0.022	1.221	0.059
	0.153	-0.052	0.356	0.140



Q= 3.484, df= 4; I^2= 0.0%, p= 0.48

Rolland et al. (2017):Get-up-goTest_6months_Trial 1; Rolland et al. (2017):Get-up-goTest_12months_Trial 2; Sampaio et al. (2016):8-footUpAnd GoTest_3monts_Trial 1; Sampaio et al. (2016):8-footUpAnd GoTest_6monts_Trial 2; Vreugdenhil et al. (2012):TUG_4months

Figure 4. Effect of MT exercise interventions on agility

Subgroup Analyses

Table 3 details the moderators of ADL effect, with the purpose of addressing the quantitative influence of characteristics of the included studies or their participants on the effect size of ADL's. Thus, only the total time (in weeks) of the MT program duration influenced the ADL effect. For each additional week of intervention, the total effect size related to ADL increased 0.007 (p<0.05). Neither age of participants (p=0.73), gender (p=0.47) or body mass index [BMI] (*p*=0.94), and other aspects concerning the studies' quality (*p*=0.75) demonstrated differences in intervention effects.

Table 3. Meta-regression analyses of MT intervention characteristics regarding ADL functionality

Variable	N (trials)	*SLOPE*	*p*-value
Age (years)	7	-0.006	0.73
% Women	7	0.003	0.47
BMI	5	0.015	0.94
Total intervention duration (weeks)	7	0.007	0.04*
Weekly frequency	7	-0.044	0.27
Session duration (min)	7	0.008	0.11
TESTEX Scale	7	-0.024	0.75
Journal Impact Factor	7	0.007	0.24

* Statistically significant difference (*p*<0.05)

Risk of bias

Publication bias effect was verified using the Egger test and analyzed trough funnel plots combined with Duval and Tweedie's "trim and fill" correction method (Figures 5 -7). No publication bias was identified for the analyzed variables (Figure 5. ADL: *g* observed= 0.311 [0.169–0.454], *g* adjusted= 0.311 [0.169–0.454]; Figure 6. Cognition: *g* observed= 0.281 [−0.000–0.563], *g* adjusted= 0.154 [−0.090–0.400] and Figure 7. Agility: *g* observed = 0.152 [-0.050–0.355], *g* adjusted= 0.067 [-0.118–0.253].

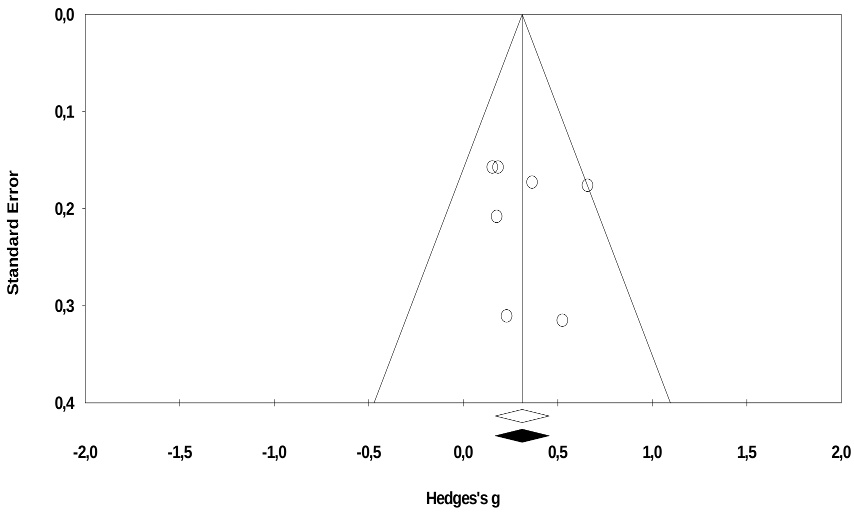


Figure 5. Funnel Plot of Standard Error by Hedge's (ADL's)

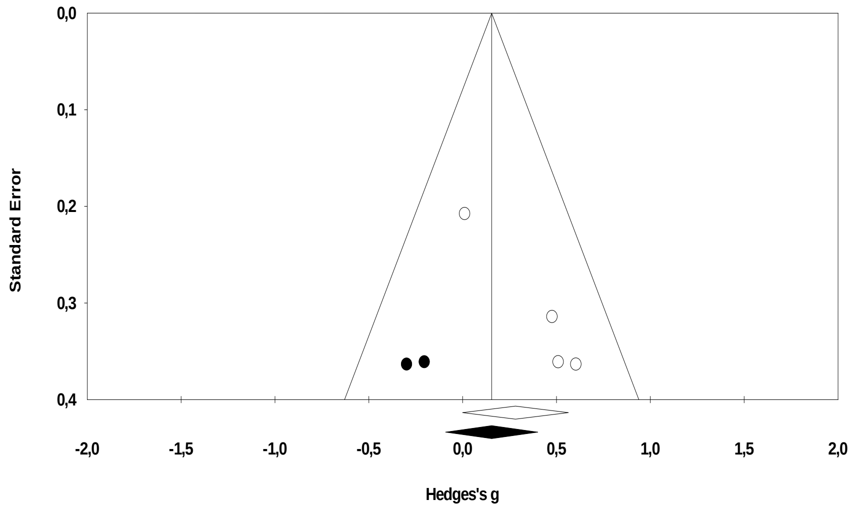


Figure 6. Funnel Plot of Standard Error by Hedge's (cognition)

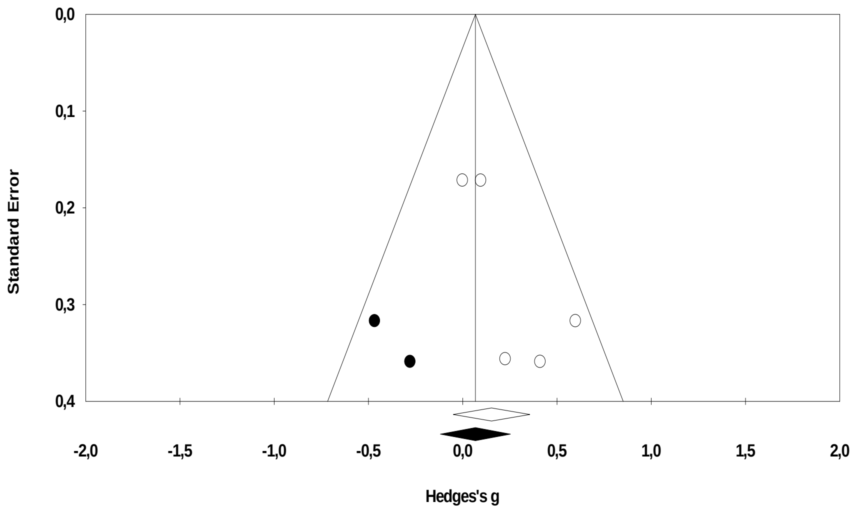


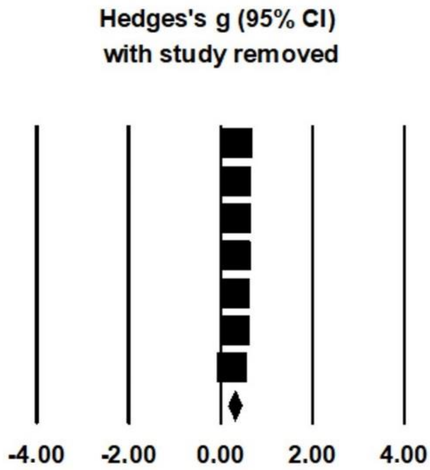
Figure 7. Funnel Plot of Standard Error by Hedge's (agility)

Sensitivity Analyses

The sensitivity analyses with studies removal over the effects sizes on ADL trials (Figure 8) did not show any influence on obtained results.

Study name	Point	Lower limit	Upper limit	p-Value
Burge et al. (2016)_Trial 2	0.354	0.193	0.514	0.000
Barreto et al. (2017)	0.330	0.178	0.482	0.000
Burge et al. (2016)_Trial 1	0.345	0.185	0.506	0.000
Vreugdenhil et al. (2012)_Trial 2	0.316	0.170	0.463	0.000
Rolland et al. (2007)_Trial 1	0.300	0.143	0.457	0.000
Vreugdenhil et al. (2012)_Trial 1	0.300	0.153	0.446	0.000
Rolland et al. (2007)_Trial 2	0.240	0.084	0.397	0.003
	0.312	0.169	0.454	0.000

(Statistics with study removed)



Barreto et al. (2017):ADCS-ADL-sev_6months; Burge et al. (2026):BI_2week_Trial 1; Burge et al. (2026):FIM_2week_Trial 2; Rolland et al. (2007):KATZ-ADL_6months_Trial 1; Rolland et al. (2007):KATZ-ADL_12months_Trial 2; Vreugdenhil et al. (2012):BI_4months_Trial 1; Vreugdenhil et al. (2012):IADL_4months_Trial 2

Figure 8. Sensitivity analysis of ADL effect size

DISCUSSION

Summary of Evidence

This review included 5 articles with a total of 438 participants. A sixth article, referring to Steinberg et al.'s (2009) study, was initially included, but due to insufficient data it could not be considered in the statistical analysis. Most participants were women, with an average age greater than 73 years. Alzheimer's disease was the most referred type of dementia, ranging from light to severe stages.

High heterogeneity was found among interventions' design, evaluation instruments and measures, as well as on the description of dementia diagnosis and/or stage. The MT intervention programs varied widely regarding the following aspects: combination of the different physical fitness components and the amount of time dedicated to each one of them; frequency, duration and intensity of exercise sessions; settings where MT intervention were implemented (e.g., nursing homes, psychiatric hospitals, or patients' home). Such diversity was also observed across physical fitness levels, functional abilities, and dementia stages, as well as regarding the sizes of exercise groups and professionals' background involved on prescription, supervision, and evaluation. Therefore, results must be analyzed with caution once these differences may have a significant impact on MT interventions results (Forbes et al., 2015; Livingston et al., 2017). Regarding control groups, routine medical care or other specific health-related care were the most frequent intervention offered to older adults diagnosed with dementia. As highlighted on previous research (Borges-Machado et al., 2019; van der Wardt et al., 2017), studies designed for individuals diagnosed with dementia should consider other types of interventions, such as monthly recreational sessions, due to retention purposes and accurate ethical procedures.

Significantly high attrition rates were reported (nearly 20%), however, adherence to intervention was also relatively satisfactory – nearly 70-80% of attendance levels on three of the included studies. These differences between attrition and adherence rates must be analyzed with caution, considering the possible influence of design settings, and the inclusion of family caregivers. Thereby, the studies conducted at home-based settings did not report any dropouts, possibly due to caregivers' influence on promoting physical exercise (Almeida et al., 2019; Steinberg et al., 2009; Vreugdenhil et al., 2012). As opposite, the MT intervention conducted with hospitalized older adults with dementia in acute psychiatric settings revealed a low overall adherence rate to the program, whose reasons have been appropriately presented (Burge et al., 2016). No serious events attributed to the studies were reported.

This meta-analysis revealed a positive impact of MT interventions on ADL functionality. Concerning cognitive function and physical fitness, specifically agility, results showed that MT intervention did not influence these outcomes.

In the analysis of ADL moderators, only the MT intervention duration influenced the effect size of this outcome. Heyn et al. (2004) also reinforced that longer exercise interventions (more than 23 weeks) were associated with greater benefits for individuals with dementia. Exercise sessions frequency or duration (min) did not influence ADL performance effect size. As stated by Forbes et al. (2015), the mitigation of dependence in ADL's, as result of dementia progressing, is critical for enhancing quality of life of both older adults with dementia and their caregivers, and may prevent or delay institutionalization.

Concerning cognitive function, the *Mini Mental State Examination* (Folstein, Folstein, & McHugh, 1975) was the only instrument used to measure this outcome. Although this cognitive screening tool is a worldwide reference, there's growing evidence referring it may be unsuitable to measure modifications on cognition of older adults diagnosed with dementia (Santana et al., 2016). Therefore, authors may consider its use as a limitation on analyzing MT intervention effectiveness. Farina et al. (2014) systematic review, whose aim was to assess the effectiveness of exercise in cognitive decline within AD, also reinforced that more important than analyzing general cognitive functions, subdomain changes must be addressed through a more comprehensive cognitive test battery. Future exercise studies might consider the importance of standardization outcome measures to evaluate cognitive function of older adults with dementia and, more importantly, include more comprehensive instruments. The high heterogeneity of studies designs also contributes for the uncertainty of effectiveness of exercise on improving cognitive function or delaying dementia progression (Erickson et al., 2019). The overall effect of MT interventions on cognition may also have been influenced by several clinical reasons, such as: different diagnostic medical criteria (DSM-IV, ICD-10 or NINCDS-ADRDA); variety of types of dementia; and dementia participants' disease severity, which ranged from mild to severe stages.

Finally, we observed that MT interventions were not effective improving agility on individuals diagnosed with dementia. Nevertheless, when analyzing the *Hedges' g* forest plots, it's possible to verify that results favors exercise. The limited number of studies included in this analysis may explain the absence of a statistically significant effect size over this outcome. In fact, although motor function, gait speed, cardiorespiratory capacity, strength, balance, and flexibility physical components had been measured, due to insufficient data, these analyses could not be performed.

To the best of our knowledge, physical fitness is not commonly considered as a primary outcome on these specific trials. However, considering the increased physical fitness' decline on older adults with dementia, and its impact over their ability to independently perform ADL functionality without fatigue, it seems imperative to be considered as such. Therefore, future exercise studies for people with dementia need to focus on measuring physical fitness effects through reliable instruments, minimizing the effects of cognitive impairment on physical performance (Forbes et al., 2015), as previously validated or, at least tested, by several authors (Blankevoort, van Heuvelen, & Scherder, 2013; Burton et al., 2015; Goncalves, Cruz, Marques, Demain, & Samuel, 2018; Lamb & Keene, 2017; Tappen, Roach, Buchner, Barry, & Edelstein, 1997).

Overall, this review and meta-analytic study highlight the impact of MT interventions (i.e., comprising several components of physical fitness), on promoting/ mitigating the decline of dementia participants' independence on performing daily tasks, which are critical to enhance theirs' and caregivers' quality of life. However, there is no strong evidence concerning the positive effects of MT training methodology on specific cognitive abilities and physical fitness. Further studies are needed for acknowledging these benefits

As long as review and meta-analytic studies only focus on generalized effects of exercise on dementia, particularly on cognitive outcomes, aerobic exercise at moderate intensity for older adults with dementia at mild to moderate stages of disease will remain the single existent guideline on exercise prescription for this health condition (American College of Sports Medicine, 2018; Erickson et al., 2019; Groot et al., 2016; Skinner et al., 2018; Smith et al., 2010). Therefore, research studies must identify the triad: stage/type of dementia; FITT variables; target outcome and defined pathway in order to effectively plan and prescribe exercise interventions for older adults with dementia (Forbes et al., 2015;

Skinner et al., 2018). It’s imperative that future review studies focus on specific training modalities (e.g., MT) to acknowledge its benefits upon a specific outcome, considering the different types/stages of dementia.

Limitations

The inclusion of only 5 studies may be a limitation of this meta-analysis. Firstly, the use of Baker et al. (2007) definition of MT methodology excludes exercise interventions that offer two or three physical fitness components, but separately on different sessions (vs. in the same session), which decreased the number of included studies. Secondly, the exclusion of several dementia types has also contributed to the removal of a considerable number of studies from our sample. However, these conditions imply adapted programs to patients’ mobility/functional limitations and disease progression specificities. The inclusion of only English studies may have also restricted our research.

Finally, the lack of statistical data from the included studies was also a limitation when analyzing the moderator effect of other variables on ADL functionality. Moreover, quality analysis of this review may be compromised by inexistent information on several criteria, as example, on methods used to control exercise sessions intensity and adverse events – determinant factors considering exercise prescription for older adults diagnosed with dementia. Therefore, researchers must ensure high methodological quality trials and provide all the information necessary for studies quality/reporting analysis (Smart et al., 2015), and describe statistical data, in order to guide strong recommendations of MT interventions for individuals diagnosed with dementia.

Future Practical Implications

With the increasing number of individuals diagnosed with dementia, this syndrome is now considered one of the main age-related health problems impacting the modern society (Alzheimer's Assocation, 2020; Arvanitakis, Shah, & Bennett, 2019), demanding a conjoint action of social and healthcare services to create and implement effective non-pharmacological strategies to treat and care the diagnosed individuals, and respective caregivers (WHO, 2019). Future research studies must consider MT intervention as a potentially effective training methodology on decreasing the progression of ADL dependence on older adults with dementia, which may impact the caregivers' ability to sustain their role. Exercise programs should be conducted by qualified professionals, in small size groups, and including enjoyable and appropriate activities for the participants, in order to sustain physical activity over a long period. Well-designed clinical trials should be conducted at community-based settings, and preferably include caregivers (Forbes et al., 2015; Heisz, Kovacevic, Clark, & Vandermorris, 2016).

Conclusions

This meta-analysis shows that MT interventions are effective in improving ADL performance of individuals diagnosed with dementia. Findings suggest that the program duration (long-term interventions) had superior influence on daily functionality than exercise sessions frequency and duration. Despite the methodological limitations, high-quality assumptions attested by heterogeneity, risk of bias and sensitivity analysis results were achieved. Finally, our results reinforce the need for future randomized controlled trials to acknowledge the effectiveness of MT interventions on cognitive function and physical fitness of older adults diagnosed with dementia, considering the combination of different intensity/frequency/time variables for different types/stages of dementia.

DECLARATIONS

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Conflict of Interest

None declared.

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Supplementary Material

Table 1. PRISMA checklist

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

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	10-11
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	11-12
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	12
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	11
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	12-13, and Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	13, and Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplementary Table 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	14-15, Only topic a, Table 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	16, Figures 2-4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	16-17, Figures 5-7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	17, Figure 8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17-21; relevance by key groups is not reported
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21-22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22-23
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2

Table 2. Literature search strategy

Source	Search Phrase	Filters
PubMed	(((exercise[MeSH Terms] OR motor activity[MeSH Terms] OR exercise therapy[MeSH Terms] OR Circuit-Based Exercise[MeSH Terms]) AND (dementia OR alzheimer's disease OR vascular dementia OR Neurodegenerative Disease OR Neurocognitive disorder)) AND (cognition[MeSH Terms] OR activities of daily living[MeSH Terms] OR physical fitness[MeSH Terms] OR Physical Conditioning, Human[MeSH Terms] OR functional performance OR functional independence OR functional autonomy OR cognitive performance OR strength OR cardiorespiratory OR balance OR mobility OR flexibility OR attention OR executive function OR memory OR language OR perceptual-motor abilities)) NOT animals study	English Humans Clin Trials Title/abstract
Web of Science	TS=((((“Exercise” OR “Exercises” OR “Physical Activity” OR “Activities, Physical” OR “Activity, Physical” OR “Physical Activities” OR “Exercise, Physical” OR “Exercises, Physical” OR “Physical Exercise” OR “Physical Exercises” OR “Acute Exercise” OR “Acute Exercises” OR “Exercise, Acute” OR “Exercises, Acute” OR “Exercise, Isometric” OR “Exercises, Isometric” OR “Isometric Exercises” OR “Isometric Exercise” OR “Exercise, Aerobic” OR “Aerobic Exercise” OR “Aerobic Exercises” OR “Exercises, Aerobic” OR “Exercise Training” OR “Exercise Trainings” OR “Training, Exercise” OR “Trainings, Exercise” OR “Motor Activity” OR “Activities, Motor” OR “Activity, Motor” OR “Motor Activities” OR “Exercise therapy” OR “Therapy, Exercise” OR “Exercise Therapies” OR “Therapies, Exercise” OR “Rehabilitation Exercise” OR “Exercise, Rehabilitation” OR “Exercises, Rehabilitation” OR “Rehabilitation Exercises” OR “Remedial Exercise” OR “Exercise, Remedial” OR “Exercises, Remedial” OR “Remedial Exercises” OR “Circuit-Based Exercise” OR “Circuit Based Exercise” OR “Circuit-Based Exercises” OR “Exercise, Circuit-Based” OR “Exercises, Circuit-Based” OR “Circuit Training” OR “Training, Circuit”) AND (“Dementia” OR “Dementias OR “Alzheimer disease” OR “Alzheimer's Disease” OR “Dementia, Senile” OR “Senile Dementia” OR “Alzheimer Syndrome” OR “Alzheimer Dementia” OR “Alzheimer Dementias” OR “Dementia, Alzheimer” OR “Dementias, Alzheimer” OR “Dementia vascular” OR “Dementias, Vascular” OR “Vascular Dementias” OR “Vascular Dementia” OR “Neurodegenerative Diseases” OR “Neurodegenerative Disease” OR Neurocognitive disorders” OR “Disorder, Neurocognitive” OR “Disorders, Neurocognitive” OR “Neurocognitive Disorder”)) AND (“Cognition” OR “Cognitions” OR “Cognitive Function” OR “Cognitive Functions” OR “Function, Cognitive” OR “Functions, Cognitive” OR “Activities of daily living” OR “ADL” OR “Activities, Daily Living” OR “Activity, Daily Living” OR “Daily Living Activities” OR “Daily Living Activity” OR “Living Activities, Daily” OR “Living Activity, Daily” OR “Limitation of Activity, Chronic” OR “Chronic Limitation of Activity” OR “Physical fitness” OR “Fitness, Physical” OR “Physical Conditioning, Human” OR “Conditioning, Human Physical” OR “Human Physical Conditioning” OR “Physical Training, Human” OR “Human Physical Training” OR “Training, Human Physical” OR “Functional performance” OR “functional independence” OR “functional autonomy” OR “cognitive performance” OR “strength” OR “cardiorespiratory” OR “balance” OR “mobility” OR “flexibility” OR “attention” OR “executive function” OR “memory” OR “language” OR “perceptual-motor abilities”)) NOT “animals study”)	English Article Not Review
SCOPUS	TITLE-ABS-KEY ((((Exercise OR “Physical Activity” OR “Physical Exercise” OR Acute OR Isometric OR Aerobic OR Training OR Motor OR Therapy OR Rehabilitation OR Remedial OR Circuit-Based Exercise OR Training) AND (Dementia OR Alzheimer OR Senile OR Vascular OR Neurodegenerative OR Neurocognitive)) AND (Cognition OR Cognitive OR “Activities of daily living” OR “ADL” OR Daily Living OR Fitness OR Physical Conditioning OR Physical Training OR “Functional performance” OR “functional independence” OR “functional autonomy” OR “cognitive performance” OR strength OR cardiorespiratory OR balance OR mobility OR flexibility OR attention OR “executive function” OR memory OR language OR “perceptual-motor abilities”)) AND NOT “animals study”)	English Article Human

SPORTSDISCUSS	(((“Exercise” OR “Exercises” OR “Physical Activity” OR “Activities, Physical” OR “Activity, Physical” OR “Physical Activities” OR “Exercise, Physical” OR “Exercises, Physical” OR “Physical Exercise” OR “Physical Exercises” OR “Acute Exercise” OR “Acute Exercises” OR “Exercise, Acute” OR “Exercises, Acute” OR “Exercise, Isometric” OR “Exercises, Isometric” OR “Isometric Exercises” OR “Isometric Exercise” OR “Exercise, Aerobic” OR “Aerobic Exercise” OR “Aerobic Exercises” OR “Exercises, Aerobic” OR “Exercise Training” OR “Exercise Trainings” OR “Training, Exercise” OR “Trainings, Exercise” OR “Motor Activity” OR “Activities, Motor” OR “Activity, Motor” OR “Motor Activities” OR “Exercise therapy” OR “Therapy, Exercise” OR “Exercise Therapies” OR “Therapies, Exercise” OR “Rehabilitation Exercise” OR “Exercise, Rehabilitation” OR “Exercises, Rehabilitation” OR “Rehabilitation Exercises” OR “Remedial Exercise” OR “Exercise, Remedial” OR “Exercises, Remedial” OR “Remedial Exercises” OR “Circuit-Based Exercise” OR “Circuit Based Exercise” OR “Circuit-Based Exercises” OR “Exercise, Circuit-Based” OR “Exercises, Circuit-Based” OR “Circuit Training” OR “Training, Circuit”) AND (“Dementia” OR “Dementias OR “Alzheimer disease” OR “Alzheimer's Disease” OR “Dementia, Senile” OR “Senile Dementia” OR “Alzheimer Syndrome” OR “Alzheimer Dementia” OR “Alzheimer Dementias” OR “Dementia, Alzheimer” OR “Dementias, Alzheimer” OR “Dementia vascular” OR “Dementias, Vascular” OR “Vascular Dementias” OR “Vascular Dementia” OR “Neurodegenerative Diseases” OR “Neurodegenerative Disease” OR Neurocognitive disorders” OR “Disorder, Neurocognitive” OR “Disorders, Neurocognitive” OR “Neurocognitive Disorder”)) AND (“Cognition” OR “Cognitions” OR “Cognitive Function” OR “Cognitive Functions” OR “Function, Cognitive” OR “Functions, Cognitive” OR “Activities of daily living” OR “ADL” OR “Activities, Daily Living” OR “Activity, Daily Living” OR “Daily Living Activities” OR “Daily Living Activity” OR “Living Activities, Daily” OR “Living Activity, Daily” OR “Limitation of Activity, Chronic” OR “Chronic Limitation of Activity” OR “Physical fitness” OR “Fitness, Physical” OR “Physical Conditioning, Human” OR “Conditioning, Human Physical” OR “Human Physical Conditioning” OR “Physical Training, Human” OR “Human Physical Training” OR “Training, Human Physical” OR “Functional performance” OR “functional independence” OR “functional autonomy” OR “cognitive performance” OR “strength” OR “cardiorespiratory” OR “balance” OR “mobility” OR “flexibility” OR “attention” OR “executive function” OR “memory” OR “language” OR “perceptual-motor abilities”)) NOT “animals study”)	English Scientific Periodicals

Table 3. Methodological quality of the studies: TESTEX scale results

Study	1	2	3	4	5	6	7	8	9	10	11	12	Scores
Barreto et al. (2017)	1	1	1	1	0	3	1	2	1	0	0	1	12
Burge et al. (2016)	1	1	1	1	1	2	1	2	1	0	0	1	12
Rolland et al. (2007)	1	1	1	1	1	2	1	2	1	0	0	1	12
Sampaio et al. (2016)	1	0	0	1	0	1	1	2	1	0	1	1	9
Steinberg et al. (2009)	1	1	0	0	1	2	1	2	1	0	0	0	9
Vreugdenhil et al. (2012)	1	1	0	1	1	1	1	2	1	0	0	0	9

1) Eligibility of the participants; 2) Random distribution; 3) Allocation concealment of all participants at the time of randomization; 4) Comparison of groups at baseline; 5) Blinding of evaluators; 6) Measurement of at least one key outcome in 85% of subjects allocated; 7) Intention to treat analysis; 8) Comparison between groups; 9) Measures of accuracy and variability; 10) Activity monitored in control groups ; 11) Constant relative exercise intensity; 12) Exercise volume and energy expenditure

Chapter 5. Effectiveness of a 6-Month Multicomponent Intervention on Physical and Cognitive Functions in Individuals with Major Neurocognitive Disorder

The present chapter includes one published paper, and another that is under review by international scientific journal with peer-review.

5.1 *Original Study I* – Contribution of a multicomponent intervention on functional capacity and independence on activities of daily living in individuals with neurocognitive disorder

Citation: Borges-Machado F, Barros D, Teixeira L, Ribeiro O, Carvalho J. (2021) Contribution of a multicomponent intervention on functional capacity and independence on activities of daily living in individuals with neurocognitive disorder. *BMC Geriatrics*. 21:625. doi: 10.1186/s12877-021-02591-2

ABSTRACT

Background: To examine the effects of a 6-month multicomponent (MT) exercise intervention in the functional capacity and ability to independently perform activities of daily living (ADL) of individuals diagnosed with neurocognitive disorder (NCD).

Methods: A quasi-experimental controlled trial with a parallel design study was conducted in multicentered community-based settings. Forty-three individuals (N Female: 30) were allocated to an exercise group (EG; N: 23; mean 75.09, SD=5.54 years) or a control group (CG; N:20; mean 81.90, SD=1.33 years). The EG engaged in a 6-month MT program (60-min sessions, twice a week). Exercise sessions were divided into a warm-up, specific training (e.g., coordination and balance, lower and upper body strength, and aerobics), and cool down. Lower body function, mobility, and gait speed were evaluated through Short Physical Performance Battery (SPPB), Timed-Up and Go test (TUG) and 6-Meter Walk test, respectively. The Barthel Index (BI) was administered to assess individuals' ADL independence. Evaluations were performed before and after the 6-month intervention.

Results: Linear Mixed Models revealed a statistically significant interaction (time X group) effect factor on SPPB (B = 2.33, 95% CI: 1.39 – 3.28, $p < 0.001$), TUG (B = -11.15, 95% CI: -17.23 – -5.06, $p = 0.001$), and 6-Meter Walk test (B = 0.17, 95% CI: 0.08 – 0.25, $p < 0.001$). No differences between groups or assessment moments were found in the ability of individuals to independently perform ADL.

Conclusions: The 6-month MT exercise intervention improves the functional capacity of older adults living with NCD.

Trial Registration: ClinicalTrials.gov – identifier number NCT04095962; retrospectively registered on 19 September 2019.

Keywords: Dementia, physical activity, functionality, physical fitness.

BACKGROUND

Major neurocognitive disorder (NCD), often referred as dementia, can be diagnosed according to DSM-5 in the presence of four criteria, being acquired decline in one or more cognitive domains the core feature of this condition, which interferes with independence in daily activities (1). Worldwide, major NCD is considered the greatest challenge of this century, as it is estimated to affect more than 152 million people by 2050 (2). Particularly in Europe, the number of cases is expected to almost double from 9.8 to 18.8 million (3).

The understanding of major NCD etiology is still shifting. Currently, there are 12 potentially modifiable risk factors (e.g., hypertension, hearing impairment, obesity, depression, and physical inactivity) capable to prevent or delay up to 40% of all cases (2, 4). Although aging is the greatest risk factor for all-cause major and minor NCDs, addressing physical inactivity should be prioritized, particularly considering the underlying direct neurological effects (e.g., increased neurogenesis, cerebral blood flow, and BDNF concentrations) and indirect influence on other modifiable cardiovascular risk factors of physical activity (5).

In this sense, after major NCD diagnosis, physical activity and specifically physical exercise are particularly relevant on counteracting/managing disease-related factors and associated symptoms (6, 7). People living with major NCD exhibit increased dependency on activities of daily living (ADL) as this syndrome progresses (1). Furthermore, the decline on basic activities such as feeding, bathing, and dressing, leads to decreased autonomy (8, 9) that may also be exacerbated by age-related physical function limitations. Indeed, community-dwelling older adults living with minor NCD and early major NCD tend to present decreased physical fitness when compared to their healthy-peers, particularly in lower-body strength, upper-and-lower body flexibility, agility/dynamic balance, and cardiorespiratory fitness (10), which are highly associated with one’s ability to perform daily activities (11). Apart from these deficits in physical fitness abilities, they tend to exhibit reduced walking speed, gait disturbances (12, 13), impaired balance, and movement coordination (14).

Although the performance in ADL relies on both cognitive and physical abilities and their interaction with the living environment (15), increasing evidence from review studies and meta-analysis supports the beneficial role of regular exercise in the ability to independently perform ADL among individuals diagnosed with major NCD (16-18). However, the appropriate training methodology, frequency, intensity, and duration of exercise sessions, program length, and outcome measurements are still to be determined in this specific population.

Multicomponent exercise interventions, combining muscle strengthening, aerobic resistance, and balance training (19) were recently recommended by the American College of Sports Medicine (11) and by the World Health Organization (WHO) (20) for individuals aged 65 years and older to improve functional capacity and prevent falls. The effectiveness of this training methodology has also been proved in older adults diagnosed with major NCD (21-24) but further evidence is needed to examine how multicomponent interventions may have an impact on functional capacity and physical fitness (25).

Functional capacity corresponds to “the composite of all the physical and mental capacities that an individual can draw on” (26), reflecting one’s ability to undertake various ADL without assistance, which in turn is directly associated with physical functioning. Given the association between functional capacity and quality of life of older adults with neurocognitive disorder (27), the need to minimize caregiver’s burden and prevent or delay institutionalization (28), it is urgent to determine the effectiveness of multicomponent training (MT) in improving physical abilities and daily functionality of individuals with NCD. As highlighted by the WHO (20), it is expected that this training methodology may have a positive impact on functional capacity of individuals with NCD, which in turn, can be reflected on their ability to independently perform ADL.

Therefore, this study aims to examine the contribution of a 6-month MT exercise intervention on the functional capacity (e.g., lower extremity function, mobility, and gait speed) in older adults living with NCD, and on their ability to independently perform ADL.

METHODS

Study Design and Setting

The present study takes part in the “Body & Brain” project. This project is registered at the US National Institutes of Health clinical trials registry - ClinicalTrials.gov (ID: NCT04095962) and its study protocol can be found elsewhere (29). A two-arm quasi-experimental controlled trial with a parallel design was conducted in multicentered settings in the metropolitan area of Porto city – Portugal, between September 2018 and May 2019.

This investigation was conducted in full compliance with the Declaration of Helsinki, and the Ethical Committee approval has been granted from the Institutional Review Board of the Faculty of Sports, University of Porto (Ref CEFADE22.2018). Following the best ethical procedures, informed consent was obtained from interested individuals with NCD and their legal representatives or significant person (complying with the legal requirements associated).

One hundred participants were recruited from public and private institutions (e.g., daycare centers, local community centers, and nursing homes), hospital centers and clinics (i.e., outpatients accompanied by psychiatrists or neurologists), Alzheimer’s and caregivers’ associations, municipalities, local journals, and social media.

Eligible participants and their caregivers/legal representatives received a complete explanation of the study purposes, risks, and procedures. After agreeing to participate, individuals were allocated into a 6-month intervention – experimental group (EG), or to a social activity group – control group (CG), according to their availability to join one of the groups (Figure 1). Therefore, both options were given to eligible participants who decided which group they wanted to adhere.

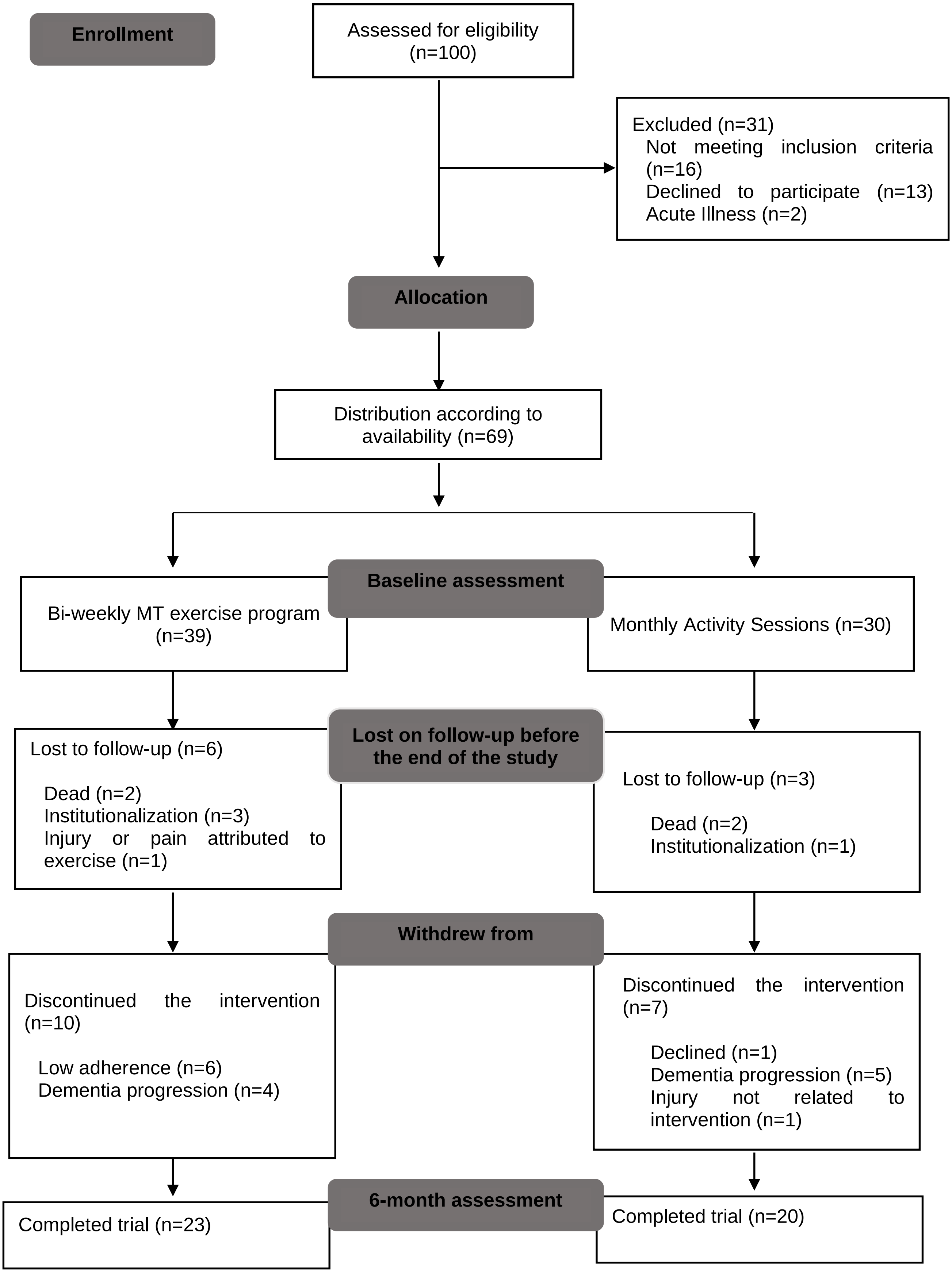

Figure 1. Study flow diagram

Participants Eligibility Criteria

The eligible subjects pool was restricted to individuals with the following characteristics: i) age ≥ 60 years; ii) clinically diagnosed by a physician for at least 6 months with major neurocognitive disorder according to *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR or DSM-5) (1), or with dementia according to the ICD-10 (30), or the NINCDS-ADRDA (31); iii) capacity to walk autonomously without an assistive device or human assistance.

Individuals were excluded if the following criteria were present: i) diagnosed with any condition or disorder in which exercise is contraindicated, such as unstable or ongoing cardiovascular and/or respiratory and/or musculoskeletal condition; ii) recent hospitalization (e.g., previous month) and/or in recovering from surgery or rehabilitation; iii) presenting an advanced stage of major NCD (e.g., ≤ 10 points on MMSE) that could affect physical performance in the exercise training sessions or testing procedures.

Interventions

Experimental Group: MT intervention

MT program was implemented by professionals specialized in exercise, that prior to the program implementation received specific training concerning NCD clinical features and progression, challenging behaviors, communication strategies, and safety issues (32).

An adaptation period was implemented before the main MT training to promote familiarization with exercises and the learning of movements execution at a low intensity. This period was also determinant for participants' socialization (33).

The exercise sessions took about 60-minutes each, were conducted twice a week for 6-months, and involved 5 to 8 participants; they were conducted during the late morning and/or early afternoon periods (32). Routine, simple, and functional exercises were preferred. The intensity was monitored using heart rate monitors.

The exercise sessions were divided into 3 main parts, following the main guidelines recommended by the American College of Sports Medicine (11) and the World Health Organization (20): warm-up (10 minutes, including slow walk, postural and mobility exercises for general activation, and stretching exercises); specific training (35-45 minutes, including balance/coordination training, strength, and aerobic exercises); and cool down (5 minutes with breathing and stretching exercises). After the warm-up, some coordination and balance exercises were included, by reducing the base of support and/or sensory input, and dynamic movements to disturb the center of gravity. Strength training included 4 to 6 multi-joint exercises involving major muscle groups. The number of repetitions decreased with the increasing load that could be lifted correctly to volitional fatigue. A rest period of 1’30’-2’’ between the two sets was completed. Finally, aerobic endurance was implemented from two periods of 5-minute (60-65% of HRmax) to two periods of 10-minutes of continuous exercise (75-80% of HRmax). Detailed information on the exercise protocol can be found elsewhere (29).

Control group: Social activity

Participants in the control group received monthly sessions regarding physical activity and information on health-related topics as a complement to standard care. No specific exercise intervention was conducted with this group. Participants were contacted regularly via phone calls to ensure retention and motivation.

Data Collection

Data collection occurred at baseline, and after the 6-months intervention. Evaluations were conducted by trained researchers, who were not masked to group assignment and were not responsible to implement the exercise program. The adherence rate was calculated considering the total number of attended sessions through the total offered. A cutoff of 70% adherence was considered.

Outcome Measures

Sociodemographic characteristics and general clinical data

Sociodemographic information such as age, gender, marital status, education, and living situation was gathered via a screening questionnaire with caregivers / legal representatives. Pharmacological treatment of participants (total number and type of prescribed daily medications) was also collected. A scale of relevant comorbid conditions (ranging from 0-15) was created to gather information and characterize the general health of individuals; it comprised the following conditions: diabetes, dyslipidemia, hypertension, myocardial infarction, cardiac insufficiency, peripheral vascular disease, stroke/transient ischemic attack, other cardiovascular diseases, osteoporosis, arthrosis, rheumatoid arthritis, respiratory disease, renal disease, or other diseases (e.g., history of cancer).

Lower Body Function

The Short Physical Performance Battery (SPPB) (34) was used to assess lower extremity function; it evaluates static balance, gait ability, and lower limb strength. The final score is the sum of points from each of the three subtests, ranging from zero (worst performance) to 12 points (best performance). A 1-point change in the total score has clinical relevance (35). The SPPB has shown excellent test-retest reliability, predictive and convergent validity (36), and good internal consistency (Cronbach's $\alpha = 0.76$) (34). Moreover, the SPPB has shown to be a valid instrument to screen frailty and predict disability, institutionalization, and all-cause mortality (37).

Mobility

The Timed-Up and Go test (TUG) (38) is a gold-standard test to evaluate older adults' functional mobility and has been widely used in individuals living with major NCD (39). This test does not require special equipment or training; it is simple, rapid to apply, and sensitive to identify those who are at increased risk for falls (40), and has been considered a predictive marker of functional dependency occurrence (41). Participants were requested to rise from a standard armchair, walk at a normal pace a 3-meters distance turning around the ground mark positioned in front, return, and sit down again. Time started after the word "go" sounded and ended once the participant sat back down on the chair. The lowest time (indicative of better performance) of the two trials was considered. Excellent relative test-retest reliability has been found on the TUG (ICC ≥ 0.94) (42, 43) in older adults with major NCD, from mild to severe stages.

Gait Speed

The 6-Meter Walk test (43) was used to evaluate participants' gait speed. Individuals were asked to walk in a 6-meter straight line at their normal pace. The time was registered for each of the two allowed attempts, and the best value, converted to walking speed (m/s), was considered. Gait speed was recognized as a reliable outcome measure to use with people diagnosed with major NCD (42) and has been extensively used with this population (14, 24, 43).

Daily Functionality

The Barthel Index (BI) (44) was used to assess individuals' ability to independently perform ADL, and was applied to the caregiver/ legal representative/ significant person. With a total score ranging from zero to 100, this questionnaire addresses ten basic daily activities: feeding, bathing, grooming, dressing, using the toilet, continence of bowels and bladder, transfers from bed to chair and return, and ambulation (on surfaces levels and climbing stairs). Lower scores are indicative of higher dependency levels. The Portuguese version of BI (45) has shown a good internal consistency (Cronbach's α = 0.89).

Statistical Analyses

Data normality was verified using Shapiro-Wilk test. Measures of central tendency and dispersion, presented as mean and standard deviation (SD), or median and interquartile range, and frequencies (percentages) were used as appropriate to describe sample characteristics. Between groups comparisons at baseline were performed with both parametric (independent t-test) and non-parametric approaches (Mann-Whitney U test) for continuous variables, and Pearson's Chi-Squared test or Fisher's Exact test for categorical variables. Longitudinal changes in the outcome measures from baseline to 6-months were analyzed using linear mixed-effects models, considering group, time, and interaction time*group as fixed effects and participant as random effect. Adjustments were performed for age and gender. The least square mean within-group difference was estimated from these models. All statistical procedures were carried out with SPSS IBM Statistical version 26.0 or with R software version 4.0.4. A significance level of $p = 0.05$ was established.

RESULTS

Participants

Sixty-nine individuals diagnosed with NCD (mean 79.50 years old (SD = 6.73), 72.5% female) were included in the "Body & Brain" project and distributed between the EG and CG according to their availability and preferences to adhere one of the groups. From those, 26 participants were lost to follow-up (n = 9) or discontinued the intervention (n = 17), which translates into a dropout rate of 38%. The flow-chart of participants during the trial is shown in Figure 1. Forty-three older adults (mean 78.26 years old (SD = 6.68), 69.8% female) have completed the intervention, 23 in the EG and 20 in the CG. Within both groups, major NCD diagnosis were established for at least 6 months and a maximum of 12 years. Twenty-seven individuals (62.8 %) had an unspecified diagnosis of major NCD or dementia, 8 (18.6 %) due to Alzheimer's disease, 3 (7.0 %) due to multiple etiologies, 3 (7.0 %) due to Parkinson's disease, 1 (2.3 %) due to Lewy bodies disease, and 1 (2.3 %) due to Korsakoff syndrome.

Study population baseline characteristics did not significantly differ between the experimental and control groups, except for age and number of diagnosed chronic comorbidities (Table 1). Dyslipidemia (74.4 %), hypertension (69.8 %), and diabetes mellitus (32.6 %) were the most prevalent diseases in both groups. At baseline, our study sample presented a mean value on BMI indicative of overweight (mean 28.87 kg/m^2 (SD = 4.88)), and 40 % (n = 16) reported the occurrence of falls (at least one) over the period of 12-months prior to the baseline evaluation moment. Seventeen (73.9 %) of the participants from the EG were female, the majority were married (52.2 %) and had at least 4 years of formal education (69.6 %). Cognitive function measured with both MMSE and ADAS-Cog was not statistically different between groups.

Table 1. Baseline sample characteristics

Characteristics	Total (*n*= 43)	EG (*n*= 23)	CG (*n*= 20)	Statistical Inference
Age (years), mean (SD)	78.26 (6.68)	75.09 (5.65)	81.90 (1.33)	$p < 0.001$ [a]
Age, range	61-89	61-83	70-89	
Gender (female), n (%)	30 (69.8%)	17 (73.9 %)	13 (65 %)	$p = 0.526$ [b]
Civil Status, n (%)				
Widow	22 (51.1 %)	10 (43.5 %)	12 (60 %)	
Married or Civil Union	18 (41.9 %)	12 (52.2 %)	6 (30 %)	$p = 0.395$ [c]
Divorced or Separated	3 (7.0 %)	1 (4.3%)	2 (10 %)	
BMI (kg/m^2), mean (SD)	28.87 (4.88)	29.72 (5.39)	27.98 (4.23)	$p = 0.257$ [a]
Year of Formal Education, mean (SD)	4.00 [3.00 – 8.25]	4.00 [3.00 – 9.00]	4.00 [3.00 – 6.00]	$p = 0.676$ [d]
Education levels, n (%)				
Low (1-3 years)	13 (31.0 %)	7 (30.4 %)	6 (31.6 %)	
Medium (4-6 years)	18 (42.8 %)	9 (39.2 %)	9 (47.4 %)	$p = 0.858$ [c]
High (7-12 years)	11 (26.2 %)	7 (30.4 %)	4 (21.0 %)	
Number of Medications, mean (SD)	7.00 [5.00 – 9.00]	8.00 [5.00 – 10.00]	7.00 [5.00 – 9.00]	$p = 0.571$ [d]
Number of Comorbidities, mean (SD)	4.02 (2.06)	4.61 (1.94)	3.35 (2.03)	$p = 0.045$ [a]
Fallers in past 12 months, n (%)	16 (40 %)	9 (40.9 %)	7 (38.9 %)	$p = 0.897$ [b]
MMSE, mean (SD)	20.93 (4.84)	20.74 (5.10)	21.15 (4.64)	$p = 0.785$ [a]
ADAS-Cog, mean (SD)	30.29 (11.68)	30.05 (12.15)	30.55 (11.44)	$p = 0.891$ [a]

Notes: Values are presented as mean (SD) (continuous variables), median [interquartile range] or percentage (categorical variables).
ADAS-Cog Alzheimer's Disease Assessment Scale – Cognitive *BMI* Body Mass Index *MMSE* Mini Mental State Examination
a: t – Independent sample T-test; b: χ^2 – Pearson's Chi-Square test; c: Fisher's Exact test; d: U – Mann-Whitney U test.
Missing: 1 – Education levels, years of formal education and ADAS-Cog, 2 – BMI, 3 – Fallers in the past 12 months, 8 – Years after diagnosis.

Over the intervention period, adherence to the bi-weekly exercise sessions was higher than 75% (mean 87%), considering the total number of sessions within the 6 months. No serious adverse events occurred during this intervention.

Outcomes

After a 6-month multicomponent exercise intervention, the EG improved their functional capacity on SPPB, TUG, and 6-Meter Walk test. As opposite, the CG performance on these outcome measurements worsened.

Table 2. Within-group differences from baseline in the SPPB, TUG, 6-Meter Walk test and BI

		Experimental		Control	
		n	Mean (SE)[a]	*n*	Mean (SE)[a]
SPPB	M1	23	7.89 (0.48)	20	8.04 (0.51)
	M2	22	8.95 (0.52)	20	6.78 (0.53)
TUG	M1	23	15.7 (2.88)	20	14.8 (2.41)
	M2	22	11.8 (2.55)	19	22.0 (2.62)
6-Meter Walk test	M1	23	0.75 (0.04)	20	0.699 (0.04)
	M2	22	0.88 (0.04)	19	0.665 (0.05)
BI	M1	23	85.7 (2.90)	23	81.6 (3.10)
	M2	19	86.1 (3.09)	20	81.5 (3.27)

a Least square mean calculated from linear-effects mixed models, averaged for gender
SE standard error*, SPPB* Short Physical Performance Battery, *TUG* Timed-Up and Go Test, *BI* Barthel Index, M1 Baseline, M2 After 6-month Intervention
*Significant difference within-group from baseline (p < 0.05)

Table 2 shown least square mean scores of SPPB and 6-Meter Walk test according to group, and they increased over time on EG, indicative of better functional capacity, and decreased in CG. The time spent raising up from a chair, turn around the ground marker and return to a seated position increased in individuals in the CG, as opposed to those in the EG. As described on Table 3, results from unadjusted fixed effects models revealed an interaction (time X group) effect factor on lower body function, mobility and gait speed measured through SPPB ($B = 2.37$, 95% CI:1.43 – 3.32, $p < 0.001$), TUG ($B = -11.38$, 95% CI: -17.48 – -5.29, $p = 0.001$), and 6-Meter Walk test ($B = 0.17$, 95% CI: 0.08 – 0.25, $p < 0.001$), respectively. These results confirmed that changes on SPPB, TUG and 6-Meter Walk test across time were different according to the group.

In addition, time was a significant effect factor on SPPB ($p < 0.001$) and TUG ($p = 0.003$), and group was a significant effect factor on 6-Meter Walk test ($p = 0.049$).

Table 3. Unadjusted linear mixed models for SPPB, TUG, 6-Meter Walk test and BI

	Fixed Effects								
	Time			Group			Time X Group		
	B	**95% CI**	***p value***	**B**	**95% CI**	***p value***	**B**	**95% CI**	***p value***
SPPB	-1.28	-1.96 – -0.60	<0.001*	1.08	-0.33 – 2.48	0.138	2.37	1.43 – 3.32	<0.001***
TUG	7.24	2.74 – 11.68	0.003*	-1.80	-7.76 – 4.16	0.558	-11.38	-17.48 – -5.29	0.001***
6-Meter Walk test	-0.03	-0.10 – 0.03	0.210	0.11	0.003 – 0.22	0.049**	0.17	0.08 – 0.25	<0.001***
BI	-0.08	-4.81 – 4.62	0.973	7.57	-0.16 – 15.29	0.060	0.67	-5.51 – 6.84	0.833

Group: control group is reference. Time: baseline is reference
SPPB Short Physical Performance Battery, *TUG* Timed-Up and Go Test, *BI* Barthel Index
*Significant time effect compared with baseline
**Significant group effect compared with control group
***Significant time X group interaction effect

After adjusting for age and gender (Table 4), interaction between time and group remained a significant factor for SPPB (B = 2.33, 95% CI: 1.39 – 3.28, p < 0.001), TUG (B = -11.15, 95% CI: -17.23 – -5.06, p = 0.001) and 6-Meter Walk test (B = 0.17, 95% CI: 0.08 – 0.25, p < 0.001). Age was a significant effect factor on lower body function (B = -0.22, 95% CI: -0.32 – -0.12, p < 0.001), mobility (B = 0.49, 95% CI: 0.03 – 0.94, p = 0.043), and gait speed (B = -0.22, 95% CI: -0.02 – -0.003, p = 0.012).

Table 4. Adjusted linear mixed models for SPPB, TUG, 6-Meter Walk test and BI

	Adjusted Fixed Effects[a]								
	Time			Group			Time X Group		
	B	95% CI	*p value*	B	95% CI	*p value*	B	95% CI	*p value*
SPPB	-1.27	-1.95 – -0.58	<0.001*	-0.16	-1.49 – 1.18	0.822	2.33	1.39 – 3.28	<0.001**
TUG	7.21	2.71 – 11.61	0.003*	0.90	-5.42 – 7.22	0.784	-11.15	-17.23 – -5.06	0.001**
6-Meter Walk test	-0.03	-0.10 – 0.03	0.268	0.11	-0.06 – 0.16	0.389	0.17	0.08 – 0.25	<0.001**
BI	-0.17	-4.77 – 4.52	0.942	4.11	-3.91 – 12.13	0.327	0.52	-5.65 – 6.65	0.870

a Adjusted for age and gender
Group: control group is reference. Time: baseline is reference
SPPB Short Physical Performance Battery, *TUG* Timed-Up and Go Test, *BI* Barthel Index
*Significant time effect compared with baseline

**Significant time X group interaction effect

No differences between groups or assessment moments were found in the individuals' ability to independently perform ADL even after adjusting models for age and gender (Table 3 and Table 4). Although age was a significant effect factor (B = -0.69, 95% CI: -1.28 – -0.11, p = 0.026), both CG and EG have increased BI total score from baseline.

DISCUSSION

The results of this study showed that a 6-month multicomponent exercise intervention improves functional capacity, namely, lower body function, mobility, and gait speed of older adults living with NCD. However, these results did not translate in significant changes in the participants' capacity to perform ADL independently, regardless of being in the experimental or control group.

Exercise has been recognized as an effective non-pharmacological therapeutic approach for individuals diagnosed with major NCD by slowing disease progression and/or improving their physical health and psychosocial well-being (46). Several meta-analytic and systematic review studies highlighted the beneficial effects of various modalities of exercise (mainly aerobic and strength) on physical fitness and functional outcomes like gait speed, walking endurance, balance, muscle strength, cardiorespiratory fitness, and agility (46, 47). The present study adds to the already existing literature, by providing evidence on the effectiveness of MT methodology on the functional capacity of individuals living with NCD, namely in the SPPB, TUG, and 6-Meter Walk test, which are greatly associated with individuals' frailty status, physical disability, and dependency (37, 39, 48).

Our results showed a significant interaction between group (experimental and control) and time (baseline and post-intervention) on SPPB and, more importantly, when analyzing the scores from baseline to post-intervention, a 1-point change (mean difference) was observed for individuals in the EG and CG, which is considered by Know et al. (2009) (35) as a substantial clinically meaningful change. Additionally, the baseline score of SPPB on both groups was on average below 10 points, which is associated with disability and all-cause mortality (37, 49). After the MT intervention, the score of SPPB increased in EG, resulting in a reduction of this risk comparing to the CG. As stated by Pavasini et al. (2016) (37), in clinical practice settings it is important to consider the SPPB as a prognostic information tool and as a valid outcome to measure intervention effectiveness in people with NCD. In addition, as recently outlined by Borges-Machado et al. (2021) (27), lower body function has been identified as a health-related physical indicator associated with self-rated quality of life in people living with NCD. In contrast to our results, Pitkala et al. (2013) (50) found that both exercise groups (home or group-based) have deteriorated on SPPB after 6-months; moreover, after 12-months of exercise, both groups have significantly declined (2-points) on SPPB. Similarly to our intervention, Barreto and colleagues (24) conducted a 6-month MT exercise program (60-min sessions, twice a week) with individuals diagnosed with dementia living in nursing homes but, in contrast to our study findings, no statistically significant differences were found on lower body function. However, compared to our sample, their participants presented substantially lower baseline scores on SPPB. To the best of our knowledge, the current study is one of the first to consider the effects of a MT intervention on SPPB for individuals with NCD. Further research is needed on this topic.

As a composite measure of functional mobility, TUG requires the executive function (to listen and initiate movements), transfer tasks (to stand and sit down), walking and balance of individuals (41). Results from our study showed the MT exercise intervention had a significant positive impact in improving the functional mobility of people with NCD, even after adjusting for confounders such as age and gender. Several prospective studies verified that TUG predicted fall risks and nursing home admission; more recently a study with 39.519 individuals conducted by Lee and collaborators (2020) confirmed, after performing follow-up evaluations on a cohort of older adults for approximately 5.7 years, that impaired mobility (TUG > 10 seconds) was associated with a higher risk of subsequent functional dependency occurrence (e.g., institutionalization or admission to a long-term care facility). Our post-intervention results demonstrate a significant improvement in the EG, which presented a mean score of 11 seconds on TUG. Conversely, the CG not only presented a higher mean score on TUG (indicative of worsening), as it also shown an incremental score from baseline to post-intervention of 7.2 seconds, which is superior to the minimal detectable change value of 4.09 seconds defined by Ries et al. (2009) (42). Therefore, results from TUG analyzes supports the effectiveness of this intervention by improving the mobility of individuals with NCD, or at least, by minimizing its decline. Similar results were reported by other authors (51-53). Lam et al.'s (2018) (14) systematic review study with meta-analysis of randomized trials, regarding the effects of exercise on physical functioning and quality of life in individuals with minor and major NCD, revealed strong evidence supporting the exercise in improving TUG and walking speed.

Despite the high gait variability among NCD severity and subtypes (e.g., stride-to-stride fluctuations in distance and time), gait impairment has been associated with neurodegeneration and cognitive impairment, and it is considered a sensitive marker of neurological dysfunction (54, 55). As highlighted by Cohen & Verghese (2019) (13) abnormal gait is common in major NCD and other neurodegenerative diseases. Designated as the “sixth vital sign” (56), gait assessment must be considered as a crucial part of managing disease, since with major NCD progression, the decline of walking and other motor abilities may lead to loss of mobility and bedridden (13). Post-intervention results showed that the CG experienced a decline of gait speed, as opposite to the EG that have showed a mean increase of 0.13 m/s, which is a clinically meaningful change (57). Lam et al. (2018) (14) analyzed seven trials that have evaluated the effect of exercise on gait speed, with 568 individuals diagnosed with moderate-to-severe major NCD, and revealed that exercise improved walking speed by 0.14 m/s. This study results must be highlighted since, even in more advanced stages of the disease, exercise seems effective in improving gait speed. More importantly, the trials that reported significant exercise effects on walking speed adopted MT training methodologies. Finally, the ability to ambulate independently is a major factor contributing to the well-being and autonomy of older populations (13) and, for this reason, must be comprehensively assessed (e.g., clinical history, observation of walking patterns, clinical and neurologic examination) in clinical practice settings.

As highlighted by a recently published systematic review and meta-analysis study (58), low scores on SPPB and gait speed are predictive of both ADL and/or instrumental ADL decline, while the low scores on TUG are associated with worsening ADL among older adults. However, despite the positive effect of our intervention on the functional capacity of individuals with NCD, no significant differences were found in the ability to independently perform ADL, like previous studies (24, 59, 60). Baseline least square mean scores on BI superior to 80 points on both groups, might be considered as one of the hypotheses that could partially justify the absence of significative differences, since a total score between 60 and 89 points is indicative of being “slightly dependent” (45).

According to Nuzum et al. (2020) (61), it is necessary to consider the role of cognition when analyzing functional independence outcomes, since cognitive deterioration tends to precede and predict functional decline. Therefore, ADL performance might not be linearly correlated with functional capacity in individuals with NCD, as other factors may have a more decisive role in this relationship. Although no baseline differences were found for cognitive performance (measured with MMSE and ADAS-Cog) between groups, authors consider that NCD subtype and/or stage might have influenced individuals' functional independence. Nevertheless, these analyzes cannot be conducted due to insufficient data on disease severity. Also, although declines in executive functions have been associated with increased dependency on everyday function (15), such functions were not measured in detail.

Clemmensen et al. (2020) (15) in a cross-sectional study concerning the association between physical performance, cognition, and ADL functions, found out a moderate correlation between general cognitive function and instrumental ADL – particularly, processing speed and attention –, as opposite to basic ADL, whereas no correlation was found, suggesting that basic ADL is less cognitively demanding and, therefore, less dependent of cognitive function. Regarding physical performance, these authors' findings indicated that aerobic fitness, mobility, strength, and endurance of lower extremities were not associated with ADL independence in people with mild-to-moderate Alzheimer's disease.

Toots et al. (2016) (60) cluster-randomized controlled trial study implemented a 4-month high-intensity functional exercise program with balance and lower body strength exercises. After 4-months of intervention, and at 7-months follow-up evaluation, this study results were consistent with ours, and no significant between-group effects were found in ADL independence. Nevertheless, in interaction analyses these authors found that the effect of exercise was significant in favor of participants with non-Alzheimer's disease dementia subtype (when comparing those with Alzheimer's disease) at 7-months in BI scores. Moreover, Toots and colleagues (2016) reinforced that the declines in ADL independence are multifactorial, and improvements in several physical function components may not be reflected in some activities, such as bladder control or feeding.

In addition, Clemmensen and colleagues (2020) also mentioned other factors beyond cognitive functioning, that may also affect individuals' ability to perform ADL; they are related with the environment inhabited (e.g., physical factors such as lightning and spatial layout) by the person diagnosed with major NCD. Lastly, the living context (e.g., home-dwelling *vs*. institutionalized) and the availability of caregivers to provide greater opportunities to the care receiver to remain functional and engaged in meaningful activities (61) may also be considered as important factors.

Despite the increasing evidence acknowledging the beneficial effect of exercise on ADL performance, results are still broadly heterogeneous and of low quality (14, 47, 61). The dose-dependent relationship remains unclear and although the BI has been used globally (62), empirical evidence regarding its validity for assessing individuals with major NCD is still scarce (63). Even though our previous research demonstrated the beneficial effect of MT intervention in ADL functionality in older adults with major NCD (25), further controlled trials are needed with larger samples considering this training methodology, and the different types/stages of major NCD.

As declared by Cadore et al. (2019) (64), MT exercise is effective in improving most, if not all, of the frailty syndrome hallmarks; for this reason, it may be considered as a cornerstone for frail individuals with cognitive impairment to mitigate/delay and/or improve physical status and cognitive function. Also, MT exercise interventions have been recently recommended by the *World Health Organization* (20) to older populations, and by the *American College of Sports Medicine* (11) specifically to people with Alzheimer's disease, since targeting multiple modes of exercise might be the most effective training methodology for enhancing flexibility, balance, strength, and endurance.

LIMITATIONS

There are some limitations to the present study that must be acknowledged. First, this study was a non-randomized controlled trial and therefore we cannot exclude the influence of bias estimates on treatment effects. Nevertheless, it is important to highlight that there were no statistically significant differences between the groups at baseline, except for age and number of comorbidities;

moreover, participants were allocated according to their availability and not by a researcher’s decision. Second, the study comprised a small sample size, so results should be interpreted carefully and not generalized. Third, the high variability in the NCD diagnosis (stage and subtype) could potentially influence our results; additionally, the authors acknowledge the lack of data on cognitive function and daily physical activity, which could also potentially influence the results. Four, data must be interpreted with caution considering the individuals’ high levels of independence (i.e., with ability to move autonomously without assistive devices and with a relatively high baseline scores on ADL performance measure), which could not totally reflect the characteristics of this specific population. Fifth, a significant number of participants experienced falls (at least one) during the previous 12-months to baseline evaluations, which was not taken into consideration during statistical analysis. Finally, only CG participants received the health-related information sessions.

CONCLUSION

Although the dose-dependent relationship remains unclear for each type/stage of major NCD and target outcome, increasing evidence advocates for MT interventions, since the associated physical and mental health benefits overcome eventual related adverse events/detrimental effects (16, 21). As stated by Nuzum et al. (2020) (61), further research is needed to clarify which training methodology may have a greater impact on individuals’ physical functioning and functional independence in all stages of various major NCD subtypes, considering different age groups and living environment (e.g., institutionalized *vs*. domiciliary). A MT methodology seems to be an effective strategy to improve individuals’ functional capacity, but further studies are needed to verify its’ impact on daily functionality.

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Authors' contributions

Study conception and design: FM, DB, LT, OR, JC; Study coordination: JC, OR; Writing – original draft: FM, DB, LT; Writing – Review & Editing: FM, DB, LT, OR, JC. All the authors have made a substantial contribution, critically revised this work, and approved the final manuscript.

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Availability of data and materials

The dataset supporting the conclusions of this article will be available upon reasonable request addressed to the corresponding author.

DECLARATIONS

Ethics Approval and Consent to Participate

The study protocol was approved by the Ethical Committee of the Faculty of Sports of the University of Porto (Ref CEFADE22.2018). The trial was registered with the US National Institutes of Health Clinical Trials Registry (ClinicalTrials.gov – identifier number NCT04095962). Informed consent was obtained from all participants and/or legal representatives/significant person included in the study prior to data collection.

Consent for Publication

Not required.

Competing Interests

The authors declare that they have no competing interests.

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5.2 *Original Study II* – Does multicomponent training work for dementia? Exploring the effects on cognition, neuropsychiatric symptoms, and quality of life

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RUNNING TITLE

Multicomponent training for dementia

ABSTRACT

Objective: To explore the effects of a multicomponent training (MT) physical exercise intervention in the cognitive function, neuropsychiatric symptoms, and quality of life of older adults with major neurocognitive disorder (NCD).

Methods: Quasi-experimental controlled trial. Thirty-six individuals (25 female) were equally distributed to an exercise group (aged 74.33 ± 5.87 years) or a control group (aged 81.83 ± 6.18 years). The Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog), the Neuropsychiatric Inventory (NPI) and the Quality of Life – Alzheimer's Disease (QoL-AD) tests were performed before and after the intervention.

Results: There was no clear interaction effect factor of intervention on ADAS-Cog (B = 1.33, 95% CI: -2.61 – 5.28, p = 0.513), NPI (B = -8.35, 95% CI: -18.48 – 1.72, p = 0.115), and QoL-AD (B = 2.87, 95% CI: 0.01 – 5.73, p = 0.058).

Conclusions: The 6-month MT physical exercise intervention did not present evidence of slowing down cognitive decline neither improving neuropsychiatric symptomatology, and quality of life of older adults with major NCD. Future studies with larger samples are needed to better understand the impact of physical exercise interventions using MT methodology on specific cognitive abilities, neuropsychiatric symptoms, and quality of life domains.

Keywords: Neurocognitive disorder, physical activity, physical exercise, cognitive function, multimodal.

BACKGROUND

Along with the decline on cognitive function that characterizes a neurocognitive disorder (NCD), individuals may suffer from the progressive severity of behavioral and psychological symptoms (e.g., agitation, apathy, anxiety, hallucinations, eating disorders, nighttime behaviors) that often lead to a lower quality of life [1].

Physical exercise, as a promising non-pharmacological therapeutical approach within dementia care [2-4] is regularly recommended given its potential positive effects on cognitive function [5-9], neuropsychiatric symptomatology [10,11], and quality of life [12] of individuals with major NCD.

However, according to previous systematic reviews and meta-analytic studies, it remains unclear whether physical exercise might slow down the decline of global cognition or improve specific cognitive domains (i.e., executive functions, complex attention, memory, among other abilities) [13-16]. Similarly, the role of physical exercise on alleviating challenging behaviours and mood disturbances is still limited [17-20] particularly in what regards other symptoms rather than depression [16,21,22]. Also, there's still insufficient and inconsistent data on the effectiveness of well-promising physical exercise interventions on quality of life [23-26].

Multicomponent training (MT) (i.e., combination of balance, strength, aerobic, gait and physical function training) [27] has been recently recommended for older adults with Alzheimer's disease [2,28,29] and would seem advisable to individuals with major NCD due to other etiological conditions (e.g., vascular disease). Nevertheless, despite its positive influence on functional capacity [30,31], few studies have focused on its effects on psychosocial outcomes. This study aims to explore the contribution of a 6-month community-based MT physical exercise intervention on the cognitive function, neuropsychiatric symptomatology, and quality of life of older adults diagnosed with major NCD.

METHODS

Study Design and Setting

The present study takes part in the “Body & Brain” project [32], a two-arm quasi-experimental controlled trial with a parallel design. This project was conducted between September 2018 and May 2019 and carried out in multiple sites in the Oporto Metropolitan Area (North of Portugal).

Participants Eligibility Criteria

Individuals aged ≥ 60 years, clinically diagnosed by a physician with major NCD or dementia (for at least 6-months) and capable to walk independently without an assistive device or human assistance were considered eligible to participate in the study. Exclusion criteria included: i) diagnosis of any condition or disorder in which exercise is contraindicated (e.g., ongoing, or unstable cardiovascular, respiratory and/or musculoskeletal condition); ii) recent hospitalization (e.g., previous month to recruitment) and/or in rehabilitation, and/or in recovery from surgery; iii) advanced stage of major NCD or dementia (e.g., ≤ 10 points on Mini-Mental State Examination [MMSE]). After agreeing to participate, eligible participants were allocated to a 6-month MT intervention – experimental group (EG), or to a social activity group – control group (CG), according to their availability.

Interventions

EG was assigned to a 6-month group-based MT intervention (two sessions per week, 60 minutes per session) involving five to eight participants. Exercise sessions were divided into three main parts: 10 minutes of warm-up (e.g., joint mobilization, general activation, and slow walking); 35-45 minutes of specific MT training (e.g., combining coordination and balance, lower and upper body strength, and aerobics) at light-to-moderate intensity; and five minutes to cool-down (e.g., stretching, mobility and breathing exercises). Proprioceptive and balance training included exercises with reduced sensory input, progressively difficult postures, dynamic movements, and exercises requiring stressing postural muscle groups (e.g., tandem walks, hell-to-toe stands and walks, and step over objects). Simple coordination exercises were performed (e.g., agility ladder drills). Resistance training included four to six multi-joint exercises involving major muscle groups (e.g., squats, biceps arm curl, triceps extension, chest press, seated row, standing leg curl). Aerobic endurance included low-impact exercises such as walking, dancing, and stationary marching.

Participants in the CG had a monthly social activity session (60 minutes each for 6-months, involving five to 12 individuals) including physical activity (e.g., breathing and relaxation activities) and the provision of information on health-related topics (e.g., falls prevention, healthy eating habits) as a complement to standard care. CG participants were contacted via phone calls to ensure retention and motivation. More information on the "Body & Brain" project study protocol can be found elsewhere [32].

Data Collection

Data collection occurred at baseline, and after the 6-months intervention. A cutoff of 70% was considered for adherence rate (i.e., calculated as dividing the number of attended sessions by the total number of sessions offered).

Outcome Measures

Evaluations were conducted by specialized and well-trained researchers, who were not responsible for implementing the MT program or the social activity sessions, and were not masked to group assignment.

Participants' sociodemographic information (age, sex, marital status, education, and living situation), and general clinical data were gathered via questionnaire.

The Alzheimer's Disease Assessment Scale - Cognitive (ADAS-Cog) [33,34] was used to examine individuals' global cognitive function; it includes 11 tasks targeting memory, praxis, and language. Scores range from zero to 68, with higher scores indicating greater severity of cognitive impairment.

The Neuropsychiatric Inventory (NPI) [35,36] was used to determine the frequency and severity of behavioural and psychological symptoms. Scores range from zero to 144 points, with higher scores suggesting worsening of neuropsychiatric symptoms.

The Quality of Life – Alzheimer's Disease (QoL-AD) [37,38], includes the individuals' and caregivers' reports on how the person with major NCD feels about 13 domains such as physical health, memory, relationship with family members, and financial situation. Scores range from 13 to 52, with higher scores indicating less impairment.

Statistical Analyses

Data normality was verified using the Shapiro-Wilk test. Measures of central tendency and dispersion were used as appropriate to describe sample characteristics. Between groups comparisons at baseline were performed with both independent t-test and Mann-Whitney U test for continuous variables, and Pearson's Chi-Squared test or Fisher's Exact test for categorical variables. Longitudinal changes in the outcome measures from baseline to 6-months were analyzed using linear mixed-effects models, considering group, time, and interaction time*group as fixed effects and participant as random effect. Adjustments were performed for age and sex. The least square mean within-group difference was estimated from these models. A significance level of $\alpha = 0.05$ was established. All statistical procedures were carried out with SPSS IBM Statistical version 27.0 and with R software version 4.0.4.

RESULTS

Participants

From the 69 individuals diagnosed with NCD (mean 79.50 years old (SD = 6.73), 72.5% female) included in the "Body & Brain" project, twenty-six were lost to follow-up or discontinued the intervention (dropout rate of 38%). Forty-three participants (mean 78.26 years old (SD = 6.68), 69.8% female) completed the intervention: 23 in the EG and 20 in the CG. Seven participants (5 from the EG and 2 from the EG) presented minor NCD and, for this reason were not considered as valid for this study analysis. The flow-chart of participants during the trial is shown in Figure 1.

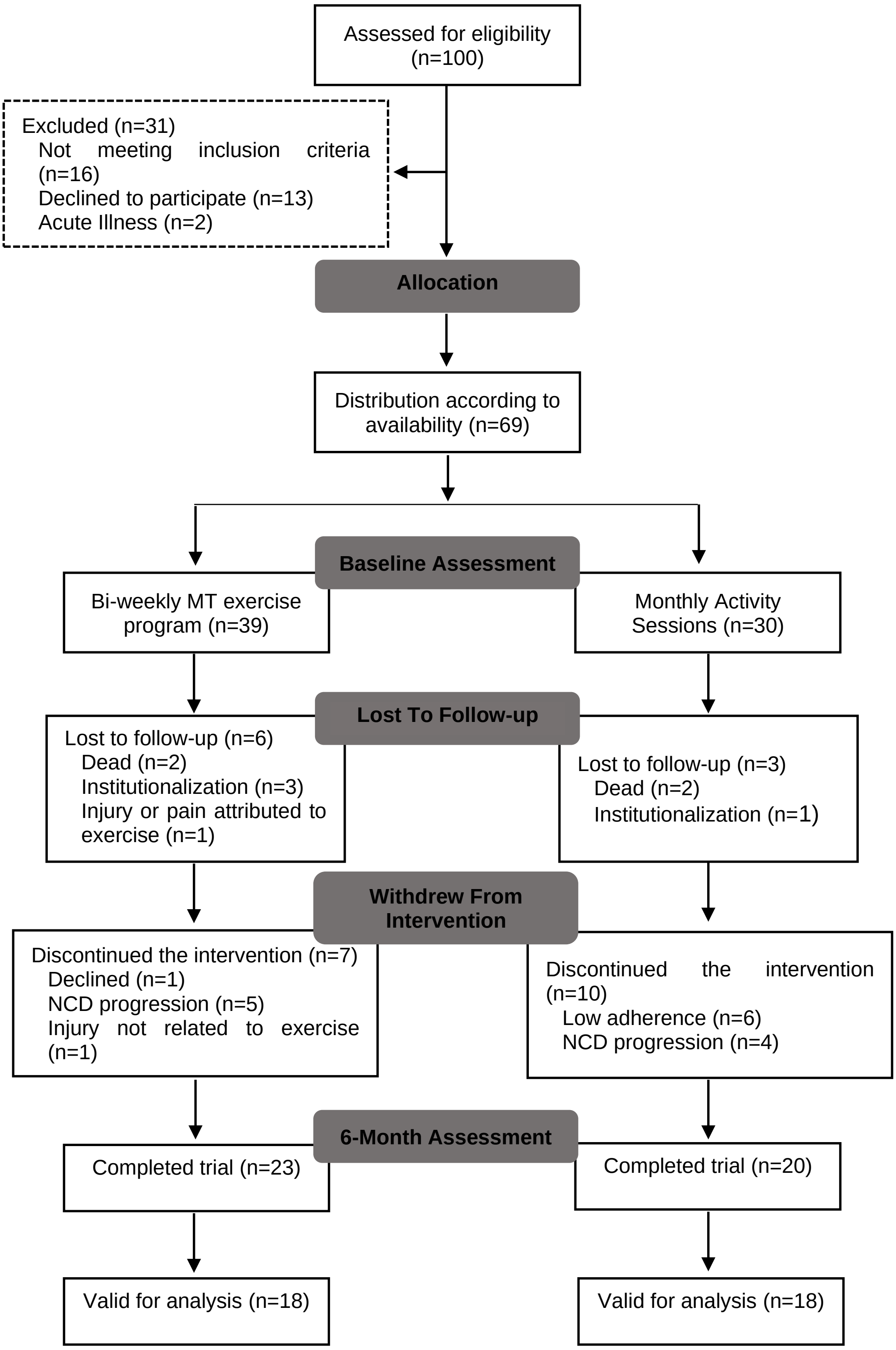

Figure 1. Study flow diagram

Thirty-six older adults (mean 78.08 years old, SD = 7.05) were included in the present study, distributed in equal number between both groups. Twenty individuals (55.6 %) had an unspecified diagnosis of major NCD or dementia, 8 (22.2 %) due to Alzheimer's disease, 3 (8.3 %) due to multiple etiologies, 3 (8.3 %) due to Parkinson's disease, 1 (2.8 %) due to Lewy bodies disease and 1 (2.8 %) due to Korsakoff syndrome. Within both groups, major NCD or dementia diagnosis were established for at least six months and a maximum of 12 years. Globally, individuals presented a baseline mean score on MMSE of 20.47 (SD = 4.91) points. More than 80% of the individuals had a prescription at the beginning of the intervention of, at least, one psychopharmacological drug. Specifically, 29 (80.6 %) participants were taking antidepressants, 12 (33.3 %) were taking hypnotics, sedatives, or anxiolytics and 7 (19.4 %) were taking antipsychotics. Twenty-five participants (69.4 %) were female, half were widowed (50.0 %), and almost half had at least 4 years of formal education (45.7 %). Most individuals (72.2 %) were living in the domiciliary context with their spouses or other family members (i.e., children, nephew). As presented in Table 1, participants' baseline characteristics did not significantly differ between the groups, except for age and number of diagnosed chronic comorbidities.

Table 1. Baseline sample characteristics

Characteristics	Total (*n*=36)	EG (*n*= 18)	CG (*n*= 18)	Statistical Inference
Age (years), mean (SD)	78.08 (7.05)	74.33 (5.87)	81.83 (6.18)	$p < 0.001$[a]
Age, range	61-89	61-83	70-89	
Sex (female), n (%)	25 (69.4)	13 (72.2)	12 (66.7)	$p = 0.727$[b]
Civil Status, n (%)				
Widow	18 (50.0)	7 (38.9)	11 (61.1)	
Married or Civil Union	15 (41.7)	10 (55.6)	5 (27.8)	$p = 0.357$[c]
Divorced or Separated	3 (8.3)	1 (5.6)	2 (11.1)	
Years of Formal Education, mean (SD)	4.00 [4.47 – 6.44]	4.00 [4.32 – 7.46]	4.00 [3.69 – 6.31]	$p = 0.463$[d]
Education Levels, n (%)				
Low (1-3 years)	9 (25.7)	4 (22.2)	5 (29.4)	
Medium (4-6 years)	16 (45.7)	8 (44.4)	8 (47.1)	$p = 0.830$[c]
High (7-12 years)	10 (28.6)	6 (33.3)	4 (23.5)	
Living Situation, n (%)				
With Spouse or Other Family Member	26 (72.2)	13 (72.2)	13 (72.2)	
Nursing Home	5 (13.9)	2 (11.1)	3 (16.7)	$p = 1.000$[c]
Alone	5 (13.9)	3 (16.7)	2 (11.1)	
Number of Medications and Supplements, mean (SD)	7.00 [6.46 – 8.71]	8.00 [6.60 – 10.40]	6.50 [5.41 – 7.92]	$p = 0.226$[d]
Number of Comorbidities, mean (SD)	3.81 (2.04)	4.50 (2.07)	3.11 (1.81)	$p = 0.039$[a]
Disease Duration (years), mean (SD)	3.00 [2.21 – 3.89]	3.00 [2.16 – 4.67]	2.00 [1.43 – 3.57]	$p = 0.285$[d]
Dementia or Major NCD Diagnosis, n (%)				
Unspecified	20 (55.6)	9 (50.0)	11 (61.1)	
Alzheimer's Disease	8 (22.2)	5 (27.8)	3 (16.7)	
Multiple Etiologies	3 (8.3)	1 (5.6)	2 (11.1)	$p = 0.748$[c]
Parkinson's Disease	3 (8.3)	1 (5.6)	2 (11.1)	
Lewy Bodies Disease	1 (2.8)	1 (5.6)	0	
Korsakoff Syndrome	1 (2.8)	1 (5.6)	0	

Notes: Values are presented as mean (SD) (continuous variables), median [interquartile range] or percentage (categorical variables)

MMSE Mini Mental State Examination, *NCD* Neurocognitive Disorder

Missing: 1 – Education Levels, Years of Formal Education; 6 – Disease Duration

a: t – Independent sample T-test; *b*: χ^2 – Pearson's Chi-Square test; *c*: Fisher's Exact test; *d*: U – Mann-Whitney U test.

No serious adverse events occurred during the intervention. Considering the total number of sessions within the 6-months, adherence to the bi-weekly exercise sessions was higher than 75% (mean 87%).

Outcomes

As presented in Table 2, a significant interaction (time X group) effect factor was not found for none of the variables. But age was a significant effect factor on NPI test (B = -0.64, 95% CI: -1.17 – -0.11, p = 0.029).

Table 2. Linear mixed models for cognitive function, neuropsychiatric symptoms, and quality of life

	Linear Mixed Effects Adjusted for Age and Sex													
	Fixed Effects									Random Effects				
	Time			Group			Time X Group			ID		Residual		
	B	95% CI	*p value*	B	95% CI	*p value*	B	95% CI	*p value*	SD	95% CI	SD	95% CI
ADAS-Cog	0.28	-2.51 – 3.07	0.847	-1.38	-8.97 – 7.64	0.795	1.33	-2.61 – 5.28	0.513	12.22	9.10 – 14.96	4.28	3.35 – 5.34
NPI[a]	9.07	1.90 – 16.30	0.019	-1.00	-9.73 – 7.74	0.829	-8.35	-18.48 – 1.72	0.115	4.69	0.00 – 8.21	10.87	8.50 – 13.25
QoL-AD	-2.57	-4.60 – -0.55	0.018	-3.17	-6.15 – -0.19	0.049	2.87	0.01 – 5.73	0.058	2.59	1.05 – 3.55	3.10	2.43 – 3.87

a Age was a significant factor
Group: control group is reference. Time: baseline is reference
ADAS-Cog Alzheimer's Disease Assessment Scale – Cognitive, *NPI* Neuropsychiatric Inventory, *QoL-AD* Quality of Life – Alzheimer's Disease

After a 6-month MT physical exercise intervention, the EG slightly improved the least square mean scores on QoL-AD test (Table 3), which is indicative of increased quality of life. As opposite, individuals in the CG decreased the scores in this variable. In parallel, participants in the EG revealed a slight increase in the ADAS-Cog score, indicative of greater severity of cognitive impairment, whereas the CG maintained the scores. Both groups experienced an increase in the NPI, which was more significative on CG individuals, suggesting worsening of behavioral and psychological symptoms.

Table 3. Within-group differences from baseline in the cognitive function, neuropsychiatric symptoms, and quality of life

		Experimental		Control	
		n	**Mean (SE)[a]**	***n***	**Mean (SE)[a]**
ADAS-Cog	M1	18	29.9 (3.71)	18	31.2 (3.35)
	M2	18	31.5 (3.71)	18	31.5 (3.35)
*NPI**	M1	18	11.4 (3.19)	17	12.4 (3.09)
	M2	18	12.1 (3.19)	18	21.5 (2.96)
QoL-AD	M1	18	29.8 (1.11)	18	32.9 (1.02)
	M2	18	30.1 (1.11)	18	30.4 (1.02)

a Least square mean calculated from linear-effects mixed models
ADAS-Cog Alzheimer's Disease Assessment Scale – Cognitive, *M1* Baseline, *M2* After 6-month Intervention, *NPI* Neuropsychiatric Inventory, *QoL-AD* Quality of Life – Alzheimer's Disease, *SE* standard error
*Significant difference within-group from baseline ($p < 0.05$)

DISCUSSION

The results from this study suggest that a 6-month MT physical exercise intervention was not effective in improving cognitive function, neuropsychiatric symptomatology, and quality of life of older adults diagnosed with major NCD. Previous studies attested MT effectiveness on improving individuals with NCD lower body function [30,31], gait speed and mobility [30,39]. However, less evidence has been shown on the effects of MT physical exercise interventions on psychosocial outcomes [40-42].

Previous meta-analytic and systematic review studies indicated that physical exercise interventions might improve cognitive function, or slow down the decline in individuals with major NCD; still, findings have been inconsistent across studies [13-16,43]. The questionable benefit of physical exercise on cognition might be explained by the methodological differences across studies (e.g., eligibility criteria, diagnostic criteria or referral protocol, design and settings), the heterogeneity of training programs in terms of frequency, type, intensity, and duration; the significant variability in cognitive assessment tools and instruments; and by the range of subtypes/stages of major NCD [5,6,13,16,44].

Knowing if physical exercise improves or not global cognition is important but insufficient to healthcare providers in advising this type of intervention [10]. Recent findings showed the effects of physical exercise in specific cognitive domains, such as working memory, cognitive flexibility, attention, and executive functions [7,8,10]; but this relationship is not always true across studies [13]. To some extent, the questionable benefit of physical exercise on cognition is attributed to the selection of evaluation measurements [13,14,43]. The ADAS-Cog instrument, which is subdivided in 11 tasks targeting three cognitive functions (memory, language, and praxis), is a widely used measure and sensitive to change [45,46], but it does not allow to examine the effects of physical exercise on planning, decision-making, working memory, responding to feedback, inhibition and mental flexibility. The slight increment on ADAS-Cog score verified in our study in the EG after the 6-months intervention may be explained, at least in part, by the pervasiveness of unspecified subtypes and/or missing data on disease stage, and by the limitations of the assessment tool (e.g., assess of global cognition), as expressed in the existing literature [19]. The development of a Core Outcome Set may be an effective solution to standardize the evaluation of physical exercise effects on each cognitive ability [44,47,48] and, thereby, help the development of clear guidelines on physical exercise prescription for people with any type of major NCD.

As for the non-observed effects on neuropsychiatric symptoms, worthwhile referring is the instrument used for data collection. The NPI test is the most widely used instrument in nonpharmacologic interventions to determine its benefit on neuropsychiatric syndromes that occur in Alzheimer's disease and other neurodegenerative disorders [11,49]; but, as underscored by Ferreira and colleagues [50], the caregivers' subjective appraisal on symptoms severity may induce variability on its evaluation. For this reason, the usage of shorter frequency ratings like the Abe's BPSD Score [51] has been described as more prone to a direct and objective assessment by caregivers [50]. Using it in research on MT interventions might be a possibility in further studies, following recent efforts on making an European Portuguese version of the instrument available for research [50]. Also, controversial findings have been reported on the influence of physical exercise as a non-pharmacological first-line treatment for the management of neuropsychiatric symptoms [17,19,52]. Kouloutbani and collaborators [11], for instance, showed the benefits of aerobic training interventions on alleviating depressive symptomatology, but the high variability on programs characteristics and inclusion of different stages of dementia did not allow these authors to drawn on firm conclusions. So far, most studies have been focusing exclusively on depression [16,21,22] and, therefore, data is sparse on other behavioural signs (e.g., aberrant motor behaviour) and psychological symptoms (e.g., apathy, anxiety, delusions, hallucinations) [17]. However, beyond changes in the NPI total score, the authors could not conduct further sub-analyses due to sample size restrictions. It is necessary, for these reasons, to further investigate the potential effects of MT interventions on alleviating specific neuropsychiatric symptoms aside from depression in individuals with major NCD from mild to severe stages through culturally validated frequency scales.

In terms of the effects of the MT physical exercise on the quality of life, our study findings showed promising results for the QoL-AD total scores, which suggests a potential positive effect. A larger and more homogenous sample (i.e., in terms of stage and subtype of dementia) could have resulted in a statistically significant interaction factor between group and time. According to Ojagbemi and Akin-Ojagbemi [24] meta-analysis study, aerobic physical exercise seems to potentially produce a larger effect (though still not statistically significant) on quality of life when compared with non-aerobic or combined methodologies, but a number of methodological issues related to training specifications (i.e., frequency, intensity, type, and time) and dementia stage/subtype affect results interpretation. In fact, there is a lack of evidence supporting physical exercise interventions (of any training modality) for improving quality of life and well-being in individuals with major NCD [23], possibly due to the limitations underlying the conceptualization and assessment of quality of life in this population [53-55]. As result, these empirical and theoretical challenges do not allow the transferability of the assumption that physical exercise may also improve the quality of life and well-being of individuals with major NCD just like it improves in the general older population [23,24]. QoL-AD is a frequently used measure, particularly in studies considering both self-rated and caregiver-rated quality of life [24,54], but future research is still needed to understand if it is the most appropriate instrument to determine the effectiveness of physical exercise interventions. As suggested by Ojagbemi and Akin-Ojagbemi [24], a combination of proxy and self-reports, as well as the examination of physical functioning, may provide a more comprehensive information about the effects of physical exercise in quality of life of people with major NCD. Furthermore, evidence is also required to attest if MT may be an effective methodology to improve quality of life and allow clear recommendations.

The quasi-experimental design and the small sample size need to be acknowledged as major limitations of our study; therefore, results should be interpreted with caution and not generalized. Due to difficulties during the recruitment process, some participants were tentatively included in the “Body &

Brain" project even if their diagnosis of major NCD was still under study at baseline evaluations; for this reason, some participants who have completed the intervention were excluded due to the later confirmation of a minor NCD diagnose, increasing the already high dropout rate. Moreover, possibly as consequence of the delayed implementation of the national strategy for dementia [56], also clinical data on dementia subtype or stage was scarce in the patients who were considered eligible to participate in the study, constraining the possibility of more detailed analysis. Such a lack of information has been reported in several national studies aiming to estimate dementia prevalence rates [57,58]. Lastly, the authors want to point out that evaluators were not blind to group assignment, which can be partially justified by the nature of this intervention and sample specifications.

FUTURE RESEARCH IMPLICATIONS

Future trials should continue exploring the effects of MT training methodologies in cognition, neuropsychiatric symptoms, and quality of life, and intent to provide more detailed information on the impact MT has on specific cognitive abilities, such as executive functions, and on distinct behavioral and psychological symptoms. For such an aim, reliable measures should be considered, as the gold standard methods may not always be the best solution. MT physical exercise has been increasingly recommended for older adults with and without functional limitations [28], and even for those already diagnosed with Alzheimer's disease [2], which justifies the need to explore the potential effect of this training methodology on different stages/subtypes of major NCD.

CONCLUSION

A MT physical exercise intervention can be an effective way to slow down cognitive decline, manage challenging behaviors and improve quality of life of individuals with NCD, but further research is necessary to attest the influence of this training methodology. There is still a long way to go in what concerns physical exercise recommendations for people with major NCD, but, in the absence of a cure or disease-modifying therapy, it is of utmost importance to explore the potential effects of validated methodologies that might slow down the disease progression or alter its course, delaying or avoiding nursing-home placement.

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Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

STATEMENTS AND DECLARATIONS

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Ethics Approval and Trial Registration

The study protocol was approved by the Ethical Committee of the Faculty of Sports of the University of Porto (Ref CEFADE22.2018). The trial was registered with the US National Institutes of Health Clinical Trials Registry (ClinicalTrials.gov – identifier number NCT04095962).

Consent to Participate and for Publication

Written informed consent was obtained from all participants and/or legal representatives/significant person included in the study prior to data collection.

Availability of Data and Materials

The dataset supporting the conclusions of this article will be available upon reasonable request.

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Chapter 6. Quality of Life of Individuals with Neurocognitive Disorder: What is the Relation with Physical Health Indicators?

The present chapter includes one published paper.

6.1 *Original Study III* – Health-related physical indicators and self-rated quality of life in older adults with neurocognitive disorder

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ABSTRACT

Purpose: This study aimed to identify the association between health-related physical indicators – sarcopenia-related factors, physical fitness, independence in activities of daily living (ADL) and habitual physical activity - and self-rated quality of life (QoL) in people with neurocognitive disorder (NCD).

Methods: This cross-sectional study included 115 participants (78.22 ± 7.48 years; 74.8% female) clinically diagnosed with NCD. Self-rated QoL was evaluated using The Quality of Life – Alzheimer's Disease (QoL-AD). Dual energy X-ray Absorptiometry, handgrip strength, Short Physical Performance Battery, and the 6-Meter Walk test were used to assess sarcopenia-related factors. Senior Fitness Test and One Leg Balance test, Barthel Index, Baecke Modified Habitual Physical Activity Questionnaire were used to determine physical fitness, independence in ADL and physical activity, respectively. Regressions analyses were performed to examine associations between these variables and QoL-AD.

Results: Data from univariable linear regression analysis revealed that self-rated QoL was associated with sarcopenia-related factors (lower body function, handgrip strength, gait speed, and appendicular skeletal muscle mass index - ASMI), physical fitness (upper-and-lower-body strength, agility/dynamic balance, cardiorespiratory fitness and body mass index), habitual physical activity and independence in ADL. Results from multivariable regression analysis showed that ASMI (B = 1.846, 95%CI: 0.165-3.527, p = 0.032) and lower body function (B = 0.756, 95%CI: 0.269-1.242, p = 0.003) were positively associated with self-rated QoL. These variables explained 20.1% of the variability seen in self-rated QoL, controlling for age, sex, marital status and education.

Conclusion: Sarcopenia-related factors, namely lower body function and ASMI, should be acknowledged in future research studies as critical health-related indicators associated with QoL in people with NCD. **Trial Registration:** ClinicalTrials.gov – identifier number NCT04095962

Keywords: Dementia, sarcopenia, physical function, physical fitness, physical activity.

INTRODUCTION

Worldwide around 152 million people will live with dementia by 2050, particularly in low-and-middle income countries due to the simultaneous increase of life expectancy and risk factors burden [1]. Also designated as major neurocognitive disorder, this syndrome is defined by a progressive and significant decline in one or more cognitive domains that interfere in daily activities [2, 3].

People diagnosed with a neurocognitive disorder (NCD) tend to have worse general health, and present more physical problems than their counterparts without such a diagnosis [1, 4]. The World Health Organization (WHO) has recognized this condition as a global social and health priority [5], a major cause of disability and dependency with a heavy impact on the quality of life (QoL) of individuals and their caregivers [6].

QoL is a multidimensional concept defined by WHO as “an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns” [7]. This subjective construct might be affected by one’s psychological state, physical health/level of independence, social relationships, personal beliefs, and relationship to their environment [7, 8]. However, there is no consensual theoretical model regarding its conceptualization and assessment in people with NCD [9].

Lawton *et al.* [10] has established the most influential dementia-specific framework, which comprises the same domains as in general people such as: competent cognitive function, ability to perform activities of daily living (ADL), favorable emotional balance between positive and negative emotions, capacity to enjoy a great time and develop social interactions. Logsdon *et al.* [11] considered Lawton’s model as a reference, establishing QoL as a multidimensional construct that includes not only objective/observable indicators of well-being, but also the individual's subjective perception of his position in life [12]. These authors created The Quality of Life – Alzheimer's Disease Scale (QoL-AD) [11], which became a widely used measure of QoL for people with NCD, regardless of disease severity [9, 12, 13].

Several authors highlighted many disease-related factors that may affect people with NCD's ability to comprehend and make complex subjective judgements about their QoL, such as communication impairment, and memory, attention or insight deficits [11, 14]. Nonetheless, most people with NCD can discuss their QoL with their own perception and desires towards life. Their perspective is particularly relevant in subjective domains where personal interpretation is pivotal [12, 15-17].

Due to the many challenges involved in QoL evaluation in people with NCD, there seems to be no univocal perspective among researchers about the factors most associated with self-rated QoL and how it can be promoted/improved [18, 19]. While a large body of evidence has extensively substantiated the association between individual or NCD-related characteristics and QoL, less attention has been paid to the role of health-related physical indicators. As referred by Logsdon *et al.* (2007) [20] both preserved independence in ADL, and physical fitness and function can also be determinant factors to QoL in individuals in dementia.

Apart from deficits in cognition and behavior, people with NCD tend to reveal increased declines on several physical fitness capacities [21, 22], particularly in balance, gait, coordination [23], aerobic capacity, agility, lower body strength and flexibility [22], which may emphasize their difficulties in performing ADL independently and thus negatively affect their QoL [22].

As predictive factors for disability and dependence in older adults, major or minor NCD, seems to be positively associated with other highly prevalent age-related comorbidities like sarcopenia [24-26]. The European Working Group on Sarcopenia in Older People (EWGSOP) has recommended that sarcopenia diagnosis is probable in the presence of low muscle strength, then confirmed by the presence of low muscle mass and, in advance, a severe stage is established if low physical performance is observed [27]. This syndrome, from a pathophysiologic viewpoint, can be considered as an organ failure, with risk of adverse health outcomes as increased mortality, physical disability, and poor QoL [24, 28].

Since physical fitness and function, and potentially incapacitating conditions like sarcopenia or frailty can be ameliorated, the study on the hypothetical association of these factors with QoL can represent an opportunity to create preventive and interventive strategies to improve QoL in this population. Thereby, this study aims to add to the already existing literature on factors related to QoL by identifying the association between health-related physical indicators – sarcopenia-related factors, physical fitness, independence in ADL and habitual physical activity - with self-rated QoL in people with NCD.

MATERIAL AND METHODS

Study Design and Participants

For this cross-sectional study, 183 individuals living in the metropolitan area of Porto (Portugal) were identified as potentially eligible participants, recruited from hospitals and clinics (i.e., outpatients followed by psychiatry and/or neurology specialists), daycare centers, nursing homes, other community settings (e.g., local centers and/or specific programs for older population), and municipalities, within a research project entitled “Body & Brain” from September 2018 to November 2019. Advertisements for selecting participants were made via phone calls, emails, informative flyers and meetings (presential and online). The “Body & Brain” project consists of a quasi-experimental controlled trial that aims to address the effects of a 6-month multicomponent training (MT) intervention and 3-month detraining on physical and cognitive function of older adults with dementia. The intervention group receives a bi-weekly MT exercise intervention, whereas the control group receives monthly recreational sessions. The main outcomes are physical function as measured by the Short Physical

Performance Battery (SPPB) and cognitive function evaluated using the Alzheimer Disease Assessment Scale – Cognitive (ADAS-Cog) at baseline, immediately after 6-months and 3-months after the end of intervention. Secondary outcomes include body composition, physical fitness, daily functionality, quality of life, neuropsychiatric symptoms and caregiver's burden. Cardiovascular, inflammatory and neurotrophic blood-based biomarkers, and arterial stiffness are also evaluated in subsamples.

The inclusion criteria were as follow: individuals aged ≥ 60, capable of walking autonomously without an assistive device or human assistance, and clinically diagnosed with NCD (or previously designated dementia or mild cognitive impairment) using accepted diagnostic criteria such as those established by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR or DSM-5) [3], ICD-10 [29], or the NINCDS-ADRDA [30]. Individuals were excluded from this study if data was missing on QoL-AD.

From the 183 individuals recruited, only 122 were confirmed as eligible participants. Of those, 7 were excluded due to missing data on QoL-AD. Therefore, this study's final sample comprised 115 participants.

Participants and their caregivers and/or proxy decision-maker received a complete explanation of the study procedures and signed the informed consent, in full compliance with the Helsinki Declaration.

This study was approved by the Ethical Committee of the Faculty of Sports of the University of Porto (Ref CEFADE22.2018) and is registered at the US National Institutes of Health clinical trials registry (ClinicalTrials.gov – identifier number NCT04095962). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement checklist for cross-sectional studies were followed, and this study is described according to its guidelines [31].

Data Collection

Individuals with NCD who accepted to voluntarily participate in the "Body & Brain" project (October 2018 and October 2019) performed the baseline evaluations in three different appointments (during October, in separate days) with specialized and well-trained researchers. At the first appointment, sociodemographic and clinical data were gathered, and all physical domain tests were performed. On the second appointment, cognitive domain tests and quality of life were evaluated; and, finally, body composition tests were performed at the third evaluation moment. Caregivers' questionnaires referring to people with NCD neuropsychiatric symptoms, daily functionality and habitual physical activity were obtained afterwards via scheduled phone interview.

Quality of life

QoL was evaluated using the Portuguese version of QoL-AD [32]. This instrument includes patients' and caregivers' reports on how the patient feels regarding 13 items, such as physical health, energy, mood, living situation, memory, relationship with family members, marriage and friends, ability to do things for fun, ability to do usual activities, and financial situation. This measure is scored on a four-point Likert-type scale ranging from 1 "being poor" to 4 "being excellent". [12]. The total score ranges from 13 to 52, with higher scores indicating better self-rated QoL [11]. The QoL-AD patient report is a valid and reliable measure for use with older adults with cognitive impairment (Cronbach's α = 0.83) [11] and was adapted and validated for the Portuguese population presenting a good internal consistency (Cronbach's α = 0.867) [32].

Individual and NCD-related characteristics

Participants' sociodemographic information (age, gender, marital status, education, and living situation) was gathered via questionnaire.

A scale of comorbidities (ranging 0-15) was created comprising the following conditions: diabetes, dyslipidemia, hypertension, myocardial infarction, cardiac insufficiency, peripheral vascular disease, stroke/transient ischemic attack, other cardiovascular diseases, osteoporosis, arthrosis, rheumatoid arthritis, respiratory disease, renal disease or other diseases (e.g., cancer). Information on the patients' pharmacological treatment (total number of prescribed daily medications) was also collected.

Cognitive function was evaluated using the Portuguese version of the ADAS-Cog [33] which comprises essential features of cognitive decline such as memory, praxis, constructive ability, language and orientation. Scores range from 0 to 68, with higher scores suggesting greater severity of cognitive impairment. Although values for internal consistency of the Portuguese version of the ADAS-Cog were below the recommended minimum (Cronbach's α = 0.55), it presents a strong convergent validity with both MMSE and MoCA [34]. Other review studies [35] have considered that ADAS-Cog is a reliable and valid test for individuals with mild to moderate dementia. To classify disease duration, the number of years since formal NCD diagnosis was considered.

The Neuropsychiatric Inventory (NPI) [36, 37] was used to determine the frequency and severity of behavioral and psychological symptoms of dementia (BPSD) over the previous month. This instrument was administrated to caregivers of people with NCD and its total score is calculated by multiplying the frequency and severity rates per domain (e.g., delusions, agitation, or motor disturbances) and adding them up – ranging from zero to 144 points, with high scores corresponding to worsening of BPSD. The Portuguese version of NPI [37] showed good internal consistency (Cronbach's α = 0.77), presented robust positive data on inter-rater and test-retest reliability, and a significant convergent validity.

Health-related physical indicators

<u>*Sarcopenia-related factors*</u>

Total Body Lean Mass in kilograms (kg) and Appendicular Skeletal Muscle Mass Index (ASMI), which is the sum of muscle masses of the four limbs described as appendicular skeletal muscle mass adjusted for height (kg/m^2), were analyzed through Dual energy X-ray Absorptiometry (DXA) (QDR 4500/A, Hologic Explorer, Bedford, USA). All procedures were conducted by a certified professional that briefly explained the full procedure to each participant. The participant was then placed in supine position on the table, with arms pronated and feet in dorsiflexion. Two X-ray attenuations took 10-20 minutes to scan the whole body. The procedure was simple and non-invasive, although DXA does expose the patient to radiation, the dose from a single whole body DXA (< 10 microSieverts) is very small [38]. Despite of being an easy protocol, it requires the participants to stay motionless during the entire procedure which can be difficult for people with NCD since it might exacerbate BPSDs. Therefore, individuals' data were excluded from analyses if they did not provide a complete valid total-body scan (e.g., by moving their head or any body part) [39]. If needed, a significant person/caregiver could remain on individuals' side during the test procedure, to guarantee participants overall well-being.

Lower extremity function was assessed using Short Physical Performance Battery (SPPB) that assesses balance, gait capacity and lower limb strength. The total score ranges from zero to 12, with higher scores indicating better function [40]. The SPPB has showed good internal consistency (Cronbach's α = 0.76) [40], excellent test-retest reliability, predictive and convergent validity [41, 42]. Gait speed was assessed using the 6-meter walk test [43], where participants were asked to walk in a 6-meter straight line at their normal pace, and the time was registered for each of the 2 allowed attempts. The outcome measure was the best value of the 2 attempts, converted to walking speed (m/s). Gait speed was recognized as a reliable outcome measure to be used with people diagnosed with dementia [44]. Finally, SPPB and gait speed were identified as "Core-battery" tests to analyze mobility and lower body function in community-dwelling older adults with cognitive impairment [45].

Handgrip strength was obtained with a Jamar Plus + Digital hand dynamometer (Sammons Preston Inc., Bolingbrook, Illinois, USA) [46]. Measurements were carried out following the American Society of Hand Therapists recommendations [47], and each participant performed three attempts with a pause of 1 minute between them. The maximum value, in kilograms of force (kgf), of the three measurements with the dominant hand was registered. The Jamar Plus + Digital hand dynamometer is considered a gold standard method and presents an acceptable concurrent validity with known weights, excellent inter-instrument reliability (0.90-0.97) and strong concurrent validity [48]. The handgrip strength has also excellent reliability for mild to moderate stages of dementia [49].

Physical fitness

Functional fitness was measured using the Senior Fitness Test (SFT) [50], which is a simple instrument to assess adults aged from 60 to 90-plus years old. This physical battery includes lower and upper-body strength (30-second chair stand and 30-second arm curl tests, respectively), lower and upper-body flexibility (chair sit-and-reach and back scratch tests, respectively), aerobic endurance (2-minute steps test), and agility/dynamic balance (8-foot up-and-go test). The SFT battery has shown high to very high test-retest reliability in community-dwelling older adults diagnosed with cognitive impairment [51], and a high intraclass correlation coefficient in all SFT items (0.93-0.98).

Body weight (kg) was measured to the nearest 0.1 kg (SECA 899, Hamburg, Germany), and the body mass index (BMI) was calculated as the weight divided by the squared height in meters (kg/m^2).

Static balance was measured with the One Leg Balance Test [52] which has been used in people with NCD [53-55] and considered a reliable measure [35]. Participants were asked to choose a leg to stand on, flex the opposite knee and balance on one leg as long as possible. The time (in seconds) standing unsupported were recorded.

ADL Independence

Participants ability to function independently in ADL was assessed using the Barthel Index (BI). This instrument addresses ten basic daily activities, such as bathing, dressing or using toilet – with total score ranging from zero to 100. Lower scores indicate higher dependency levels [56]. The Portuguese version of BI has showed a good internal consistency (Cronbach's $\alpha = 0.89$) [57].

Habitual Physical Activity

The Modified Habitual Physical Activity Questionnaire (Baecke), adapted for the Portuguese population, was administrated to the caregivers regarding the people with NCD to determine participants habitual physical activity in two different domains: sports activities (4 items) and leisure activities (4 items) [58]. The total physical activity index is calculated with a specific formula that considers the intensity of the practiced type of sport, its frequency and regularity through the last year, and the sum of scores of leisure activities – with higher scores indicating higher levels of habitual physical activity. The Portuguese version of Modified Baecke has showed good internal consistency (Cronbach's α = 0.78), and acceptable convergent validity [58]. Although this questionnaire is not validated for people with NCD, the majority of studies have been using it by allowing a proxy to respond [59].

Statistical Analysis

Descriptive characteristics of the sample were presented as mean and standard deviation (SD) for continuous variables and as frequency and percentages for categorical variables. Univariable linear regression models were performed to examine associations between the independent variables and self-rated QoL. Multivariable linear regression model was built by entering those variables that were statistically significant in the univariable analysis. Age, sex, marital status and years of education were considered as covariates. A stepwise approach was used to obtain the final model. Regression outputs (e.g., P-P plot) were inspected to assess normality of residuals of the regression and homoscedasticity. Multicollinearity was checked between independent variables prior to building the models, and Variance Inflation Factor (VIF) threshold of 10 was used to indicate probable multicollinearity. Statistical analyses were conducted with SPSS IBM Statistical Software version 26.0 (SPSS, Inc., Chicago, IL) and a significance level of 0.05 was considered.

RESULTS

Participants' characteristics are described in Table 1. The final sample comprised 115 participants (74.8% female) with an overall mean age of 78.22 (7.48) years. Overall, 47% of the participants were married and 74.8% lived in the community. The medium score of ADAS-COG was 34.46 (3.72) and of NPI was 14.25 (11.05). Most participants had the clinical diagnosis of major NCD (91.3%), and the underlying subtype was mostly unspecified (38.1%) or due to

Alzheimer's disease (35.2%); most commonly, the diagnosis lasted for at least 2.85 (2.24) years. Participants' self-rated QoL-AD presented a mean score of 31.43 (5.35).

Table 1. Sample characteristics

Domain		Measure	Total (n=115)[a]
Sociodemographic and Clinical Condition Characteristics	***Individual and NCD-related Characteristics***	Age, years	78.22±7.48
		Gender, female %	86 (74.8%)
		Education, years	5.86±3.65
		Marital Status	
		Married, n (%)	65 (47%)
		Living Situation	
		Institutionalized, n (%)	29 (25.2%)
		Comorbidities, number	3.36±1.94
		Polypharmacy, number	7.56±3.20
		Disease Duration, years	2.85±2.24
		Cognitive Function, score	34.46±13.72
		Neuropsychiatric symptoms, score	14.25±11.05
Health-related Physical Indicators	***Sarcopenia-related Factors***	Total Body Lean Mass, kg	37.97±6.62
		ASMI, kg/m^2	6.37±0.86
		Lower Body Function, score	7.90±3
		Gait speed, m/s	0.72±0.23
		Handgrip strength, kgf	19.20±6.84
	Physical Fitness	Upper-body strength, reps	9.63±3.86
		Lower-body strength, reps	9.93±3.84
		Upper-body flexibility, cm	-29.80±15.5
		Lower-body flexibility, cm	-19.46±12.32
		Agility/dynamic balance, s	13.08±7.28
		Cardiorespiratory capacity, reps	48.95±19.46
		Balance, s	5.31±10.14
		BMI, kg/m^2	27.72±4.23
	ADL Independence	Barthel Index, score	86.49±15.2
	Level of Physical Activity	Modified Baecke, score	3.29±0.93
Quality of Life		Self-rated QoL-AD, score	31.43±5.35

[a] Missing person on Polypharmacy, Cognitive Function, Lower-body Function, Lower-Body Flexibility, Agility/dynamic Balance, Barthel Index – 1; Neuropsychiatric Symptoms, Upper-body Flexibility, Cardiorespiratory capacity – 2; Lower-body Strength – 3; Education – 4; Handgrip Strength – 5; Upper-body Strength – 6; Disease duration – 15; Modified Baecke – 17; Total body lean mass – 19; ASMI, BMI – 20.
Note: ASMI - appendicular skeletal muscle mass index; BMI – body mass index; QoL-AD – Quality of Life-Alzheimer's Disease.

Results from univariable linear regression models are depicted in Table 2. Overall, individual characteristics and NCD-related domain were not associated with self-rated QoL ($p > 0.05$). From the physical fitness domain, all variables were positively associated with self-rated QoL ($p < 0.05$), with the exception of balance (B = 0.04, 95%CI: -0.057-0.139, p = 0.408) and upper/ lower body flexibility (B = 0.032, 95%CI: -0.033-0.097, p = 0.326; B = 0.037, 95%CI: -0.044-0.118, p = 0.371, respectively). Moreover, other health-related physical indicators, as independence in ADL and habitual physical activity were positively associated with self-rated QoL. Finally, several sarcopenia-related factors as ASMI (B = 1.707, 95%CI: 0.427-2.986, p = 0.009), lower body function (B = 0.609, 95%CI: 0.294-0.923, $p < 0.001$), gait speed (B = 7.675, 95%CI: 3.517-11.83, $p < 0.001$), and handgrip strength (B = 0.154, 95%CI: 0.007-0.301, p = 0.040) were also found to be positively associated with self-rated QoL.

Table 2. Univariable regression models

Domain		Measure	B (95% CI)	*p-value*
Sociodemographic and Clinical Condition Characteristics	***Individual and NCD-related Characteristics***	Age, years	0.008 (-0.126-0.141)	0.910
		Gender [ref: male]	0.109 (-2.176-2.393)	0.925
		Education, years	0.058 (-0.224-0.340)	0.685
		Marital Status [ref: not married]	-0.454 (-2.440-1.532)	0.651
		Living Situation [ref: not institutionalized]	-0.016 (-2.301-2.268)	0.989
		Comorbidities, number	-0.494 (-0.998-0.011)	0.055
		Polypharmacy, number	-0.066 (-0.379-0.248)	0.678
		Disease Duration, years	0.181 (-0.309-0.671)	0.464
		Cognitive Function, score	-0.022 (-0.095-0.052)	0.560
		Neuropsychiatric symptoms, score	-0.020 (-0.111-0.071)	0.663
Health-related Physical Indicators	***Sarcopenia-related Factors***	Total Body Lean Mass, kg	0.015 (-0.002-0.032)	0.076
		ASMI, kg/m^2	1.707 (0.427-2.986)	0.009*
		Lower Body Function, score	0.609 (0.294-0.923)	<0.001*
		Gait speed, m/s	7.675 (3.517-11.83)	<0.001*
		Handgrip strength, kgf	0.154 (0.007-0.301)	0.040*
	Physical Fitness	Upper-body strength, reps	0.534 (0.286-0.781)	<0.001*
		Lower-body strength, reps	0.456 (0.205-0.707)	<0.001*
		Upper-body flexibility, cm	0.032 (-0.033-0.097)	0.326
		Lower-body flexibility, cm	0.037 (-0.044-0.118)	0.371
		Agility/dynamic balance, s	-0.156 (-0.291- -0.021)	0.024*
		Cardiorespiratory capacity, reps	0.092 (0.043-0.141)	<0.001*
		Balance, s	0.041 (-0.057-0.139)	0.408
		BMI, kg/m^2	0.291 (0.033-0.549)	0.027*
	ADL Independence	Barthel Index, score	0.091 (0.027-0.154)	0.005*
	Level of Physical Activity	Modified Baecke, score	1.696 (0.586-2.805)	0.003*

[a] Missing person on Polypharmacy, Cognitive Function, Lower-body Function, Lower-Body Flexibility, Agility/dynamic Balance, Barthel Index – 1; Neuropsychiatric Symptoms, Upper-body Flexibility, Cardiorespiratory capacity – 2; Lower-body Strength – 3; Education – 4; Handgrip Strength – 5; Upper-body Strength – 6; Disease duration – 15; Modified Baecke – 17; Total body lean mass – 19; ASMI, BMI – 20.
Note: ASMI - appendicular skeletal muscle mass index; BMI – body mass index; QoL-AD – Quality of Life-Alzheimer's Disease.

Independent variables that reached a statistically significant effect on the univariable analyses were included in the multivariable regression model. The final model retained only two significant factors adjusted by age, sex, marital status and education: ASMI and SPPB score (Table 3). Higher scores of ASMI (B = 1.846, 95%CI: 0.165-3.527, p = 0.032) and SPPB (B = 0.756, 95%CI: 0.269-1.242, p = 0.003) were associated with higher self-rated QoL. These two variables explained 20.1% of the variability seen in self-rated QoL, after adjusting for covariables.

Table 3. Multivariable linear regression model

Domain (Measure)	B (95% CI)	*p-value*	*VIF*
Sarcopenia-related Factors			
ASMI, kg/m^2	1.846 (0.165-3.527)	0.032	1.222
Lower body function, score	0.756 (0.269-1.242)	0.003	1.163
Age, years	0.138 (-0.085-0.361)	0.219	1.374
Gender [ref: male]	1.652 (-1.668-4.973)	0.324	1.298
Education, years	-0.047 (-0.401-0.307)	0.792	1.048
Marital status [ref: not married]	0.944 (-1.911-3.800)	0.511	1.252

*Model adjusted by age, sex, marital status and years of education
Note: ASMI - appendicular skeletal muscle mass index.

DISCUSSION

This study explored the association between health-related physical indicators and self-rated QoL in people with NCD. Our results showed that sarcopenia-related factors (ASMI, handgrip strength, gait speed, lower body function), physical fitness (upper-and-lower-body strength, agility/dynamic balance and cardiorespiratory fitness, BMI), independence in ADL and habitual physical activity were associated with self-rated QoL. After controlling for age, gender, marital status and education, only sarcopenia-related factors, particularly, ASMI and lower body function, were positively associated with QoL-AD. Overall, these findings suggest that health-related physical indicators, although rarely considered in research as associated factors in QoL in people with NCD, seem to be of particular relevance, and need further investigation.

Sarcopenia is a progressive skeletal muscle disorder that is associated with increased risk to adverse outcomes. This condition is defined by low muscle strength, low muscle quantity and quality, and low physical performance [60], and it is associated with falls, fractures, physical disability; it has also been linked to cognitive impairment and QoL [24, 61]. Furthermore, recent evidence shows that sarcopenia is three times more prevalent among people with dementia than those without this syndrome [26]. In line, Burns *et al*. [62] found that lean mass was reduced in persons with early AD compared to those without dementia, and was also associated with brain atrophy and cognitive performance. Adding to these results, Kim *et al.* [63] reported that increased muscle tissue was associated with a lower probability of AD in older adults, whereas visceral adipose tissue was not correlated with the probability of AD. These findings support that sarcopenia might be closely related to dementia pathophysiological process [64].

Sarcopenia and its markers (low handgrip strength, low muscle mass and low performance) are associated with ADL dependency [65], which is an important factor for the preservation of QoL in people with NCD [9]. The relationship between sarcopenia and QoL in people with major NCD was described by Umegaki *et al*. (2020) [25]. The authors found a significant negative association between sarcopenia and self-rated QoL in people with NCD, independent of the confounding factors. In line, our results show an association between ASMI, lower body function (which are factors related to sarcopenia) with QoL in people with NCD. Conversely, Bonfiglio and colleagues [66] stated that people with NCD and sarcopenia have not reported lower QoL, when compared to others without sarcopenia, which could be in result of the non-dementia-specific instrument used to asses this outcome.

Our study revealed that after controlling for age, gender, marital status and education, BMI and other physical fitness variables were not associated with self-rated QoL-AD. These findings are in accordance with previous results from Sampaio *et al*. (2019) [67], which showed that after controlling for important factors (i.e., age, gender, educational level and BMI), not a single physical fitness variable was associated with self-rated QoL-AD in institutionalized older adults diagnosed with dementia. To the best of our knowledge, only few studies [66-68] reported the association of the several physical components with QoL in individuals diagnosed with cognitive impairment.

As stated by Lam et al. (2018) [23] deficits in balance, gait and movement coordination are also highly prevalent in people diagnosed with cognitive impairment. Data from our study revealed that static balance may not be an important factor in self-rated QoL. Nevertheless, this physical ability is linked with sarcopenia, and consequently with an increased risk of falls [24], but further evidence is needed to verify this association.

Bonfiglio and colleagues [66] also investigated the association between physical inactivity and self-rated QoL, and besides the absence of statistically significant results, their multiple linear regression models showed a negative relation between these variables. In our study, habitual physical activity did not remain significantly associated with self-reported QoL after controlling for important factors. A systematic review study of exercise-based interventions for QoL in people with NCD [14] highlighted the lack of evidence supporting this association. Based on this assumption, Huang *et al.* (2020) [69] confirmed the existence of an indirect relationship between physical activity and QoL, through slowing down dementia-related functional decline and reducing depressive symptoms, while a direct effect remains unclear yet. As concluded by Huang and colleagues, the effect of higher level of physical activity and regular exercise on QoL need further evidence.

An important systematic review and correlational meta-analysis study regarding the factors related to QoL, subjective well-being or life satisfaction in people with dementia conducted by Martyr and colleagues, included 198 QoL studies and highlighted that better functional ability was significantly associated with better self-rated QoL of people with dementia [9]. This finding is consistent with the emphasis on functional ability in Lawton's dementia-specific model of QoL. In agreement with our study results, Kisvetrova *et al.* (2019) highlighted the independence in ADL and physical fitness as positive predictors of QoL in people with dementia [68]. This study findings are consistent with the assumption that people with NCD with increased physical abilities tend to maintain their ability to function independently on daily activities and, therefore, report better QoL [68, 70]. Similar results were published by Gare-Olmo and collaborators [71] and Bonfiglio *et al.* (2019) [66].

Our study findings present significant contributions to the knowledge about the factors associated with self-rated QoL in people with NCD, identifying the importance of sarcopenia-related factors, physical fitness, independence in ADL and physical activity outcomes. Nearly 20% of the variability on self-rated QoL-AD could be explained by SPPB total score and ASMI values, which reinforces the need to address, measure and control physical and functional decline, and loss of muscle mass, since these factors might be detrimental on self-rated QoL of people with NCD.

Highly related with sarcopenia, lower body function and lean mass, when measured with gold-standard instruments (i.e., DXA), should also be considered in future multidimensional evaluations of QoL in people with NCD. Likewise, future research studies should focus on physical fitness, independence in ADL and daily physical activity factors, and their association with QoL in people with NCD, whether considering self or proxy reports.

LIMITATIONS

This study presents some strengths that are worth mentioning. We explored multiple health-related physical indicators which are uncommonly seen in this type of studies. Furthermore, we used gold standard evaluations on body composition and an extensively physical fitness battery reliable for people with NCD. Nevertheless, this study also presents several limitations. First, the study's cross-sectional design does not allow to determine a cause-and-effect relationship between self-rated QoL and health-related physical indicators. Secondly, our results might not be generalizable due to our small sample size, and due to the unequal distribution of participants from both genders. Thirdly, an objective indicator of comorbidities, as Modified Charlson's Comorbidity Index, could be important to improve our sample characterization in order to address its interaction with QoL in a more accurate manner. Finally, authors want to point out the risks that might be connected with the lack of control/ scarce monitoring of several factors, as nutritional status, risk of fall, bone mineral density, and other physiologic variables, often associated with health-related physical indicators.

FUTURE RECOMMENDATIONS

Findings from this article illustrate the need for practitioners and researchers to consider sarcopenia-related factors, namely lower body function and ASMI, as valid and informative indicators of QoL in people with NCD.

Furthermore, investments in early detection through screening and effective interventions (e.g., physical exercise) addressing physical and functional decline may help to maintain or even improve QoL in people with NCD. Future research is needed to determine health-related physical indicators associated with QoL for each subtype/stage of NCD, as well as for specific living conditions (e.g., institutionalized vs. community dwelling older adults). Additional studies with a longitudinal design and larger sample size are necessary to confirm our results.

DECLARATIONS

Conflict of Interest

The authors report no conflicts of interest.

Ethics Approval

Ethical Committee of the Faculty of Sports of the University of Porto (Ref CEFADE22.2018). The trial was registered in the US National Institutes of Health Clinical Trials Registry (ClinicalTrials.gov – identifier number NCT04095962).

Informed Consent

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

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Availability of Data and Material

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

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Chapter 7. Influencing Factors on Individuals with Neurocognitive Disorder Adherence to a Community-based Physical Exercise Intervention

The present chapter includes two papers that are under review by international scientific journals with peer-review.

7.1 *Original Study IV* – Contributing factors for (non)adherence to a physical exercise program for people with neurocognitive disorder from the caregivers' point-of-view

Citation: Borges-Machado F, Barros D, Silva P, Marques P, Carvalho J, Ribeiro O. (*under review*) Contributing factors for (non)adherence to a physical exercise program for people with neurocognitive disorder from the caregivers' point-of-view.

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ABSTRACT

Purpose: To explore the perception of informal caregivers about the barriers, motivators, and facilitators towards the participation of care recipients with neurocognitive disorder (NCD) in a physical exercise program.

Methods: This is an exploratory qualitative study, including 20 informal caregivers (67.5 ± 13.94 years old; age range: 37-86; 65% male) from the "Body & Brain" community intervention project. Semi-structured interviews were performed by a trained researcher; data analysis followed the Braun and Clarke's Thematic Analysis guidelines, under the socio-ecological framework.

Results: Two main barriers, three motivators, and five facilitators were perceived by caregivers, illustrating the relation between the intrapersonal, interpersonal, and community levels towards individuals' participation. Care recipients' reluctance to participate and physical environment constraints emerged as main barriers for participation, whereas the health professionals' advice, the need for a stimulating activity, and the potential physical and mental health benefits emerged as motivators. Factors facilitating the involvement and maintenance in the program included care recipients' satisfaction and enjoyment, benefits on their general health, routine, and social connectedness; an overall positive evaluation of the physical exercise program's structure and organization was also highlighted.

Conclusions: Exercise interventions targeting people with NCD should promote a welcoming environment that facilitates individuals' well-being and social interaction. Caregivers have a key role in promoting care recipients' motivation. Health professionals play an important role in recommending participation by raising awareness of potential benefits. Future interventions should be conducted in appropriate community settings and implemented by specialized professional in small groups. These findings provide insights into the factors that may increase the success rate of exercise interventions specifically designed for individuals with NCD.

Keywords: Dementia, physical activity, caregivers, qualitative research, socio-ecological model, major neurocognitive disorder.

CLINICAL IMPLICATIONS

- There is a need to identify the socio-ecological factors that hamper, prompt, or facilitate the individuals with NCD PA adherence, specifically to structured exercise programs.
- Health professionals are key pieces in raising awareness on the potential benefits of physical exercise in individuals with NCD and in advising for participation in physical exercise programs. Caregivers are effective allies in counteracting the unwillingness of individuals with NCD to participate in physical exercise programs, and in guaranteeing their motivation and compliance.
- Group-based physical exercise programs offering a welcoming environment promote individuals with NCD wellness and social connectedness.

INTRODUCTION

Neurocognitive disorders (NCD) encompass a group of conditions that affect the brain in which the primary clinical deficit is cognitive function. The effects of physical activity (PA), specifically exercise, as a nonpharmaceutical approach to prevent, delay or reverse the course of NCD have been extensively explored.[1-3] A large body of evidence highlights the potential benefits of PA and exercise on cognitive function,[4] ability to independently perform activities of daily living (ADL),[5] functional capacity,[6,7] and physical fitness[8] in individuals with NCD. Yet, this population is reported to be highly sedentary, and the small amount of PA they perform tends to be of lower intensity when compared to their healthy peers.[9] Therefore, there is a need to identify the barriers, motivators and facilitators of PA behavior that affect these individuals.[10]

The factors that hamper, prompt, or facilitate PA adherence are particularly relevant to consider when designing exercise programs for people with NCD, to establish further adherence support strategies that promote their engagement in exercise interventions.[11-13] In 2016, a systematic review study on the factors that facilitated or hindered the PA participation of individuals diagnosed with NCD identified 35 barriers, 26 motivators, and 21 facilitators.[14] The main barriers included the individuals' physical and mental limitations, and the caregivers' difficulties with guidance and organization of PA activities; the most common motivators included physical and mental health benefits and participation in preferred PA options; the most reported facilitators included access to appropriate PA options, available support and guidance, and strategies to avoid disease-related or health problems. These results must, however, be interpreted with caution as most studies comprised in the review had reduced sample sizes, and some included quantitative correlates of PA. Moreover, the authors generalized their findings on PA behavior by including the participation in both structured exercise programs (e.g., home-based balance intervention) and physically active recreation activities (e.g., outdoors walks or cycling), though specific factors can be exclusively attributed to the participation in one but not the other. To the best of our knowledge, this is the only published review with its findings organized under the socio-ecological model, specifically accounting for the factors associated with PA adherence in this population.

The socio-ecological model provides a multilevel framework for classifying the complex and dynamic interaction of factors that affect one's physical activity behavior, including intrapersonal factors (e.g., biological, socio-demographic, or psychological), interpersonal factors (e.g., social support, cultural norms, and practices), organizational factors (e.g., organizations, institutions), community factors (e.g., relationships among organizations and the built and natural environment), and policy factors (e.g., regulations and laws).[15-17] Along the different levels of the socio-ecological model, Gebhard and Mir (Austria)[18] investigated the motivators and barriers concerning PA in individuals with dementia living in nursing homes. Similarly, Hobson and colleagues (Canada)[19] explored the barriers, facilitators, and preferences for physical exercise among community-dwelling older adults diagnosed with MCI or early dementia. As acknowledged by these authors, the lack of accessible exercise opportunities specifically targeted or inclusive of older adults with NCD, with different mobility levels and other health-related conditions, is perceived as one of the major barriers to PA in this population. Notwithstanding these findings, it is important to highlight that both studies only identified barriers and motivators or facilitators and included individuals living in care homes who were not involved in a structured physical exercise program.

Identifying the barriers, motivators, and facilitators within the different levels of the socio-ecological model may provide a guide to increase the implementation success rate of future physical exercise interventions. Following this theoretical framework, the present study aims to explore the informal caregivers' point-of-view about the contributing factors for (non)adherence to a group-based physical exercise program for people with NCD living in the community.

METHODS

Design and ethics

This exploratory qualitative study was nested in the "Body & Brain" project (ClinicalTrials.gov – ID: NCT04095962), which is a quasi-experimental trial aiming to investigate the effect of a multicomponent training (MT) exercise intervention on the cognitive function and functional capacity of people with major NCD.[20-22] Eligibility criteria included: individuals aged ≥ 60, clinically diagnosed by a physician for at least 6 months with major NCD, and capable of walking autonomously and independently, i.e., without an assistive device or human assistance.

This study relies on the information retrieved from semi-structured interviews conducted with informal caregivers of individuals who were participating in the project's community-based physical exercise program.

This qualitative study followed the 32-item checklist of the Consolidated Criteria for Reporting Qualitative Research (COREQ),[23] and was conducted in full compliance with the Declaration of Helsinki. The Ethical Committee approval was granted from the Institutional Review Board of the Faculty of Sports of the University of Porto (Ref CEFADE22.2018). Written informed consents were obtained from interested individuals with NCD and their legal representatives, significant person, or assigned main caregiver (complying with the legal requirements associated).

Participants

This purposive sample comprised caregivers of older adults diagnosed with NCD from the “Body & Brain” project, who were participating in the 6-month physical exercise program since September 2019. This MT exercise program was conducted in three different community-based contexts: at a sports university setting, at a community center sports hall, and at a psychiatric hospital that has a specific psychogeriatric unit devoted to dementia care (i.e., with outpatients). The bi-weekly group-based exercise sessions took about 60 minutes each and included five to eight participants. The exercise sessions were subdivided into three main parts: 10 minutes for warm-up (e.g., general activation, joint mobilization and stretching); 35-45 minutes dedicated to specific training (e.g., balance and coordination, upper-and-lower body muscle strength, and aerobic endurance) at light-to-moderate intensity; and final five minutes to cool-down (e.g., slow walking, mobility, stretching and breathing exercises). Simple and functional exercises were preferred. Music accompanied sessions to promote appropriate exercise intensity, social interaction, and enthusiasm, particularly during aerobic endurance. The MT program was implemented by professionals specialized in physical exercise who received specific training concerning NCD clinical features and progression, challenging behavioral and psychological symptoms, communication strategies, and safety issues. More detailed information on the “Body & Brain” project physical exercise plan can be found elsewhere.[22] Only caregivers of community-dwelling individuals were recruited for this qualitative study, regardless of their care recipient's attendance rate to the MT exercise program.

Twenty-two caregivers were contacted by telephone to participate and, from those, only two caregivers were not included in the final sample: one refused to participate in the interviews, and the other was unavailable due to professional reasons. From the 20 caregivers who were interviewed (67.5 ± 13.94 years old; age range: 37-86; 13 men), four shared the task of providing care with a secondary caregiver. Most participants (70%) were retired and spouses of their care recipients.

Data Collection

Questionnaires

Within the scope of the "Body & Brain" project, a series of measures relating to the participants' sociodemographic characteristics, general clinical data, cognitive function, and independence in ADL were obtained during the baseline evaluations.[22] Additionally, data was collected on the caregivers' sociodemographic characteristics and caregiving situation (i.e., relationship to care recipients, frequency of care, number of hours/per day providing care, number of years as the main caregiver, and if the caregiving task was shared with another person).

Interviews

Qualitative semi-structured interviews were conducted by telephone, between April and May 2020, by a trained qualitative research assistant (PM) who was not involved in the "Body & Brain" project. The interview guide was developed based on previous studies,[24-27] covering the barriers, motivators, and facilitators toward the participation in a physical exercise program.

Prior to the study, a pilot interview was conducted to verify if the questions were properly structured to facilitate caregivers' understanding and the adequacy of the interview guide. The final interview guide (Table 1) was discussed among the research team. The interviews started with an introductory statement about the purpose and procedure, followed by an authorization request to record the phone call. Interviewees were reminded that they could refuse to answer any of the questions, withdraw at any moment, and that anonymity was guaranteed.

Table 1. Key questions forming the semi-structured interview

Questions
1. How did you and your care recipient find out about this physical exercise program?
2. What took your care recipient to participate and continue in this program?
3. I would like you to elucidate me about how your care recipient feels before, during and after exercise sessions. 3.1 What does your care recipient transmit you (or what do you perceive) when going to exercise sessions? And when leaving the sessions?
4. This program has started in October 2019, with two sessions per week for 1-hour. 4.1 What has this program brought to your care recipient life?
5. I would like to ask you to think about the less positive aspects. 5.1 What were the main obstacles and difficulties that your care recipient felt from participating in this physical exercise program?
6. What did your care recipient like about the program? 6.1 And what did your care recipient dislike about the program? Please, explain me why.
7. Considering how this physical exercise program did turn out until March 2020, which suggestions/ recommendations would you and your care recipient like to make to improve it?
8. Is there anything else you think we should know?

Data analysis

The interviews were recorded using an encrypted voice recorder. Each interview lasted around 40 minutes (between 20 and 90 minutes) and was transcribed verbatim. The analysis of interviews was based on Braun and Clarke's Thematic Analysis guidelines.[28] Following standard qualitative research procedures, identifying information was removed to ensure that interviewees' anonymity was maintained. The software analysis programme NVIVO (Version 12, QSR International, Southport, UK) was used to assist with data management and analysis.

All interviews were coded by the first author. The data were coded using a deductive approach, meaning that codes and subthemes were theory-driven and grouped into larger themes of "barriers", "motivators" and "facilitators", following the conceptual framework of the socio-ecological model.[29,30] Trustworthiness was attained through category refinement via discussions and triangulations to reduce the effect of researcher bias. To support transferability and transparent interpretation of results, a detailed description of study design, data collection methods, and participants' characteristics is reported in this paper.[28,31]

An initial coding frame was developed, using the principle of constant comparison, to include data-driven themes and patterns. A second researcher independently analyzed approximately 20% of the transcripts. The two researchers met to reflect and discuss the coding and analysis to ensure credibility. Discussion of the analytic process and findings were shared within the research team, who further informed themes refinement. Disagreements regarding the identification, description, analysis, or interpretation of data were resolved through discussion and further analysis. Verbatim quotations were included to support the interpretation of the identified themes and subthemes.

RESULTS

Care recipients' characteristics

Individuals with NCD (mean age 74 years; range 65-84 years; 15 female) were mostly married (80%), female (75%), diagnosed with major NCD (75%) with a mean Mini-Mental State Examination (MMSE) score of 18.6 (6.24) points, and highly independent in ADL (Barthel Index > 80). At baseline evaluations, none of the participants with NCD attended a day care center nor received domiciliary professional care. Table 2 and Table 3 summarize the care recipients' and caregivers' characteristics, respectively.

Table 2. Care recipients' characteristics

Characteristics	Care recipients (N=20)
Age (years), mean (SD)	74 (5.46)
Age, range	65-84
Gender (female), N (%)	15 (75)
Years of Formal Education, mean (SD)	5.15 (2.87)
Education Levels, N (%)	
Low (1-3 years)	5 (25)
Medium (4-6 years)	10 (50)
High (7-12 years)	5 (25)
Marital Status, N (%)	
Widow	3 (15)
Married or Civil Union	16 (80)
Divorced or Separated	1 (5)
ADAS-Cog, mean (SD)	30.2 (14.32)
Level of Independence, mean (SD)	
Barthel Index	95.5 (6.86)
Lawton & Brody	3.0 (1.76)
Diagnosis, N (%)	
Dementia or Major NCD	15 (75)
Multiple Aetiologies	6 (40)
Alzheimer's Disease	5 (33.33)
Unspecified	3 (20)
Vascular Disease	1 (6.67)
Mild cognitive impairment or Minor NCD	5 (25)

Note: Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog)

Table 3. Caregivers' characteristics

Characteristics	Caregivers (N=20)
Age (years), mean (SD)	67.5 (13.94)
Age, range	37-86
Gender (female), N (%)	7 (35)
Years of Formal Education, mean (SD)	7.9 (3.11)
Education, N (%)	
Medium (4-6 years)	6 (30)
High (7-12 years)	13 (65)
Superior (>12 years)	1 (5)
Professional situation, N (%)	
Working	6 (30)
Retired	14 (70)
Caregiver relationship, N (%)	
Partner	14 (70)
Adult Child	4 (20)
Other relative	2 (10)
Number of years as a caregiver, mean (SD)	4.25 (2.36)
Sharing the task of providing care, N (%)	4 (20)
Frequency of care, N (%)	
Continuously	17 (85)
Working days / weekends / rotationally	3 (15)
Providing care (hours/day), N (%)	
0-3h	5 (25)
4-7h	2 (10)
8-10h	1 (5)
>10h	12 (60)

Findings from thematic analysis

Two main barriers, three motivators, and five facilitators were identified. Each of these themes and subthemes are next presented considering the three levels of the socio-ecological model: intrapersonal factors, interpersonal factors, and community factors. Care recipients' unwillingness to participate and physical environment constraints emerged as factors that limited the individuals' participation in the physical exercise program. Advice from health professionals, the need for a stimulating activity, and possible physical and mental health benefits emerged as factors that motivated and/or triggered individuals to engage in this intervention. The factors that facilitated the involvement and maintenance in the program included care recipients' satisfaction, well-being, and enjoyment of exercise sessions, which according to the interviewees were reflected in positive mood changes. Caregivers' perceptions regarding exercise benefits on care recipients' health and social connectedness were also mentioned. Alongside care recipients' need for having a routine, going outdoors, and enjoying spare time, the overall positive evaluation of the physical exercise program structure and organization was also reinforced as facilitator.

Barriers

The unwillingness of individuals with NCD to go to the exercise sessions (intrapersonal level) was mentioned by caregivers as a challenging situation. When proposing the exercise sessions to their care recipients, caregivers described their difficulty in helping them understand what the program entailed. This was often accompanied by a lack of interest and/or motivation to participate, which hindered the caregivers' task to take them to sessions.

> "Going [to exercise sessions] is very difficult because she does not want to go. She ends up going because I managed to convince her." (male, 83, spouse)

> "So, when I tell her to go [to exercise sessions], she never wants to, and she even gets a little flustered. Then I take her by car (…)

> and when she gets there, she says: “Here again?!”. I think she forgets from one time to another, but when she arrives there, [and starts exercising] she remembers it again.” (male, 75, spouse)

Some characteristics of one specific setting where the exercise sessions took place (psychogeriatric unit at a psychiatric hospital) were perceived as a barrier (community level), due to space limitations and restrictions for using music during sessions (as it could interfere with other activities occurring in the same building). This setting was also identified as a barrier since care recipients negatively perceived it as a disease-related environment.

> “There are certain types of exercise that if you had the appropriate music, people would get involved, and it might help. Of course, music cannot be played there because it will interfere with the rest of the hospital” (male, 75, spouse)

> “It has to do with the fact that it is in the hospital and, sometimes, I can tell that my mother’s resistance had to do with the fact that she didn’t associate herself [with the surrounding context].” (female, 45, daughter)

Motivators

Participants mentioned that their care recipients were getting socially isolated and physically inactive due to the lack of accessible activities specifically targeting their condition. In this sense, the “Body & Brain” project was perceived as an opportunity to get involved in a stimulating community-based initiative (intrapersonal level).

> “I wanted my mom to get out of home, and I wanted her to have another type [of activity] ... something that she was interested in, and something that could also be stimulating. Being alone most of the time, just with the television, the cat and nothing else… was making her to lose her abilities and skills more and more...” (female, 45, daughter)

> “She [mother-in-law name] was a very active person, (…) and then she stayed at home after retirement. She started to decline and became very inactive, in addition to her health problem… The physical exercise program was a reason for her to be able to get together with people, to play and talk, which is what she likes and something she was missing” (female, 51, daughter-in-law)

Acknowledging the potential physical and mental health benefits (interpersonal level) associated with being physically active and/or involved in a specialized physical exercise program emerged as a factor that influenced caregivers to motivate their care recipients to participate in the physical exercise program. The encouragement and support given by health professionals (e.g., doctors, nurses, occupational therapists, psychologists) was also reported as being a significant motivator (community level).

> “I foresaw that it [the physical exercise program] would be beneficial, and that led me to incentivize my wife” (male, 75, spouse)

> “What led me [to participate] was the fact that the doctor herself thought that maybe it would be good for her (care recipient), due to her problem.” (male, 67, spouse)

Facilitators

Participants reported that their care recipients “had a good time” and that they observed joy, contentment, and positive changes in mood by taking part in the exercise sessions (intrapersonal level), making the perceived emotional well-being and satisfaction important facilitators for participation.

> “She always feels well when she goes to the exercise sessions; and when she comes back, she feels even better!! It’s very good for her, she likes the environment and the people… It moves her. She gets much better.” (male, 45, son)

> "Sometimes she is at home, and she says: "Ouch! Today my ankle and my knee are hurting. (…) I'm not going today. [Caregiver name], sorry but I'm not going today, I'm in pain." (quoting his wife) (…). [Then] she arrives there, and she is one of the best. She forgets that her knee and ankle are hurting. And she does everything wonderfully without hurt. (…) She gets there and becomes a new person!" (male, 86, spouse)

The absence of meaningful daily activities at home and the consequent need to have a routine and enjoy spare time also facilitated the care recipients' participation in the exercise sessions. As inherent aspects of the physical exercise program adherence, the responsibility to get ready and get out of the house on specific days of the week were considered by caregivers as valuable indirect benefits, and therefore facilitators for participation (intrapersonal level). In addition, the perceived benefits on physical and mental health, whether due to improvements in physical function and/or maintenance of cognitive abilities (interpersonal level), were also mentioned.

> "When he goes to exercise sessions, he has the responsibility to get up early and go out to sessions." (female, 78, spouse)

> "Frankly, I saw that both physically and mentally, my mother progressed a lot... What a difference! (…) It [the physical exercise program] brought her life! I noticed differences in small things. I remember she couldn't reach the top of the cabinets to put some dishware. I vividly remember noticing things that she didn't do, like putting her knee on the floor; I was surprised because these were things she could not do." (female, 45, daughter)

The exercise sessions provided an opportunity for care recipients to meet new people, socialize with peers living in a similar situation, and establish a rewarding relationship with the professionals, resulting in a significant engagement factor (interpersonal level).

> "It [the physical exercise program] brought him good things because he met the people, he met the monitors. He's more

> socially engaged. I think it brought him good things. His social life improved" (female, 71, spouse)

Finally, the overall positive evaluation of the physical exercise program structure and organization (e.g., total length, session frequency, and time) and characteristics (e.g., exercise adequacy and sequence, materials during sessions) were reinforced as a facilitator (community level). Caregivers mentioned the technical and relational skills of the professionals leading the activity as factors that enabled the adaptation and integration into the program. They also recognized the program's quality, since it was adapted to this specific population, conducted by specialized professionals, and involved no financial costs. It promoted the social inclusion of care recipients in the community, which was greatly appreciated.

> "I think that everything they [professionals implementing the program] have done…really deserves our recognition because they have been very thoughtful and careful. And what they do totally benefits the participants. (…) I think that the program is ideal for people in her [wife's] condition, with her limitations. You're not supposed to do more demanding things. (…) For these people for whom the program is intended (people with NCD), I think it's good" (male, 78, spouse)

> "I think the program is fantastic. I think it was great to have this program for these people because it is really good. (...) The exercises are good; they are easy to do; they're great because they move every part of their body… and are very simple to do. I can tell you, I think it [the physical exercise program] is exceptional, and everyone [professionals implementing the program] is affectionate and attentive." (female, 51, daughter-in-law)

DISCUSSION

This qualitative study explored the barriers, motivators, and facilitators to the participation of community-dwelling older adults with NCD in a structured physical exercise program from the perspective of informal caregivers, under the conceptual framework of the socio-ecological model. It illustrates the dynamic relationship between intrapersonal, interpersonal, and community factors towards individuals' exercise adherence. As such, the identified barriers across intrapersonal and community levels may be overcome by the motivators and facilitators through interpersonal and community levels.

Overall, and in line with previous research,[32,33] our results revealed a greater number of facilitators to exercise engagement when compared to barriers. Intrapersonal factors were found to be the most predominant, reinforcing the need for tailored and person-centered interventions[18,34] that meet participants' needs and preferences (e.g., considering pre-existing comorbidities, chronic medication, sensory or locomotory disabilities, behavioral and psychological symptomatology, past sports involvement, among others).[35] On the other hand, the unwillingness of care recipients to participate in exercise sessions was the main barrier identified to adherence, which configures a challenge to surpass with the help of health professionals and caregivers, who are key actors in promoting exercise participation. Health professionals may have an essential role in helping to overcome the caregivers' doubts about potential health-related benefits; and these, in turn, are of crucial importance in shifting care recipients' attitude about exercise.

Above all, caregivers highlighted that the reported wellness and satisfaction of care recipients for participating in the exercise sessions were key factors that promoted their engagement and counteracted the initial reluctance. These results are in accordance with Lamb et al.'s study, as caregivers mentioned that the care recipients' enjoyment was attributed to being with other people (group-based exercise), the exercise itself, and for having something to do regularly.[36] The authors consider that these outcomes might be a consequence of the welcoming environment (i.e., promoting positive changes in mood and avoiding frustration), and the fact that individuals feel comfortable being around others whom they identify with (e.g., cognitive/caring status, gender, and/or age) that can understand and accept their condition.[37] Providing exercise sessions with small groups seems to positively impact individuals' engagement through social cohesion.[14,35]

Caregivers pointed out that this program was an opportunity for socialization, significantly improving care recipients' adherence and involvement. The social connectedness and familiar environment established between participants and professionals were even emphasized over the benefits of exercise. In this sense, the professionals who led the exercise sessions had a major influence on facilitating a socially favorable atmosphere;[14,37] probably as a result of the specific training that they received concerning NCD clinical features and progression, communication strategies, challenging behaviors, and safety issues.[12] Evidence suggests that having a knowledgeable, understanding, and friendly exercise provider is as much important as having a technically skilled professional.[19,38,39]

In addition, according to our study results, caregivers were interested in this intervention because they believed in the potential benefits to their care recipients' physical and mental health. In fact, along with care recipients' participation, the observed positive effects of exercise on maintenance and/or mitigation of cognitive and functional capacities were identified by caregivers as factors that facilitated the continuity of care recipients in the program. As highlighted by several authors, the exercise-related benefits might be an important motivator or facilitator that should be individualized.[13,19,37] In this regard, caregivers' awareness about the health benefits of exercise, considering their care recipients' specific comorbidities, functional capabilities, and social environment should be provided to support engagement. Hence, the advice given by clinicians might be helpful.[13] In accordance, our study findings revealed that the advice given by health professionals was a significant motivator. The authors consider that the encouragement, support, and, more importantly, the trusting relationship between these professionals and the dyads were essential to adherence to this type of physical exercise program.

Professionals should acknowledge the role informal caregivers play in facilitating disease treatment and management, for example, by ensuring that people with NCD have access to appropriate community-based services.[40] Dementia caregiving dyads still suffer from stigma and increased social isolation,[41] and struggle to access the scarce post-diagnostic support opportunities available.[42] In this regard, the “Body & Brain” project was seen by caregivers as an opportunity to stimulate care recipients’ physical and cognitive health. Whether due to low levels of daily physical activity and sedentary behavior, or the absence of social participation, or even the lack of tailored interventions, caregivers promoted their care recipients’ participation in this physical exercise program as they perceived it as a specialized integral solution. Moreover, caregivers also highlighted the importance of having an established routine and the need to go outdoors and enjoy free time as factors that contributed to permanency in the program. Routine is a key factor to a successful caregiving task and having a meaningful activity to be involved in twice a week for several months is important for the quality of life of the caregiving dyads.[24] Additionally, the characteristics of the program seem to have influenced participants’ engagement, and these include the fact that the bi-weekly exercise sessions were divided into three main parts (warm-up; balance/coordination, strength, and aerobic training through functional exercises; and cool down), and cognitively demanding challenges were avoided.

With respect to barriers, the unwillingness of care recipients to participate in the program was a central concern. As stated by van Alphen and colleagues, individuals with NCD usually present a loss of motivation to stay physically active, which may be partly explained by the neuropsychiatric symptomatology, in particular apathy.[14,19] Personality traits[19] or NCD-related factors like the loss of insight may also justify the care recipients’ reluctance to participate in exercise sessions.[14] Along with these, the authors consider that the individuals’ unwillingness could also be explained by the difficulty to disrupt the day-to-day routine that is highly based on the home environment.[13,14,32] However, the unwillingness of care recipients to participate in exercise sessions can be attenuated by caregivers' awareness of potential benefits associated with exercise and health professionals' support. In fact, caregivers have a key role in facilitating care recipients' access to this type of activity outside the domiciliary context, and, for this reason, professionals must guarantee an effective care management.

Finally, the space dedicated to exercise – in particular, at the psychiatric hospital – limited the sessions' implementation. This setting was perceived as a non-inviting environment due to the disease-related context, though simultaneously safe. Moreover, this unit was also a space dedicated to other therapies (e.g., cognitive stimulation), which restricted the regular use of music. Caregivers whose care recipients were included in other groups did not report any barrier concerning the physical environment. In this sense, although clinical settings are commonly considered for implementing exercise programs for people with NCD, these topics must be considered in future interventions specifically designed for this population.[14,18,35,38]

LIMITATIONS & STRENGTHS

It is important to recognize the limitations of this study. One limitation relies on the fact that it was not possible to understand the influence of organizational and policy factors toward the participation of individuals with NCD in a group-based physical exercise program, which requires further investigation to establish adherence support strategies and guidelines. Moreover, the authors acknowledge that the care recipients' perceptions were not collected for this study, due to the difficulties associated with conducting telephone-based interviews with this population, which, however, was the only available option during the COVID-19 pandemic. Notwithstanding these limitations, the authors want to emphasize that this study adds to the already existing literature on the barriers, motivators, and facilitators of people with NCD to a specific training methodology, namely MT. The recently published *FITT* recommendations for individuals diagnosed with major NCD (only Alzheimer's subtype) by the *American College of Sports Medicine* reinforced that this special population benefits from multiple exercise modes (e.g., aerobic, strength, coordination, flexibility, and balance) [43], due to its potential to improve subjects' functional capacity and reduce the risk of falls, which may be considered in future research studies [44].

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STATEMENTS AND DECLARATIONS

Conflicts of Interest

None declared.

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Ethics Approval

The study protocol was approved by the Ethical Committee of the Faculty of Sports of the University of Porto (Ref CEFADE22.2018).

Clinical Trial Registration

The trial was registered with the US National Institutes of Health Clinical Trials

Registry (ClinicalTrials.gov – identifier number NCT04095962).

Consent to Participate and for Publication

Written informed consents were obtained from interested individuals with NCD and their legal representatives, significant person, or assigned main caregiver (complying with the legal requirements associated).

Data Availability

The dataset supporting the conclusions of this article will be available upon reasonable request addressed to the corresponding author.

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7.2 *Original Study V* – Should caregivers also be included in physical exercise-based interventions for people with a neurocognitive disorder?

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RUNNING TITLE

Caregivers' participation in exercise sessions

ABSTRACT

This study aimed to explore the views of caregivers of people with neurocognitive disorders (NCD) about taking part in a physical exercise intervention with their partners, and to explore the perceived impact of this program on those caregivers who enrolled in it. Semi-structured interviews were conducted with 20 caregivers (67.5 ± 13.94 years; seven female) from the "Body & Brain" project. Ten took part in the physical exercise sessions (active-participating caregivers) and the others did not (social-participating caregivers). Regardless of their participation level, all caregivers reported their inclusion to be important to enhance partners' initiation and engagement in the sessions, and perceived personal benefits. Active-participating caregivers reported exercise-related benefits on general health, enjoyment, and social connectedness. Social-participating caregivers considered this intervention an opportunity for respite and appreciated being involved only occasionally (i.e., festive gatherings or telephone contacts). Findings support the inclusion of caregivers in physical exercise interventions designed for partners with NCD. Still, the possibility to choose to be enrolled or not in the program should be given and anticipated.

Keywords: Care-partner, dementia, qualitative research, physical activity, exercise.

WHAT IS KNOWN ABOUT THIS TOPIC?

- Previous studies confirmed caregivers' decisive role in guaranteeing partners' participation in physical exercise sessions, which may potentially influence the impact of exercise in people with NCD. However, little is known about caregivers' perspectives about being involved in these programs that are specifically designed for their partners.

WHAT DOES THIS PAPER ADDS?

- Findings suggest that caregivers confirm the importance of their inclusion, regardless of their participation level. Both active- and social-participating caregivers consider that they have a decisive role in assuring partners' access, compliance, and engagement with the program; and that it may represent an opportunity to benefit from potential exercise-related direct effects, both in terms of physical and mental health. Caregivers who were actively involved in the sessions perceived a positive impact from their participation on general health, enjoyment, and social connectedness. Future community-based interventions designed for individuals with NCD should consider giving caregivers the opportunity to choose whether they want or not to be actively involved in the physical exercise sessions.

INTRODUCTION

In 2019, according to the *World Health Organization*, 55.2 million people worldwide were diagnosed with a neurocognitive disorder (NCD) (World Health Organization, 2021). NCD encompass a group of conditions that affect the brain and in which the primary clinical deficit is in cognitive function (American Psychiatric Association, 2013). Presently, more than 21 million people in OECD countries are estimated to have a diagnosis of NCD (OECD, 2021). Informal caregivers, in 2019, spent over 89 billion hours providing unpaid care and support on daily activities (World Health Organization, 2021). Caregiving disproportionately affects women, particularly in low- and middle-income countries, who are responsible for nearly 70% of informal care worldwide (OECD, 2021; World Health Organization, 2021). Evidence suggests that the burden and stress associated with care responsibilities increase caregivers' susceptibility to health complications and diseases (Alzheimer's Association, 2021) and that those experiencing higher levels of emotional or mental strain may be at higher risk for death (Alzheimer's Association, 2021; Schulz & Beach, 1999).

Caregivers often do not have time to engage in interventions targeting health and well-being, such as physical exercise training (Hill & Lee, 2021; Lamotte et al., 2017; Tatangelo et al., 2018), and therefore, they tend to be less physically active compared to non-caregivers (Lamotte et al., 2017; Loi et al., 2014), and to present a generally worse psychological health (Gusi et al., 2009; Madruga et al., 2020).

Previous controlled trials investigating the effectiveness of home-based physical exercise programs specifically targeting caregivers have consistently demonstrated that this type of intervention may positively impact their daily physical activity levels and quality of sleep, and reduce the occurrence of weariness and subjective burden (Castro et al., 2002; Hirano et al., 2011; Loi et al., 2014; Orgeta & Miranda-Castillo, 2014). A recently published study by Madruga et al. (2021) highlights that a 9-month home-based individually tailored physical exercise intervention supervised by a personal trainer may even reduce caregivers' risk of depression. However, individualized interventions require significant financial resources and personnel, which supports the relevance of group-based approaches conducted in community settings (Madruga et al., 2021).

Despite the growing evidence attesting physical exercise benefits on caregivers' psychological health, very few interventions have evaluated the effectiveness of community-based physical exercise programs targeting caregivers of people with NCD (Orgeta & Miranda-Castillo, 2014). More research is also needed regarding the indirect benefits of interventions exclusively conducted with partners with NCD (e.g., reduced burden of care due to improvements in physical and cognitive functioning of people with NCD) (Forbes et al., 2015; Iliffe et al., 2015; Lamotte et al., 2017).

A growing body of literature acknowledges the mutual beneficial effect of physical exercise interventions designed for caregiving dyads (Doyle et al., 2020; Lamotte et al., 2017), in which caregivers and partners with NCD are enrolled and participate together. Dyadic interventions may enhance social participation and overcome barriers to engagement in physical activity (e.g., having someone to look after the partners with NCD while caregivers undertake the exercise sessions alone) (Doyle et al., 2020; Hill & Lee, 2021). As reported by Lamotte et al. (2017), exercise sessions may represent an opportunity for caregivers to foster a bonding experience and establish a mutual purpose with partners. Also, along with the general health-related benefits associated with regular exercise, such sessions may positively impact their caregiving capacities and burden. However, caregivers may consider that planned respite or access to other types of interventions (i.e., support groups) may be more advantageous to them than being enrolled in a physical exercise program (Doyle et al., 2020; Lamotte et al., 2017).

When planning an exercise intervention specifically for people with NCD, researchers should reflect on caregivers' involvement, i.e., whether to offer a dyadic intervention, other simultaneously occurring activity, usual care, or the opportunity to take part in physical exercise sessions. Caregivers play a decisive role in guaranteeing people with NCD participation, providing task assistance, transportation, and encouraging engagement (Di Lorito et al., 2020; Doyle et al., 2020; Kim et al., 2018; Lamotte et al., 2017), and for this reason, their involvement may be incontrovertible and potentially influence the impact of physical exercise interventions in people with NCD.

Presently, caregivers are often overlooked for participation and examined only secondarily in physical exercise programs targeting partners with NCD (Doyle et al., 2020). Likewise, little is known about their beliefs and perspectives about being involved in interventions specifically designed for people with NCD (Kim et al., 2018). Given the likelihood of impacting people with NCD initiation and maintenance, it is of utmost relevance to better understand the caregivers' preferences to inform future interventions design, dosage, and implementation (Doyle et al., 2020).

The present qualitative study aims to explore the views of caregivers of people with NCD about taking part in a community-based physical exercise intervention with their partners; complementarily, it aims to explore the subjective impact of the physical exercise program on those caregivers who have exercised together with their partners with NCD.

MATERIALS AND METHODS

Design and ethics

The "Body & Brain" project is a quasi-experimental trial (ClinicalTrials.gov – ID: NCT04095962) that aims to investigate the effect of a multicomponent training (MT) exercise intervention on the physical and cognitive function of older adults diagnosed with major NCD (Borges-Machado et al., 2021a, 2021b; Carvalho et al., 2021), in which the present exploratory qualitative study takes part. Ethical approval was obtained from the Institutional Review Board of the Faculty of Sports of the University of Porto (Ref CEFADE22.2018). Written informed consents were obtained from interested individuals with NCD and their legal representatives, significant person, or assigned main caregiver (complying with the legal requirements associated).

Participants

This purposive sample comprised caregivers of individuals with NCD who were participating in a group-based physical exercise program that was conducted in several community settings in the Oporto Metropolitan Area (Portugal), specifically: at a sports university setting, at a community center sports hall, and at a psychogeriatric unit devoted to dementia care located in a psychiatric hospital campus (i.e., with outpatients). Only caregivers of community-dwelling individuals were recruited for this qualitative study. The bi-weekly exercise sessions took about 60 minutes in nonconsecutive days. They were subdivided into three main parts: 10 minutes for warm-up (e.g., general activation, slow walking, mobility exercises), 35-45 minutes dedicated to specific training (e.g., balance/coordination, strength, and aerobic exercises) and five minutes to cool-down (e.g., mobility and stretching conditioning), as described in detail elsewhere (Carvalho et al., 2021).

Caregivers were invited to participate in this MT physical exercise program as class members, according to their availability and willingness. In other words, this program was designed for people with NCD and not as a dyadic intervention.

Caregivers freely decided whether they wanted or not to participate in the physical exercise sessions before the 6-month intervention. Those who agreed to participate, from now on designated as “active-participating caregivers”, could perform the exercises proposed by the professionals or support their partners during exercises if necessary. In contrast, caregivers who did not want to take part in the physical exercise sessions, from now on designated as “social-participating caregivers”, were invited to attend specific recreational activities (i.e., two festive gatherings) and received occasional telephone contacts (i.e., to clarify any doubts about their partners’ participation in the program).

Twenty-two caregivers were contacted by telephone to participate in this qualitative study; only two caregivers were not included in the final sample: one refused to participate in the interviews, and the other was unavailable due to professional reasons. The semi-structured telephone interviews were conducted with both active- and social-participating caregivers and took place between April and May 2020.

Data collection

This study followed the 32-item checklist of the Consolidated Criteria for Reporting Qualitative Research (COREQ) (Tong et al., 2007). The interview guide was developed based on previous similar studies (Karuncharernpanit et al., 2016; Lamb et al., 2018; Suttanon et al., 2012; Yu & Swartwood, 2012). The first author (FBM) contacted the caregivers of community-dwelling individuals to explain the study, request their participation, and ascertain their time availability.

The semi-structured interviews were conducted by a trained qualitative research assistant (PM) who was not involved in the “Body & Brain” project, during a previously scheduled telephone call. The interviews were recorded using an encrypted voice recorder and lasted around 40 minutes (between 20 and 90 minutes). Interviewees were reminded that anonymity was guaranteed, and they could refuse to answer any of the questions or withdraw at any moment.

Questions aimed to explore caregivers’ point-of-view about taking part in a community-based physical exercise program designed for their partners diagnosed with NCD (Table 1). Caregivers who took part in the physical exercise sessions with their partners were also invited to freely talk about the impact this intervention had on their lives. Caregivers’ sociodemographic characteristics and caregiving situation was collected during baseline evaluations within the scope of the “Body & Brain” project (Carvalho et al., 2021).

Table 1. Interview guide

Active-participating caregivers	Social-participating caregivers
As you know, there are other physical exercise programs similar this one that do not include caregivers as participants on exercise sessions. What do you think about this program, particularly in what refers the inclusion of the caregivers as attendees to exercise sessions? This program has started in September 2019, with two sessions per week for 1-hour. What has this program brought to your live? Has this program influenced your tasks as caregiver or burden? I would like you to elucidate me about how do you fell before and after exercise sessions	As you know, there are other physical exercise programs similar to this one that include caregivers as participants on exercise sessions. What do you think about this program about not including the caregivers as attendees to exercise sessions?

Data analysis

Each interview was transcribed verbatim and reviewed for accuracy by the first author (FBM). Interviewees' identifying information was removed to ensure anonymity. The software analysis programme NVIVO (Version 12, QSR International, Southport, UK) was used to assist with data management and analysis. Analysis of interviews was based on Braun and Clarke's Thematic Analysis guidelines (Clarke & Braun, 2017), using an inductive approach.

All interviews were coded by the first author (FBM). An initial coding frame was developed, using the principle of constant comparison, to include data-driven themes and patterns. To ensure coding consistency, independent parallel coding was carried out by a second researcher (DB) that analyzed 20% of the transcripts. Subsequently, the two researchers met to reflect on and discuss the coding and analysis to ensure credibility. Discussion of the analytic process and findings were shared among the research team members, who further informed themes refinement. Disagreements regarding the identification, description, analysis, or interpretation of data were resolved through discussion and further analysis. Trustworthiness was attained through category refinement via discussions and triangulations between researchers to reduce the effect of bias (Clarke & Braun, 2016; Shenton, 2004). Illustrative verbatim quotations were included to support the interpretation of the identified themes.

RESULTS

From the 20 caregivers who were interviewed, ten were active-participating caregivers (mean age 72.9 years; range 59-83 years; 2 female), whereas the other ten were social-participating caregivers (mean age 62.0 years; range 37-86 years; 5 female) who cited work or restrictive health-related issues (e.g., unstable cardiovascular disease and osteoarticular condition in which exercise is medically contraindicated) as main reasons for not attending the physical exercise sessions with their partners. Most caregivers provided care daily, for more than ten hours. Four social-participating caregivers shared the task of providing care to their partner with NCD, and five combined the task of caring with a working professional life. Table 2 summarizes caregivers' characteristics.

Table 2. Caregivers' characteristics

Characteristics	Caregivers (N=20)	Active-participating Caregivers (N= 10)	Social-participating Caregivers (N= 10)
Age (years), mean (SD)	67.5 (13.94)	72.9 (7.06)	62.0 (17.16)
Age, range	37-86	59-83	37-86
Gender (female), N (%)	7 (35)	2	5
Years of Formal Education, mean (SD)	7.9 (3.11)	7.1 (3.00)	8.7 (3.16)
Education, N (%)			
Medium (4-6 years)	6 (30)	4	2
High (7-12 years)	13 (65)	6	7
Superior (>12 years)	1 (5)	0	1
Professional situation, N (%)			
Working	6 (30)	1	5
Retired	14 (70)	9	5
Caregiver relationship, N (%)			
Spouse/ Partner	14 (70)	9	5
Adult Children	4 (20)	0	4
Other relative	2 (10)	1	1
Number of years as a caregiver, mean (SD)	4.3 (2.36)	4.4 (2.41)	4.1 (2.42)
Sharing the task of providing care, N (%)	4 (20)	0	4
Frequency of care, N (%)			
Continuously	17 (85)	10	7
Working days / weekends / rotationally	3 (15)	0	3
Providing care (hours/day), N (%)			
0-3h	5 (25)	0	5
4-7h	2 (10)	1	1
8-10h	1 (5)	1	0
>10h	12 (60)	8	4

Data analysis identified two common themes in both the active-participating and social-participating caregivers regarding their inclusive perspectives on taking part in the physical exercise intervention with their partners: "determinant to the partners' participation" and "for caregivers' benefit".

Determinant to the partners' participation

Both groups identified the inclusion of the caregiver in the exercise sessions as crucial, considering that it would play a key role in the partners' participation, making them feel safe, supported, and motivated, knowing their limitations and capacities, and, therefore, guaranteeing their adherence and involvement. Caregivers also mentioned the possibility to provide comfort and tranquility to partners throughout the intervention, whenever/if needed.

> "In my opinion, I think that she (partner with NCD) gets more motivated if she's with the caregiver. (…) I think that it is great to include the caregiver!" *(male, 67, spouse, active-participating caregiver, BB04)*

> "I think it's pleasant and it brings benefits to the person (partner with NCD) as he feels accompanied, right?! (…) I think the person feels more confident. (…) He (partner with NCD) feels more protected." *(female, 56, daughter, social-participating caregiver, BB29)*

For caregivers' benefit

Caregivers perceived this program as an opportunity to fulfill their own needs for physical activity and recognized the potential benefits, both in terms of physical and mental health.

> "I think that it is very good that the caregiver is accompanying, in this case, I am accompanying my wife. (…) What would I do when she was on the exercise? Wait for her? At least I'm there to accompany her, and it is also beneficial for me." *(male, 76, spouse, active-participating caregiver, BB16)*

> "I think it's good because it's a great benefit for caregivers, whether they have a lot of [health] problems, like me, or not. Actually, I think it's great!" *(male, 86, spouse, social-participating caregiver, BB17)*

Data retrieved from interviews about the impact of this physical exercise program on active-participating caregivers showed the presence of two main advantages: "personal benefits and enjoyment" and "social connectedness".

Personal benefits and enjoyment

When presenting the perceived effects of the program with those caregivers who enrolled in exercise sessions with their partners, they exclusively pointed out the positive aspects, being the physical and mental health benefits the most representative. Although physical exercise prescription was focused on their partners, these caregivers were fully involved during sessions and performed every activity the professionals proposed. Active-participating caregivers also described how they felt well and satisfied during sessions, enjoying this time for themselves.

> “I always felt good (at the end of the exercise sessions). When it was time to go home, I used to say: Is it time already?! Today time flew, it was fast! (…) I have never disliked it… never, because if I did or if I felt sad or something else, I wouldn’t go, right? (…) I went there for her (the partner with NCD) and then I took advantage myself!” *(male, 72, spouse, active-participating caregiver, BB126)*

> “As for physical health, as I said, I feel more relaxed. There is no doubt that that hour was sacred. It is very good, and I think it makes us feel lighter.” *(male, 70, spouse, active-participating caregiver, BB134)*

Active-participating caregivers also highlighted the major importance this program had on their daily routines and distinguished how they felt motivated being part of such a program with their partners; some even mentioned how being actively enrolled in the sessions positively influenced them in providing care. Several participants also outlined that during sessions they did not play the role of caregivers, and, for this reason, these moments represented an opportunity for joy and even a break from their regular caregiving activities at home.

> “It [participating in the program] was not a burden, it was an hour that went fast, and we even got entertained. (…) It is practically the same (as caregiving). I mean, there is a difference since we are not used to having an hour twice a week outside our environment.” *(male, 83, spouse, active-participating caregiver, BB116)*

Social connectedness

Being able to socialize, particularly with peers living in a similar situation, was also an important perceived advantage for many caregivers. Taking part in physical exercise sessions allowed these individuals to get out of their caregiving environment (home), meet new people, and be entertained. They described how it felt good to talk with others and how it also helped them to put their personal problems in perspective. Above all, they enjoyed the familiar environment, the social interaction between participants and professionals, and felt relieved while exercising.

> "The conviviality, the conversation, saying this or that, it entertained us a bit (…) Because it's something that was a little out of the everyday routine, you see? And since it is out of the routine, we went there and then we talked about this and that (…) We become more relieved. (…) I've always enjoyed meeting people." *(male, 72, spouse, active-participating caregiver, BB126)*

> "At least I get out of home and socialize with others! If I have a big problem, I realized others may have a bigger one! (…) There, we are all the same and everything is good for us… we become more fulfilled and aware of the reality." *(male, 75, spouse, active-participating caregiver, BB130)*

Two common themes also emerged among social-participating caregivers regarding their involvement in the physical exercise intervention: "occasional involvement" and "opportunity for respite".

Occasional involvement

Caregivers reported their appreciation for being enrolled in the program only in sporadic recreational moments (e.g., scheduled meetings with researchers for evaluations or festive gatherings) or by occasional telephone contacts. These individuals, either full-time workers or retired, considered that this option was appropriate and, more importantly, it best met their own needs.

> “I honestly don't say that I wouldn’t participate, but not on a regular basis, I mean, not in every class. I think the caregivers are not present (during exercise sessions), but you include them a bit from time to time in these snack parties, even in a meeting or in a conversation, or even over the phone (...) I think that the caregiver’s involvement [in sporadic recreational moments] is very important." *(female, 51, daughter-in-law, social-participating caregiver, BB26)*

Opportunity for respite

Social-participating caregivers identified this intervention as an opportunity for respite during sessions. In other words, although acknowledging the importance of taking part in the sessions, some of them decided not to attend the bi-weekly sessions because it represented a break in their caregiving tasks and/or an opportunity to have some free useful time to deal with personal issues.

> “I don't want to participate (in the exercise sessions) because I already spend 24 hours with him (partner with NCD). And I wanted to be a moment away to rest a little. He goes one way, I go to another, and when we get home, we're together again. (...) And while he goes to the gym (exercise sessions), I stay alone (referring to the activities/tasks that she does while the partner is on the exercise sessions) and I can feel free. (…) otherwise, I always have this burden. It sets me free! Some days are not easy, you know?” *(female, 71, spouse, social-participating caregiver, BB124)*

DISCUSSION

This qualitative study explored the caregivers’ perspectives about being enrolled in a physical exercise program for their partners diagnosed with NCD. Additionally, the subjective impact of this intervention was explored among caregivers who exercised with their partners. In summary, our study findings suggest that caregivers confirm the importance of their inclusion in the physical exercise sessions, not only due to their decisive role in their partners' participation, but also due to the associated physical and psychosocial potential effects. Moreover, those who were active-participants reported a beneficial impact on general health, enjoyment, and social connectedness. Notwithstanding, caregivers should be given the opportunity to choose whether they want or not to be involved in physical exercise programs designed for people with NCD, acknowledging their own needs. This data is particularly important when planning and prescribing future community-based exercise interventions for individuals with NCD, considering the benefits that both people with NCD and caregivers can have from participating in this type of intervention. Future physical exercise interventions should be methodologically prepared and consider caregivers as potential participants of physical exercise sessions.

As mentioned by several authors, individuals with NCD living in their homes depend to a large extent on their caregivers' support to be physically active, get prepared to leave the family environment, arrive at sessions, and engage in community-based interventions (Di Lorito et al., 2020; Farina et al., 2021; Hobson et al., 2020; Malthouse & Fox, 2014; Nyman et al., 2018; Stubbs et al., 2014; van Alphen et al., 2016; van der Wardt et al., 2020). In this study, caregivers were invited to enroll in the MT physical exercise program and take part in exercise sessions along with their family members considering their importance in guaranteeing the partners' participation. According to their willingness and availability, they freely decided whether they wanted to participate in the bi-weekly sessions or only to be occasionally involved in recreational activities. Regardless of their type and level of participation, most caregivers agreed with their inclusion, recognizing their determinant role in enabling partners' access and compliance to a non-pharmacological therapy, namely by guaranteeing practical aspects like transportation and assistance with exercises, but also motivating and boosting partners' confidence.

In line with Kim et al. (2018), our results suggest that future physical exercise interventions targeting people with NCD should enhance caregiver's confidence to support partners' participation, and/or encourage caregivers' to increase their own daily physical activity levels, and/ or promote caregivers' awareness on health-related exercise benefits. Therefore, we consider that the usage of these strategies, along with the possibility to enroll caregivers in the sessions, may positively influence partners' exercise adherence.

Findings from our study reveal that both groups of caregivers recognized the potential exercise-related benefits on their health and perceived this intervention as an opportunity to fulfill their physical activity needs while taking care of their loved ones, and, for these reasons, agreed on their inclusion. Active-participating caregivers who were retired questioned the interviewer about what they would do during exercise sessions if they could not attend, which may indirectly reflect how caregiving tasks are an essential structure in their daily routines (Brodaty & Donkin, 2009; World Health Organization, 2017). These findings might reveal the lack of activities specifically targeting and/or including caregivers, even though they have shown interest in engaging in new experiences. As stated by the *Alzheimer's Disease International*, dementia caregiving dyads still suffer from stigma and social isolation and struggle to access post-diagnostic support opportunities (Alzheimer's Disease International, 2016, 2020). Particularly in Portugal, although a national strategy for dementia has been defined in 2018 (Diário da República, 2ª Serie, n.º 116, 19th June), and a formal statute for caregivers has been approved through a law (Portuguese ministerial order n.º256/2020, 28th October; Law n.º 100/2019), these legislations and policies have not reflected yet an additional availability and/or utilization of support services (e.g., information or advice on legal rights, financial benefits, social security protection, training and education, respite services, among others) (OECD, 2021; World Health Organization, 2021). In a recently published exploratory study with 179 Portuguese informal caregivers of people with major NCD, Teles and colleagues showed that only 25.7% of these individuals were benefiting from one of the five psychosocial interventions under analysis (i.e., psychoeducational programs, support groups, mutual-aid groups, individual psychological support, specialized counseling), and 91% of them perceived access as being very difficult/difficult (Teles et al., 2021), reinforcing the need to raise caregivers' awareness on available community services. In this regard, further studies, with larger samples and using mixed methods methodologies are necessary to better understand (older) caregiving dyads' needs, difficulties, and preferences to ensure adequate access to the (still scarce) available support services, of which physical exercise programs might be considered.

When analyzing the perceived impact this intervention had on those caregivers who actively and regularly engaged in the physical exercise activities with their partners, personal benefits and enjoyment for participation were emphasized as valuable outcomes. Several caregivers even reported that they initially enrolled in exercise sessions due to their partner but, after a while, they enjoyed the sessions for themselves. It's worth noting that this physical exercise program was prescribed to people with NCD and, therefore, it not always met caregivers' physical fitness needs, even though individual adaptations were made whenever necessary following the international guidelines for exercise prescription (American College of Sports Medicine, 2021; Carvalho et al., 2021). In general, caregivers executed the proposed activities by professionals, which may explain the perceived benefits in physical and mental domains. Corroborating findings of the present study, a systematic review study conducted by Doyle and colleagues (2020) highlighted that caregivers are more likely to experience improvements in both psychosocial and physical health when co-participating in exercise sessions compared to when partners with NCD exercise independently.

Caregivers who participated in the sessions also reported that the program was essential for their daily routines, allowing them to get out of the home environment twice a week and promoting their motivation to better provide care for their family members. Some caregivers described how they felt relaxed during exercise sessions since they did not play their conventional role as caregivers, which facilitated their own engagement. These statements may reinforce the relevance of this novel strategy, which allows caregivers to decide what suits them better. Interestingly, active-participating caregivers did not mention anything regarding the opportunity to establish a mutual purpose and a bonding relationship with partners throughout the physical exercise program, as usually mentioned in the literature (Lamotte et al., 2017). However, it was apparent how important the social interaction factor was for them. Caregivers appreciated the opportunity to meet new people and felt motivated and comfortable joining a group with others with whom they could share their experiences and were in a similar situation. As stated by Long et al. (2020), this shared experience of NCD is significant for participants and, although this was not the purpose of our program, caregivers mentioned on several occasions the relationship established with others, which was maintained even outside the context of the program. This social connectedness factor is thought to be a determinant to overcome caregivers' social isolation, and for this reason, it may also be considered when planning future group-based physical exercise programs. As previously highlighted by Guerra et al. (2012) in a qualitative study regarding the evaluation of a multidimensional programme for Portuguese informal caregivers of individuals with major NCD, the opportunity to share experiences with others is crucial to attenuate emotional and social isolation, and normalize some feelings and thoughts. Another recently published study (Paul et al., 2019), also conducted in Portugal, showed that a 10-week community-based psychoeducational program for primary informal caregivers of people with NCD improved individuals' mental health, satisfaction with care, and lessened caregiver strain. These findings strengthen the need for community-based interventions conducted in groups to counteract the lack of support and services available for caregivers.

Finally, social-participating caregivers appreciated being involved in the program only sporadically in recreational activities, mentioning that it would be sufficient for their needs. A bi-weekly physical exercise program for 6-months was perceived to be demanding, particularly for full-time working caregivers. In fact, this type of commitment may represent a significant burden for those who still carry professional responsibilities (Alves et al., 2020; Eurocarers, 2015). Other caregivers also mentioned physical limitations or conditions in which exercise is medically contraindicated as a reason for not being involved in this program. As stated by Lamotte et al. (2017), older individuals and/or with severe comorbidities may not be able to provide support and follow an exercise regimen, which reinforces the importance of offering them the possibility to be involved by telephone or in-person sporadic recreational moments. In addition, Lamotte and colleagues (2017) highlighted an important topic related to the increased time dyads must spend together if caregivers' inclusion is mandatory for partners' participation, which may increase the already high levels of distress. In this regard, and according with our study findings, the planned respite was perceived as an advantage for some caregivers (Doyle et al., 2020).

In addition, the authors want to acknowledge this study's limitations that hinder the generalizability of its results. First, active-participating caregivers' adherence to physical exercise sessions was not registered, which may have biased our study results considering that caregivers with higher-adherence rates may have perceived more benefits from participating. Second, the active-participating caregivers' actual involvement throughout the exercise sessions (e.g., if they supported partners in performing exercises or completed exercises independently) was not registered. Third, social-participating caregivers' adherence to the pre-scheduled recreational activities was not equally registered, as well as the total number of telephone contacts with each one of the caregivers. Fourth, due to COVID-19 restrictions on conducting in-person interviews, it was not possible to collect the perspective of people with NCD about the inclusion of caregivers. Fifth, the differences in age, gender, professional situation, and hours of providing care must be taken into consideration when comparing both groups. Lastly, the authors recognize that the small sample size, innovative approach within the Portuguese context, and the exploratory nature of this study limits the replication of our study findings.

Overall, our results suggest that caregivers agree with their inclusion in community-based physical exercise programs designed for their partners with NCD. Notwithstanding, caregivers should be able to choose whether they want to be actively involved or not in the physical exercise sessions, acknowledging every individual reason/need to participate or not in the program. In contrast to specifically designed dyadic interventions, this physical exercise program did not require caregivers' assistance and supervising roles, can be adapted to each caregiving situation, and promotes caregivers' social integration in a dementia-friendly environment. In this regard, this approach may be seen as an alternative to physical exercise programs only designed for people with NCD or caregivers, dyadic interventions, and to those interventions that offer a simultaneous intervention to caregivers (e.g., support groups).

STATEMENTS AND DECLARATIONS

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Competing Interests

The authors declare that there is no conflict of interest.

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Ethics Approval

The study protocol was approved by the Ethical Committee of the Faculty of Sports of the University of Porto (Ref CEFADE22.2018). The trial was registered with the US National Institutes of Health Clinical Trials Registry (ClinicalTrials.gov – identifier number NCT04095962).

Consent to Participate and for Publication

Written informed consents were obtained from interested individuals with NCD and their legal representatives, significant person, or assigned main caregiver (complying with the legal requirements associated).

Authors' Contributions

Study conception and design: FBM, PS, JC, OR; Study coordination: JC, OR; Data collection – PM; Data analysis – FBM, DB, OR; Writing – original draft: FBM, DB, OR; Writing – Review & Editing: FBM, DB, PS, PM, JC, OR. All the authors have made a substantial contribution, critically revised this work, and approved the final manuscript.

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PART IV – Discussion and Future Implications

Chapter 8. Discussion

This chapter provides an overall discussion integrating the results of the six studies that support the thesis. A description of the general limitations is also provided.

8.1 Main Research Findings

The accumulated evidence from this thesis revealed the positive impact of a 6-month physical exercise intervention in improving functional capacity in individuals with NCD (*original study I*). The conflicting results obtained on the ability to independently perform ADL (*systematic review and original study I*), suggested that MT interventions might have a potential impact on mitigating the decline on ADL functionality, but further research is needed to confirm these results. Moreover, the observed positive impact did not reflect any significant changes in other psychosocial outcomes, such as cognitive function, neuropsychiatric symptoms, and quality of life (*original study I and II*). The results obtained in this thesis also reinforce the need to address health-related physical indicators – namely, lean mass and lower extremity function – due to their association with quality of life in this specific population (*original study III*). Lastly, when exploring the factors that influence the adherence to a community-based physical exercise intervention, results from the exploratory qualitative studies (*original study IV* and *original study V*) identified two main barriers, three motivators and five facilitators, and exposed the inclusive perspective of caregivers about taking part of exercise interventions designed to their care-receivers with NCD. Taken together, the thesis' results confirm that this research field urges for future studies to better confirm the positive influence of MT methodology on physical and cognitive functions of individuals with major NCD. We next summarize the main findings of the 6 papers produced to address the thesis' primary and secondary objectives.

A recently published overview study including 30 systematic reviews found that physical exercise can significantly improve the ability to function in ADL; specifically, MT programs at moderate intensity might be more effective than other types of physical exercise, particularly when including cognitive, physical and multitasking exercises (Begde et al., 2021). These findings are consistent with our *systematic review* (*chapter 4*). In fact, a substantial body of recent evidence was found in support of the role of physical exercise in improving ADL functionality (Almeida et al., 2019; Braz de Oliveira et al., 2022; Lewis et al., 2020; Nuzum et al., 2020; Zhu et al., 2020).

In line with our *original study I* (*chapter 5*), Casas-Herrero et al. (2022) findings from *Vivifrail* training program revealed a mean increase on the physical exercise group over usual care of 1.40 points on SPPB after 3-months of MT program on community-dwelling frail/prefrail older adults with MCI and mild dementia. Results showed that 1-month is sufficient to improve functional capacity in the oldest old. In addition, the significant benefits in cognitive function, muscle function (i.e., handgrip strength) and depression in the physical exercise group showed that MT is a safe intervention and provides significant benefits in frail older adults with dementia over usual clinical care. These authors reinforced that MT may help to mitigate the trajectory of frailty and disability and provide benefits in important domains of intrinsic capacity (e.g., locomotor capacity). In sum, as emphasized by Casas-Herrero and colleagues, tailored MT should be considered as a “frontline treatment for preventing functional decline, cognitive impairment, and function deterioration that commonly occurs during the aging process” (Casas-Herrero et al., 2020, p. 8), and should be prescribed for older adults living with NCD.

The accumulation of evidence has sustained the first FITT recommendations ever published by ACSM for individuals diagnosed with Alzheimer’s disease (American College of Sports Medicine, 2021), and once again it was highlighted that training targeting multiple modes of physical exercise might be more effective for enhancing balance, strength, flexibility, and aerobic endurance. As stated by ACSM, despite the increased chance of distraction, overestimation of one’s ability to perform activities or forgetting what one is doing, individuals with

Alzheimer’s disease are safe to perform physical exercises as long as the physical exercise prescription is monitored and progressed similarly to what happens with cognitively healthy older adults (American College of Sports Medicine, 2021). In addition to the general recommendations about physical exercise regimen implementation, further considerations were made regarding the participation of caregivers: “there may be benefits of training and exercising with the caregiver to help provide support, motivation, and monitoring of safety” (American College of Sports Medicine, 2021, p. 386).

Despite the poor understanding of the optimal window in the disease course to start a physical exercise regimen, and the need for future research to examine the parameters and modes of activity that are optimal to treat/ counteract the symptoms of Alzheimer’s disease (American College of Sports Medicine, 2017, 2021), this new ACSM considerations and recommendations represent a major progress on this field of research and should be considered when planning future physical exercise interventions targeting individuals with Alzheimer’s disease or other dementia subtypes.

As verified in our *systematic review* and *original study II,* and further corroborated by other recent meta-analysis studies, it is not possible to draw a firm conclusion on the effects of MT in improving or slowing the decline of cognition in people with major NCD (Cardona et al., 2021; Du et al., 2018; Faieta et al., 2021; Nuzum et al., 2020; Park & Cohen, 2019). Several reasons can be addressed to justify, at least partially, the absence of definitive conclusions on the effect of physical exercise (e.g., MT) on cognition: i) most studies do not focus on a specific type/stage of NCD and/or in a specific training methodology (e.g., MT) (Alzheimer's Association, 2021; Erickson et al., 2019; Forbes et al., 2015; Livingston et al., 2020; Livingston et al., 2017; Park & Cohen, 2019; Skinner et al., 2018); ii) there is still a limited knowledge on underlying physiological mechanisms that mediate the benefits of physical exercise on cognition in people with major NCD, particularly with other subtypes than Alzheimer’s disease (Lopez-Ortiz et al., 2021; Nuzum et al., 2020; Valenzuela et al., 2020); iii) the usage of different diagnostic criteria (e.g., DSM-5, DSM-IV-TR, ICD-11, ICD-10 or NINCDS-ADRDA) or referral protocol for the diagnosis of major NCD (Balbim et al., 2022), and pervasiveness of mixed etiologies (Alzheimer's Association, 2021); iv) the methodological differences regarding the assessment tools used to evaluate the various cognitive abilities; and v) most studies only focus on global cognitive function, rather than on specific cognitive domains (Law et al., 2020).

Some of the above mentioned factors can also be extended to justify, at least partially, the absence of definitive conclusions on the effects of MT on alleviating neuropsychiatric symptoms in individuals with major NCD from mild to severe stages (Marquez et al., 2020; Ojagbemi & Akin-Ojagbemi, 2019), as revealed in our *original study II*. Still, future studies should consider the usage of more accurate outcome measures to assess individual psychological and behavioral symptoms, taking in consideration who is the informant-rated (e.g., informal caregiver or professional) (Ferreira et al., 2021).

Considering the multifaceted impact that the mismanagement of neuropsychiatric symptoms may have on individuals with major NCD and those around them, particularly in what regards their quality of life, the promising evidence presented in *chapters 5* and *6* cannot go unnoticed. Enabling individuals with a chronic disease like NCD to “live well” with the condition is a priority for policy and practice (Martyr et al., 2018; World Health Organization, 2020). Not only new insights were given on the promising positive influence of MT (*original study II*), but also on the importance of sarcopenia-related factors, specifically lower body function and ASMI (*original study III*).

Regardless of the target outcome (quality of life, physical fitness, or cognitive function), individuals’ adherence to the physical exercise intervention is fundamental for a meaningful effect. When exploring the factors that influenced individuals with NCD adherence to a community-based physical exercise intervention (*chapter 7*), findings from the *original study IV* revealed the dynamic and complex relationship between intrapersonal, interpersonal and community factors (i.e., two barriers, three motivators and five facilitators). Currently available evidence suggests that dementia-friendly physical exercise interventions targeting people with major NCD should be tailored to individuals’ functional capacity/mobility level and disease severity, conducted in adequate physical environments in the community, promote social cohesion, offer a welcoming environment, and be implemented by specialized professionals in small groups (Gebhard & Mir, 2021; Hobson et al., 2020; Laventure & Aherne, 2010; Long et al., 2020). More importantly, caregivers and health professionals may be effective allies in guaranteeing individuals' motivation and compliance (Heisz et al., 2016).

Several studies have reinforced the caregivers' pivotal role in ensuring care-receivers adherence, particularly as the clinical condition progresses (Di Lorito, Bosco, Booth, et al., 2020; Di Lorito, Bosco, Pollock, et al., 2020; van der Wardt et al., 2020). However, so far, existing evidence does not clearly describe what type of involvement informal caregivers might have on physical exercise interventions designed to care-receivers, i.e., whether they have access to a simultaneously occurring activity *vs*. they assume a supervision role *vs*. taking part in physical exercise sessions. This *original study V* (*chapter 7*) expands the available evidence and supports the inclusion of caregivers in physical exercise programs designed to people with NCD: not only due to their decisive role on the care-receivers participation, but also due to the perceived physical and psychosocial benefits. Notwithstanding, caregivers should have the opportunity to choose whether they want or not to be involved. These findings are of particular importance when planning future community-based interventions

Bottomline, this thesis offers important insights for professionals by boosting their confidence to encourage individuals with NCD to participate in community-based MT programs. Moreover, this research adds important knowledge to guide future interventions, clinical practice, guideline developers and policymakers in their decisions on improving access to physical exercise programs for people living with major NCD.

8.2 Limitations

The present thesis has some limitations that need to be acknowledged. An important one regards the COVID-19 pandemic. Due to the national lockdown, the 2nd cycle of intervention had to be interrupted and, consequently, the final sample only included half of the number of participants determined through power estimation analysis. Although efforts were made to recruit eligible participants, which has resulted in a cooperation partnership with 17 public and private entities, the identification of a larger number of individuals was not possible.

Another limitation regards the high heterogeneity in terms of physical functionality levels observed in our sample. Unfortunately, due to the difficulties to reach out individuals living in the community, we decided to contact day care centers and nursing homes to include a larger number of participants and get closer to the sample size estimations. Efforts were made to neutralize these discrepancies, through the following strategies: i) a handbook was created with the different physical exercises and activities; ii) sessions were planned in advance and, whenever appropriate, different groups complied with the exact same plan; and iii) sessions were supervised regularly to guarantee the uniformization of the MT intervention.

As identified in our *systematic review and* confirmed as a limitation in *original studies I* and *II*, it is essential to further explore more reliable methods to control the physical exercise sessions intensity. Similarly, data is still missing on validated methods to measure the daily physical activity levels, once the subjective questionnaires imply a proxy-report of a family member, informal caregiver, or professional that may not be completely aware of the care-receiver physical activity levels. Additionally, the research team also faced several obstacles in conducting some of the physical fitness and body composition tests (e.g., guarantee that participants remained static for the DXA protocol, and assure that cognitive limitations did not hinder individuals' performance in physical fitness tests), that although considered as gold standard methods for older adults, and already used with this specific population, may require several adaptations. In pursuing the objectives of this thesis, several questions also remained unaddressed: due to difficulties on post-intervention data collection it was not possible to attest the MT intervention impact on physical fitness outcomes and body composition variables, specifically, measured through SFT, One Leg Balance Test and DXA.

When reflecting on the limitations related to the CG, we want to acknowledge some aspects that may hinder the comparison between groups: i) the monthly health-related information sessions were not previously structured; iv) CG participants' attendance levels were not registered; and iii) informal caregivers were not given the opportunity to participate in the monthly recreational/social activity sessions.

Despite these limitations, the thesis builds on and contributes to the body of knowledge in MT for individuals with NCD. It includes studies with different methodologies that support the relevance of community-based MT interventions.

Chapter 9. Future Implications

This chapter provides several recommendations for future research as well as implications for clinical practice.

Future high-quality RCTs (e.g., including a detailed description of training protocol, NCD-diagnostic criteria, subtype and stage, dropout rates, attrition and adherence data, and adverse events) with larger samples are warranted to strengthen the findings of this thesis. In addition, future RCTs are needed to examine the effectiveness of community-based MT interventions on physical fitness (e.g., muscle strength, agility, mobility, flexibility, aerobic capacity, balance) and specific cognitive functions (e.g., complex attention, executive functions, among other domains). Complimentary variables of interest like sleep quality and caregivers' burden, considering the combination of different intensity/frequency/time variables for different types/stages of NCD, are also to be further considered. Likewise, further research should verify the feasibility of MT interventions in different settings (such as long-term care units, hospitals, or domiciliary contexts) and consider long-term follow-up evaluations to determine detraining effects must be included.

Of utmost importance, there is a need of uniformization on the most reliable, feasible and sensitive assessment methods and instruments to determine the effects of physical exercise (e.g., particularly using MT) on people diagnosed with different types/stages of NCD. The development of Core Outcome Sets may represent an important step forward.

Also of great importance, cost-effectiveness analysis should be performed in order to promote sustained physical exercise programs in the current public health context characterized by limited resources, verifying its impact on hospitalizations, emergency visits, falls rate, fall-related injuries and mortality (Brett et al., 2021; de Souto Barreto et al., 2018; Toots et al., 2019).

Additionally, when concerning individuals' adherence to structured physical exercise programs, there is a need for supplementary evidence on barriers, motivators, and facilitators towards individuals with NCD participation, specifically, considering their personal perspective and the perception of professionals involved in the program to foster the development and implementation of effective interventions. More research is also needed regarding the participation of informal caregivers in physical exercise interventions designed for their care-receivers, particularly to determine what should be their role during physical exercise sessions (e.g., supervising and providing help to their care-receivers in physical exercise performance, or only executing the physical exercises proposed by professionals), and comparing their point-of-views at the beginning and at the end of the intervention.

Based on the built evidence through the present thesis, future MT interventions should be implemented and prescribed by qualified professionals, and in collaboration with different stakeholders (i.e., municipalities, medical specialists, primary care services, associations) to guarantee the integration of treatment and care (World Health Organization, 2017, 2021b). MT interventions might be considered as a potential “polypill” to deal with the high levels of morbidity and dependency associated with the progression of major NCD, at least, to avoid a faster decline (American College of Sports Medicine, 2021; Fiuza-Luces et al., 2013; Valenzuela et al., 2019; World Health Organization, 2017).

In line with the WHO *Global Action Plan on the Public Health Response to Dementia 2017-2025,* specifically, people with major NCD should be empowered to live in the community and to receive integrated, person-centered, accessible, affordable health and social care aligned with their wishes and preferences. By developing evidence-based MT interventions, potentially effective in decreasing the progression of functional dependence, policymakers, researchers, and clinical practitioners will be enabling and supporting people with major NCD to preserve their autonomy and independence (World Health Organization, 2017, 2021a).

As a matter of fact, the burden and losses of the COVID-19 pandemic have been particularly high among people with dementia and their caregivers (Alzheimer's Disease International, 2020; Gauthier et al., 2021; World Health

Organization, 2021b), and as we are entering in a transition to endemic it is urgent to improve the dementia care paradigm, particularly in Portugal (Balsinha et al., 2022; Barros et al., 2020). As stated by the WHO (2021b), it is more important than ever to develop plans to strengthen health and social care systems for people with dementia, and invest on professionals training. Based on this assumption, several psychosocial intervention programs validated for dementia were recently reunited by the Portuguese Minister of Health (Gonçalves-Pereira & Marques, 2022) bringing together the existing training offers for professionals, in which the “Body & Brain” project is included. The presence in this national portfolio as a formative proposal for professionals is not only a recognition of our work, but mainly the realization of the Open Science concept of the United Nations (UNESCO, 2021). By making the “Body & Brain” project openly available, accessible, and reusable to everyone, particularly to societal actors – beyond the traditional scientific community – we are facilitating the communication and sharing of information on the benefits of physical exercise for people with major NCD.

Finally, the use of new technologies might be a future step forward to assure that individuals living in more remote geographic areas have access to this type of intervention. As tested by our research team during the COVID-19 pandemic, synchronous physical exercise sessions could also be an alternative for this population (Borges-Machado et al., 2021). More than that, the possibility to offer training on MT intervention implementation to other professionals might allow the replication of the “Body & Brain” project, facilitating its access and continuity in the entire national territory. To assure its quality and uniformization, long-distance mentoring to these professionals can be guaranteed through regular videoconferences and remote meetings.

Chapter 10. Conclusions

Overall, the present thesis contributed to enrich the body of evidence on MT programs targeting individuals with major NCD, and on a novel community-based multicentered intervention designed to improve the physical and cognitive functions. Specifically, this thesis provided an overview of the existing literature on MT interventions for older adults with major NCD. This thesis also presented an innovative intervention outstanding the potential benefit of MT methodology in improving functional capacity. However, its impact on cognitive function, neuropsychiatric symptoms, quality of life and ADL independence remains uncertain. Lastly, it revealed the factors that influenced care-receivers adherence and engagement in the “Body & Brain” physical exercise program.

Despite the difficulties during the recruitment process, the diagnosis limitations, and restrictions due to COVID-19 pandemic, this 6-month MT intervention showed promising results and reflected on several operationalization features that might be taken in consideration when planning future physical exercise interventions in community-based settings.

In conclusion, this thesis adds to the already existent literature new important insights to research and clinical practice on MT methodology and impact, supporting its implementation in community-based contexts, facilitating informal caregivers’ involvement in physical exercise sessions, and implemented by specialized professionals. These interventions may potentially benefit individuals’ functional capacity which, in turn, can mitigate or delay the disease progression.

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APPENDICES

Appendix 1. List of publications produced within the PhD timeframe

Articles
Carvalho J, **Borges-Machado F**, Pizarro A, Bohn L, Barros D. (2021) Home confinement in active older adults: influence on physical fitness, physical activity and sitting time and its relation with depressive symptoms. *Frontiers in Psychology.* May 20; 12:643832, 2021. doi: 10.3389/fpsyg.2021.643832
Bohn L, Barros D, **Borges-Machado F**, Pizzaro A, Carrapatoso S, Carvalho J. (2021) Active older adults keep aerobic capacity and experience small reductions in body strength during confinement due to covid-19 outbreak. *Journal of Aging and Physical Activity.* Apr 23;1-8. doi: 10.1123/japa.2020-0395
Barros D, **Borges-Machado F**, Andrade da Silva W, Nascimento A, Carvalho J, Bohn L. (2021) Different subjective and objective measures and cut-points of physical activity in frailty phenotype screening: A need for standardization? *Archives in Gerontology and Geriatrics.* Sep-Oct 96:104479. doi: 10.1016/j.archger.2021.104479
International Journal Supplement (Abstract)
Borges-Machado F, Barros DGM, Ribeiro O, Carvalho J. (2021) Effects of a 6-month multicomponent training on lower body function of older adults diagnosed with neurocognitive disorder – data from Body&Brain project. *Alzheimer's & Dementia*. 17 (S17): e05109. doi:10.1002/alz.051097
Ribeiro O, **Borges-Machado F**, Barros D, Teixeira L, Carvalho J. (2021) Does a 6-month multicomponent training improve functional capacity of individuals diagnosed with a neurocognitive disorder?. *Innovation in Aging*. 5 (S1): 893-894, doi: 10.1093/geroni/igab046.3247
Ribeiro O, Marques P, Barros D, Silva P, Carvalho J, **Borges-Machado F.** (2021) Caregivers' perception about their participation in a community-based exercise intervention - Body&Brain project. *Innovation in Aging*. 5 (S1): 893. doi: 10.1093/geroni/igab046.3245
Ribeiro O, **Borges-Machado F,** Barros D, Carvalho J. (2020) Effectiveness of a 6-month multicomponent training on physical frailty in older adults with cognitive impairment. *Innovation in Aging*. 4(S1): 175. doi: 10.1093/geroni/igaa057.565
Barros DGM, **Borges-Machado F**, Bohn L, Sampaio A, Ribeiro O, Carvalho J. (2020) Body&Brain Project: Effectiveness of a 6-month multicomponent training on cognitive function, quality of life and functional capacity of older adults with dementia. *Alzheimer's & Dementia*: 16(S7): e042980. doi: 10.1002/alz.042980

Carvalho J, **Machado F,** Sampaio A, Marques-Aleixo I, Magalhães J, Barros D, Ribeiro, O. (2020) Multicomponent training for dementia patients: Body&Brain project primary results on functional fitness. *Medicine & Science in Sports & Physical Exercise.* 52(7S): 450-451. doi: 10.1249/01.mss.0000678808.14141.31

Ribeiro O, **Borges-Machado F,** Lima N, Farinatti P, Carvalho J. (2019) Effectiveness of multicomponent exercise interventions in older dementia patients: a systematic review. *Innovation In Aging.* 3(S1): 909. doi: 10.1093/geroni/igz038.3317

Machado F, Ribeiro O, Meireles J, Sampaio A, Carvalho J. (2019) Cardiorespiratory effects of a multicomponent exercise program on individuals diagnosed with Alzheimer's disease: pilot study. *Medicine & Science in Sports & Physical Exercise.* 51(6S): 842. doi: 10.1249/01.mss.0000563016.17275.25

Carvalho J, Caçote P, **Machado F,** Sampaio A. (2019) Role of physical exercise on cognition & falls risk factors in Alzheimer's disease. *Medicine & Science in Sports & Physical Exercise.* 51(6S): 212. doi: 10.1249/01.mss.0000561145.22005.9b

Book Chapter

Carvalho J, **Machado F**, Sampaio A. (2020) Demência: contextualização e comparação entre Portugal e Brasil. *Envelhecimento no Contexto Rural: Tecendo Redes Entre a Realidade do Brasil e Portugal*. In: Ferretti F., Santos M.P.M. (eds) Editora CRV, Curitiba, Brasil. doi: 10.24824/978655578762.7

National Journal Supplement (Abstract)

Sampaio A, **Machado F,** Barros D, Marques-Aleixo I, Magalhães J, Ribeiro O, Carvalho J. (2020) Effects of a multicomponent exercise intervention on physical fitness among dyslipidemic individuals with dementia. *Acta Portuguesa de Nutrição.* 23(out-dez): 86. doi: 10.21011/apn.2020.2301

Borges-Machado F, Barros D, Sampaio A, Marques-Aleixo I, Magalhães J, Ribeiro O, Carvalho J. (2019) Contributions of a multicomponent exercise program for dementia patients: body composition preliminary data. Re*vista Portuguesa De Cirurgia.* (Supl. Nov):42

Proceedings Book (Abstract)

Queirós C, **Machado F,** Barros D, Sampaio J, Sampaio A, Barros R, Moreira P, Carvalho J, Padrão P. (2022) Excreção urinária de sódio, de potássio e estrado de hidratação em idosos com perturbação neurocognitiva. *IN Book of Abstracts* 16º Congresso Português do AVC. pp. 120

Machado F, Ribeiro O, Marques-Aleixo I, Magalhães J, Sampaio A, Carvalho, J. (2020) Contributions of a multicomponent exercise program for people with dementia: cognitive preliminary data. *IN Book of Abstracts* Alzheimer’s Disease International Conference. pp. 470

Fomenko E, Sampaio A, **Machado F,** Barros D, Santos M, Carvalho J. (2019) Body & Brain project: experience report of the pilot intervention. *IN Book of Abstracts* I Congresso De Atividade Física e Saúde Mental. pp.50-51

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Effectiveness of Multicomponent Exercise Interventions in Older Adults With Dementia: A Meta-Analysis

Author: Borges-Machado, Flávia; Silva, Nádia

Publication: Gerontologist, The

Publisher: Oxford University Press

Date: 2020-07-11

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Contribution of a multicomponent intervention on functional capacity and independence on activities of daily living in individuals with neurocognitive disorder

Author: Flávia Borges-Machado et al

Publication: BMC Geriatrics

Publisher: Springer Nature

Date: Nov 3, 2021

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Appendix 3. Clinical trial registry

ClinicalTrials.gov PRS
Protocol Registration and Results System

ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: February 12, 2021

ClinicalTrials.gov ID: NCT04095962

Study Identification

Unique Protocol ID:	BB01
Brief Title:	Effects of a Multicomponent Exercise Intervention on Physical and Cognitive Function of Older Adults With Dementia (Body&Brain)
Official Title:	Body and Brain: Effects of a Multicomponent Exercise Intervention on Physical and Cognitive Function of Older Adults With Dementia
Secondary IDs:	

Study Status

Record Verification:	September 2020
Overall Status:	Recruiting
Study Start:	September 1, 2018 [Actual]
Primary Completion:	August 2021 [Anticipated]
Study Completion:	March 2022 [Anticipated]

Sponsor/Collaborators

Sponsor:	Universidade do Porto
Responsible Party:	Sponsor
Collaborators:	Fundação para a Ciência e a Tecnologia

Oversight

U.S. FDA-regulated Drug:	No
U.S. FDA-regulated Device:	No
U.S. FDA IND/IDE:	No
Human Subjects Review:	Board Status: Approved Approval Number: CEFADE 22.2018 Board Name: The Ethics Committee of the Faculty of Sport from the University of Porto Board Affiliation: University of Porto Phone: +351 22 04 25 200 Email: cefade@fade.up.pt, Address: R. Dr. Plácido da Costa 91, 4200-450 Porto, Portugal

Data Monitoring:

Study Description

Brief Summary: Dementia is a leading cause of death and disability that was declared as one of the greatest health and social care challenges of the 21st century. Regular physical activity and exercise have been proposed as a non-pharmacological strategy in disease prevention and management. Multicomponent Training (MT) combines aerobic, strength, balance, and postural exercises and might be an effective training to improve both functional capacity and cognitive function in individuals with dementia (IwD). Nevertheless, data on the effects of MT in IwD are still limited and the extent to which IwD can retain improvements after an exercise intervention still needs to be elucidated. The aim of "Body & Brain" study is to investigate the effects of a 6-month MT intervention and 3-month detraining on the physical and cognitive function of IwD. Additionally, we aim to explore the impact of this intervention on psychosocial factors and physiologic markers related to dementia.

Detailed Description: Although exercise interventions for IwD seem to be feasible and well tolerated, resulting in positive effects on ADL functionality for people at mild-to-moderate stages [1, 2], the therapeutic role of physical activity, particularly exercise, after dementia diagnosis still needs further evidence [3-5], - especially when considering community-based contexts and caregivers as participants on exercise sessions [6]. It also matters to highlight that the dose-dependent relationship remains unclear [1, 7, 8]. Therefore, research is needed to identify the triad: stage/type of dementia, FITT variables (frequency, intensity, type, and time) of exercise intervention, and target outcome [7, 9]. Regarding exercise modality, Multicomponent Training (MT) [10] – combining aerobics, strength and balance exercises – seems to be effective at improving functional and cognitive performances in older adults with neurodegenerative disorders, particularly dementia [11-13]. Exercise programs previously developed by our group confirmed that a 6-month MT intervention can positively impact the physical and cognitive function of institutionalized older adults with AD [14, 15] and can be beneficial in physical fitness and ADL functionality performance among community-dwelling patients [9, 16]. However, the extent to which IwD can retain these improvements after the cessation of MT intervention still need to be elucidated [17] in order to understand how detraining affects functionality and cognition following the cessation of MT stimulus.

This study is a quasi-experimental controlled trial using a parallel-group design. The study sample consists of community-dwelling individuals aged ≥ 60 years who are clinically diagnosed with dementia or major neurocognitive disorder. Participants will be either allocated into the intervention group or the control group. The intervention group will participate in MT biweekly exercise sessions, whereas the control group will receive monthly sessions regarding physical activity and health-related topics for 6 months. The main outcomes will be physical function as measured by the Short Physical Performance Battery (SPPB) and cognitive function evaluated using the Alzheimer Disease Assessment Scale – Cognitive (ADAS-Cog) at baseline, after 6-months and 3-months after the end of intervention. Secondary outcomes will be body composition, physical fitness, daily functionality, quality of life, neuropsychiatric symptoms and caregiver's burden. Cardiovascular, inflammatory and neurotrophic blood-based biomarkers, and arterial stiffness will also be evaluated in subsamples.

Conditions

Conditions: Dementia

Alzheimer Disease
Vascular Dementia
Neurocognitive Disorders

Keywords: Functionality
Multimodal
Cognition

Study Design

Study Type: Interventional

Primary Purpose: Supportive Care

Study Phase: N/A

Interventional Study Model: Parallel Assignment

Number of Arms: 2

Masking: None (Open Label)

Allocation: Non-Randomized

Enrollment: 110 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Experimental Group Training protocol will be held for 6 months, twice per week/ 60 min per sessions.	Exercise The MT program will be conducted for 6 months, twice a week in 60 minutes sessions. Sessions will be divided in warm-up (10 minutes, including slow walk, postural and mobility exercises for general activation, and stretching exercises), specific training (35-45 minutes, including balance/coordination training, strength and aerobic exercises) and cool down (5 minutes with breathing and stretching exercises for the main worked joints and muscles) following the main guidelines recommended by the American College of Sports Medicine [18] and the WHO [19]. Other Names: • Multicomponent training
No Intervention: Control Group Participants in the control group will receive monthly sessions regarding physical activity and health related topics as a complement to standard care. No specific exercise intervention will be conducted for this group.	

Outcome Measures

Primary Outcome Measure:

1. Change from Baseline on Short Physical Performance Battery (SPBB)
   The Short Physical Performance Battery (SPPB) is a standardised assessment tool of lower limb function, testing 3 dimensions: standing balance, walking speed, and chair stands. Each component is scored between 0-4, total score from 0 (poor performance) to 12 (best performance).

   [Time Frame: Assessment at baseline, immediately after 6 months of intervention, and at 3 months follow-up for experimental and control groups]

2. Change from Baseline on Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)
   To evaluate cognitive function with a total scoring ranging between 0 – 68. A score of 68 represents the most severe impairment and 0 represents the least impairment.

   [Time Frame: Assessment at baseline, immediately after 6 months of intervention, and at 3 months follow-up for experimental and control groups]

Secondary Outcome Measure:

3. Change from Baseline on 30-second Chair-stand Test
   Physical fitness is going to be measured via the Senior Fitness Test (SFT).This physical battery includes lower and upper-body strength (30-second chair stand and 30-second arm curl tests, respectively), lower and upper-body flexibility (chair sit-and-reach and back scratch tests, respectively), aerobic endurance (2-minute step test), and agility/dynamic balance (8-foot up-and-go test).

   Lower body strength was measured using the 30 s chair stand test. Participants were asked to sit in a 43-cm armless chair with their arms crossed at the wrists and held against the chest. The score was the total number of stands executed correctly within 30 s.

   [Time Frame: Assessment at baseline, immediately after 6 months of intervention, and at 3 months follow-up for experimental and control groups]
4. Change from Baseline on 30-second Arm Curl Test
   Physical fitness is going to be measured via the Senior Fitness Test (SFT).This physical battery includes lower and upper-body strength (30-second chair stand and 30-second arm curl tests, respectively), lower and upper-body flexibility (chair sit-and-reach and back scratch tests, respectively), aerobic endurance (2-minute step test), and agility/dynamic balance (8-foot up-and-go test).

   Upper body strength was assessed using the arm curl test. Participants performed as many biceps curls as possible in 30 s, using a dumbbell (3.63 kg and 2.27 kg for men and women, respectively). The score was the total number of hand-weight curls performed through the full range of motion within 30 s.

   [Time Frame: Assessment at baseline, immediately after 6 months of intervention, and at 3 months follow-up for experimental and control groups]
5. Change from Baseline on 2-minute Step Test
   Physical fitness is going to be measured via the Senior Fitness Test (SFT).This physical battery includes lower and upper-body strength (30-second chair stand and 30-second arm curl tests, respectively), lower and upper-body flexibility (chair sit-and-reach and back scratch tests, respectively), aerobic endurance (2-minute step test), and agility/dynamic balance (8-foot up-and-go test).

   Cardiorespiratory fitness was measured using 2-min step test. Participants were asked to raise each knee to a point midway between the patella (kneecap) and iliac crest (top hip bone). The score was the number of times the right knee reaches the required height.

   [Time Frame: Assessment at baseline, immediately after 6 months of intervention, and at 3 months follow-up for experimental and control groups]
6. Change from Baseline on 8-Foot Up and Go Test
   Physical fitness is going to be measured via the Senior Fitness Test (SFT).This physical battery includes lower and upper-body strength (30-second chair stand and 30-second arm curl tests, respectively), lower and upper-body flexibility (chair sit-and-reach and back scratch tests, respectively), aerobic endurance (2-minute step test), and agility/dynamic balance (8-foot up-and-go test).

   Participants were asked to as quickly as possible, in a sitting position, stand up, walk 8-foot distance (2,44 meters), turn the cone marker around and return to the seated position. The time, in seconds, necessary to complete this test was registered.

   [Time Frame: Assessment at baseline, immediately after 6 months of intervention, and at 3 months follow-up for experimental and control groups]
7. Change from Baseline on Back Scratch Test
   Physical fitness is going to be measured via the Senior Fitness Test (SFT).This physical battery includes lower and upper-body strength (30-second chair stand and 30-second arm curl tests, respectively), lower and upper-body flexibility (chair sit-and-reach and back scratch tests, respectively), aerobic endurance (2-minute step test), and agility/dynamic balance (8-foot up-and-go test).

Upper-body flexibility was measured through the back-scratch test. The participants were asked to, in standing position, place the preferred hand over the same shoulder, reaching down the middle of the back as far as possible – elbow pointed up. Then, the participants were asked to place the other arm around the back of the waist with the palm up and in attempt to touch (or overlap) the extended middle fingers of both hands. The nearest distance (in centimeters) was measured between the tips of the middle fingers (minus or plus, depending if overlapping or not)

[Time Frame: Assessment at baseline, immediately after 6 months of intervention, and at 3 months follow-up for experimental and control groups]

8. Change from Baseline on Sit and reach Test
Physical fitness is going to be measured via the Senior Fitness Test (SFT).This physical battery includes lower and upper-body strength (30-second chair stand and 30-second arm curl tests, respectively), lower and upper-body flexibility (chair sit-and-reach and back scratch tests, respectively), aerobic endurance (2-minute step test), and agility/ dynamic balance (8-foot up-and-go test).

The chair sit-and-reach test was used to assess lower-body flexibility. Participants were asked to sit at the front edge of a chair and with one leg extended (dominant) reach the toward toes as far as possible, bending the upper body forward at the hip joint. The other leg must be bent and slightly off to one side with the foot flat on the floor. The number of centimeters (plus or minus) were registered between the extended fingers (hands overlapping) and the tip of the toe – maintaining the position for at least 2 seconds.

[Time Frame: Assessment at baseline, immediately after 6 months of intervention, and at 3 months follow-up for experimental and control groups]

9. Change from Baseline on Modified Bruce Treadmill Test
This sub-maximal test with incremental protocol including seven stages and performed on a treadmill. To assess Peak oxygen uptake (VO2 peak), standard an open-circuit spirometer technique (Cosmed K4b2, Cosmed, Rome, Italy) will be used.

[Time Frame: Assessment at baseline, immediately after 6 months of intervention, and at 3 months follow-up for experimental and control groups]

10. Change from Baseline on One Leg Balance Test
The static balance will be measured with the One Leg Balance Test. Participants will be asked to choose a leg to stand on, flex the opposite knee and balance on one leg as long as possible. The time (in seconds) standing unsupported will be recorded.

[Time Frame: Assessment at baseline, immediately after 6 months of intervention, and at 3 months follow-up for experimental and control groups]

11. Change from Baseline on Handgrip test
Handgrip strength will be obtained with a Jamar Plus + Digital hand dynamometer (Sammons Preston Inc., Bolingbrook, Illinois, USA).Measurements will be carried out following the American Society of Hand Therapists recommendations, and each participant will perform three attempts with a pause of 1 min between them. The maximum value, in kilograms of force (kgf), of the three measurements with the dominant hand will be registered.

[Time Frame: Assessment at baseline, immediately after 6 months of intervention, and at 3 months follow-up for experimental and control groups]

12. Change from Baseline on Appendicular Skeletal Muscle Mass Index (ASMI)
Appendicular Skeletal Muscle Mass Index (ASMI), which is the sum of muscle masses of the four limbs described as appendicular skeletal muscle mass adjusted for height (kg/m2), will be analyzed with Dual Energy X-ray Absorptiometry (DXA) (Hologic QDR 4500, Explorer model, version 12.4).

[Time Frame: Assessment at baseline, immediately after 6 months of intervention, and at 3 months follow-up for experimental and control groups]

13. Change from Baseline on Body mass, fat-free mass, fat mass
Body mass (kg), fat-free mass (kg) and fact mass (kg) will be analyzed with Dual Energy X-ray Absorptiometry (DXA) (Hologic QDR 4500, Explorer model, version 12.4)

[Time Frame: Assessment at baseline, immediately after 6 months of intervention, and at 3 months follow-up for experimental and control groups]

14. Change from Baseline on Barthel Index (BI)

To evaluate independence on performing basic activities of daily living, ranging from 0-100 and with higher scores representing increased functionality.

[Time Frame: Assessment at baseline, immediately after 6 months of intervention, and at 3 months follow-up for experimental and control groups]

15. Change from Baseline on Lawton & Brody (IADL)
Assessment of instrumental activities of daily life. It evaluates the following categories and subcategories: A. Ability to Use Telephone; B. Shopping; C.Food Preparation; D.Housekeeping; E. Laundry; F. Mode of Transportation; G. Responsibility for Own Medications; H. Ability to Handle Finances. Range 0-8. Lower scores are indicative of increased difficulties to independently perform instrumental activities.

[Time Frame: Assessment at baseline, immediately after 6 months of intervention, and at 3 months follow-up for experimental and control groups]

16. Change from Baseline on Mini-Mental State Examination (MMSE)
The Mini Mental State Examination (MMSE) a widely used test of cognitive function among older adults will be used and consists of a 30-item instrument (with higher scores indicating better cognitive performance) that is organized in six cognitive domains – orientation, retention, attention and calculation, delayed recall, language, and visuo-constructive ability.

[Time Frame: Assessment at baseline, immediately after 6 months of intervention, and at 3 months follow-up for experimental and control groups]

17. Change from Baseline on Trail-making test (TMT)
The executive functions will be assessed with the Trail Making Test part A – attention, visual scanning, speed of eye-hand coordination, and information processing; and part B – working memory and the ability to switch between different stimuli. Time and number of errors will be registered.

[Time Frame: Assessment at baseline, immediately after 6 months of intervention, and at 3 months follow-up for experimental and control groups]

18. Change from Baseline on Neuropsychiatric inventory (NPI)
NPI is used to determine the frequency and severity of behavioral and psychological symptoms of dementia (BPSD) with a total score ranging from zero to 144 points with high scores corresponding to worsening of BPSD.

[Time Frame: Assessment at baseline, immediately after 6 months of intervention, and at 3 months follow-up for experimental and control groups]

19. Change from Baseline on Quality of Life in Alzheimer's Disease scale (QoL-AD)
The QoL-AD will be used to measure the dementia participants' quality of life. The questionnaire includes 13 items such as physical health, energy, mood, memory, family, marriage, friends, and ability to do things for fun. The QoL-AD provides the participant and the caregiver reports of the participant's QoL and is scored on a 4-point Likert-type scale ranging from 1 to 4 (excellent), with total scores ranging between 13 and 52 point, and higher scores indicating better quality of life.

[Time Frame: Assessment at baseline, immediately after 6 months of intervention, and at 3 months follow-up for experimental and control groups]

20. Change from Baseline on Caregiver subjective burden (CarerQol-7D)
The Care-related Quality of Life instrument (CarerQol) will be used to address subjective burden (CarerQol-7D). The subjective burden is measured in seven dimensions: fulfillment, relational problems, mental health, daily activities problems, physical health and support. Total CarerQol-7D score ranges from 0 to 14 points with higher scores indicating better caregiving situation.

[Time Frame: Assessment at baseline, immediately after 6 months of intervention, and at 3 months follow-up for experimental and control groups]

21. Caregiver subjective well-being (CarerQol-VAS)
The Care-related Quality of Life instrument (CarerQol) will be used to address caregivers' well-being (CarerQol-VAS), using a visual analogue scale to ask about happiness between 0 (completely unhappy) and 10 (completely happy).

[Time Frame: Assessment at baseline, immediately after 6 months of intervention, and at 3 months follow-up for experimental and control groups]

22. Change from Baseline on Blood triglycerides (TG), total cholesterol (TC), Low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C)

Determination of TG (mg/dL), TC (mg/dL),LDL-C (mg/dL), HDL-C (mg/dL) concentrations in plasma.

[Time Frame: Assessment at baseline, immediately after 6 months of intervention, and at 3 months follow-up for experimental and control groups]

23. Change from Baseline on Circulating levels of Glycated Hemoglobin (HbA1c)
    Determination of HbA1c(μg/mL) concentrations in blood.

    [Time Frame: Assessment at baseline, immediately after 6 months of intervention, and at 3 months follow-up for experimental and control groups]

24. Change from Baseline on Circulating levels of Interleukin-6 (IL-6),Interleukin-8 (IL-8), Interleukin-10 (IL-10)
    Plasma IL-6 (pg/ml), IL-8 (pg/ml), IL-10 (pg/ml) concentrations will be measured using V-PLEX Human Biomarker 40-Plex Kit pro-inflammatory.

    [Time Frame: Assessment at baseline, immediately after 6 months of intervention, and at 3 months follow-up for experimental and control groups]

25. Change from Baseline on Circulating levels of C-Reactive Protein (CRP) and Tumor Necrosis Factor (TNF-alfa)
    Plasma CRP (μg/mL) and TNF-alfa (μg/mL) concentrations will be measured using V-PLEX Human Biomarker 40-Plex Kit pro-inflammatory.

    [Time Frame: Assessment at baseline, immediately after 6 months of intervention, and at 3 months follow-up for experimental and control groups]

26. Change from Baseline on Circulating levels of free brain-derived neurotrophic factor (BDNF),Vascular Endothelial Growth Factor (VEGF), intercellular adhesion molecule 1 (sICAM-1), vascular cell adhesion molecule-1 (sVCAM-1), metalloproteinase-9 (MMP-9)
    BDNF (pg/ml), VEGF (pg/ml), sICAM-1 (pg/ml), sVCAM-1 (pg/ml), MMP-9 (pg/ml) concentrations will be analysed using the ELISA method (enzyme-linked immunosorbent assay).

    [Time Frame: Assessment at baseline, immediately after 6 months of intervention, and at 3 months follow-up for experimental and control groups]

27. Change from Baseline on Circulating levels of Insulin-like growth factor-1 (IGF-1)
    Plasma IGF-1 (ng/ml) concentrations will be measured by the DiaSorin using a LIAISON ® kit and analysed by CLIA method.

    [Time Frame: Assessment at baseline, immediately after 6 months of intervention, and at 3 months follow-up for experimental and control groups]

28. Change from Baseline on Systolic and Diastolic Blood Pressure
    Systolic and Diastolic Blood Pressure (mmHg) will be measured using a digital sphygmomanometer.

    [Time Frame: Assessment at baseline, immediately after 6 months of intervention, and at 3 months follow-up for experimental and control groups]

29. Change from Baseline on Arterial stiffness
    Arterial stiffness is going to be measured as carotid-femoral pulse wave velocity (cfPWV) using applanation tonometry (SphygmoCor, AtCor Medical, Australia). Procedures will follow international guidelines. In brief, sequential and consecutive carotid and femoral pressure waves are going to be registered together with the electrocardiogram, which will serve as a reference to calculate the transit time between the recording's sites. The distance traveled by the pressure wave will be the direct distance between the recording points at the femoral and carotid arteries, corrected by the factor 0.8. The value of cfPWV is going to be calculated as the direct distance (in meters) divided by the transit time (in seconds). All measurements will be performed in duplicate by the same trained researcher.

    [Time Frame: Assessment at baseline, immediately after 6 months of intervention, and at 3 months follow-up for experimental and control groups]

Other Pre-specified Outcome Measures:

30. Change from Baseline on Daily Physical Activity levels
    Physical activity levels will be collected with the activity monitors GT3X+ (ActiGraph), located at the waist, to measure the activity intensity (counts per minute) during one week.

[Time Frame: Assessment at baseline, immediately after 6 months of intervention, and at 3 months follow-up for experimental and control groups]

Eligibility

Minimum Age: 60 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Individuals aged ≥ 60 years capable of walking autonomously without an assistive device or human assistance;
- Individuals diagnosed with dementia or major neurocognitive disorder using accepted diagnostic criteria such as that established by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR or DSM-5), ICD-10, or the NINCDS-ADRDA; by a physician for at least for 6-months.

Exclusion Criteria:

- Individuals diagnosed with certain disorders or conditions in which exercise is contraindicated such as unstable or ongoing cardiovascular and/or respiratory disorder;
- Hospitalized individuals and/or recovering from surgery or rehabilitation;
- Individuals presenting an advanced stage of dementia (e.g., scored 3-points in CDR or ≤ 10 points on MMSE) that could affect physical performance in the exercise training sessions or testing procedures.

Contacts/Locations

Central Contact Person: Joana Carvalho, PhD
Telephone: +351 220425316
Email: Jcarvalho@fade.up.pt

Central Contact Backup:

Study Officials: Joana Carvalho, PhD
Study Principal Investigator
Universidade do Porto

Locations: **Portugal**
Faculty of Sports of University of Porto
[Recruiting]
Porto, Portugal, 4200
Contact: Joana Carvalho, PhD +351220425316
Principal Investigator: Joana Carvalho, PhD

IPDSharing

Plan to Share IPD: No

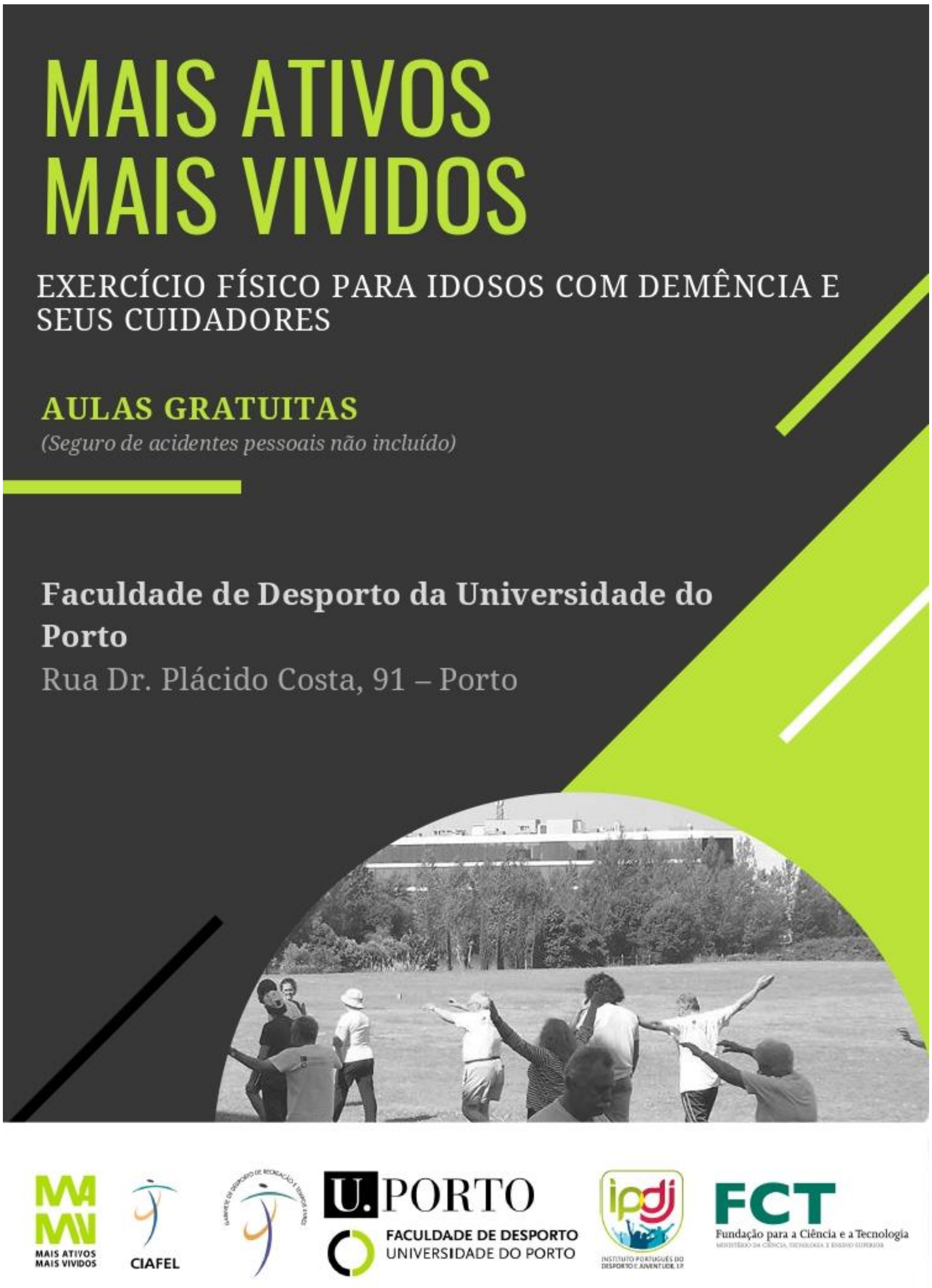
References

Citations:

Links:

Available IPD/Information:

Appendix 4. Flyer used to disseminate the "Body & Brain" project




A FACULDADE DE DESPORTO PROMOVE
PROGRAMA DE EXERCÍCIO FÍSICO INOVADOR
PARA PESSOAS COM
DEMÊNCIA E SEUS CUIDADORES
Este programa tem como objetivo **preservar a capacidade cognitiva e funcional** e promover um **estilo de vida saudável** junto da população idosa com diagnóstico de **Demência**, e respetivos **cuidadores formais ou informais.**
Consiste numa prática **desportiva regular, em ambiente informal e recreativo** que visa atenuar a **progressão da doença** e promover **a autonomia quotidiana.**
As sessões são gratuitas* e decorrem **2 vezes por semana**, nas instalações da Faculdade, no **Pólo da Asprela** ou noutro espaço da sua **comunidade.**
INFORMAÇÕES E INSCRIÇÕES:
220 425 293
939398909; acsampaio@fade.up.pt
964050967; f_93_machado@live.com.pt
www.facebook.com/Maisativosmaisvividos
** A participação implica o pagamento de um seguro de acidentes pessoais.*

Appendix 5. Ethical approval letters

U.PORTO
FACULDADE DE DESPORTO
UNIVERSIDADE DO PORTO

Ethics Committee

ETHICS OPINION

Process **CEFADE 22.2018**

The Ethics Committee of the Faculty of Sport from the University of Porto analyzed the project entitled "Contributos de um Programa de Exercício Físico Multicomponente para Indivíduos com Diagnóstico de Doença de Alzheimer" presented by MSc.Flávia Alexandra Borges Machado. Considering the project's characteristics, as well as the competence of the research team, the Ethics Committee addresses a positive opinion, because the ethical principles that govern this type of scientific work are respected.

Porto and Faculty of Sport, 21st February, 2019

The chairman of the Ethics Committee,

José Alberto Ramos Duarte

Extrato da Ata Nº 44 da Comissão de Ética das Áreas de Saúde e Social da Santa Casa da Misericórdia do Porto, relativo à reunião de 25/09/2018

"Foi ainda apresentado o projeto "Mais Ativos, mais Vividos", da responsabilidade da FADEUP, já aprovado neste órgão para o DIS, mas agora de forma a ser também desenvolvido no Centro de Dia São João de Deus – CHCF. O referido projeto foi aprovado."

A Secretária da Comissão de Ética

Anabela Monteiro

Anabela Monteiro

07/05/2019

Rua das Flores, 5
Apartado 6018
4051-801 Porto
T. 222 074 710 F. 222 050 116
scmp@scmp.pt

UNIDADE LOCAL DE SAÚDE DE MATOSINHOS HOSPITAL PEDRO HISPANO	INFORMAÇÃO	Nº 96/CE/JAS Data: 11-10-2019

Para: Serviço de Gestão do Conhecimento
De: Comissão de Ética

Assunto: Pedido de autorização para realização de um estudo intitulado "**Body and Brain: efeitos de uma intervenção de exercício multicomponente na função física e cognitiva em idosos com Demência**"

INFORMAÇÃO

Exmo. Senhor,

A Comissão de Ética analisou o pedido de autorização para realização de um estudo intitulado "**Body and Brain: efeitos de uma intervenção de exercício multicomponente na função física e cognitiva em idosos com Demência**" proponente CIAFEL - Centro de Investigação em Actividade Física, Saúde e Lazer, e cuja Investigadora Principal é a Dra. Maria Joana Mesquita Cruz Barbosa de Carvalho, no âmbito de protocolo com a ULSM, e a desenvolver na UCC da Sra. Hora.

A Comissão de Ética para a Saúde da ULSM, deliberou, por unanimidade, nada opor à realização deste estudo.

Com os melhores cumprimentos

Dr. José Alberto Silva
Presidente da Comissão de Ética
da ULSM Matosinhos

Dr. José Alberto Silva
(Presidente da Comissão de Ética da ULSM, E.P.E.)

Autorizo

hospital de magalhães lemos EPE

HOSPITAL DE MAGALHÃES LEMOS, EPE
Reunião do C.A. 13/5/19
Acta n.º 17/2019
António Leuschner Presidente
Alberto Peixoto Vogal Executivo
Joaquim Ramos
João Teles Enfermeiro Director

COMISSÃO DE ÉTICA

Hospital de Magalhães Lemos, EPE

Parecer Nº 8 / 2019

Identificação do(s) Proponente(s)
Nome(s): Flávia Alexandra Borges Machado
Filiação Institucional: Centro de Investigação em Actividade Física, Desporto e Lazer, Fac. de Desporto, Universidade do Porto.
Investigador Responsável/orientador: Profª. Joana Carvalho (FADEUP).

Título do Projeto: *"Contributos de um programa de exercício físico multicomponente em indivíduos com o diagnóstico de demência"*

Considerando que:

O estudo decorrerá no Serviço de Psicogeriatria do HML, sob a supervisão da sua Directora, Dra. Rosa Encarnação. Está ligado a um programa doutoral da Faculdade de Desporto da UP e tem a orientação científica da Prof. Joana Carvalho. Está integrado no projecto *Body and Brain*, da mesma escola, patrocinado pela Fundação para a Ciência e a Tecnologia. Tem por objecto analisar os efeitos do exercício físico sobre a evolução das doenças demenciais, e em particular determinar os benefícios que dessa actividade podem resultar para a manutenção do bem-estar e funcionalidade dos enfermos (programa *Mais Activos, Mais Vividos*).

O número de participantes será entre 8 e 16. A intervenção consiste em sessões bissemanais de exercício físico multicomponente adaptado às condições dos doentes. Haverá comparação com um grupo de controlo. Os doentes serão acompanhados pelos respectivo cuidadores. Os médicos e outros técnicos do serviço assegurarão a assistência usual e intervirão se necessário. Será feita uma rigorosa avaliação dos efeitos, através de medições antropométricas, escalas de avaliação e análises clínicas.

O risco envolvido é mínimo, e proporcionado ao benefício esperado. Os participantes - doentes, seus familiares e cuidadores informais - serão informados sobre o objectivo e natureza da intervenção, e prestarão consentimento escrito nas condições previstas no Hospital. A confidencialidade estará assegurada.

Parecer:

A Comissão de Ética considera que este projecto respeita as condições exigíveis e não faz objecções à realização do estudo.

Data: 22 / 04 /2019

O Presidente da Comissão de Ética: João Barreto

Appendix 6. Informed consent forms

Consentimento Informado, Livre e Esclarecido para participação em investigação – Participante

De acordo com a Declaração de Helsínquia[5], Convenção de Oviedo[6] e o Regulamento Geral de Proteção de Dados[7]

Por favor, leia com atenção a seguinte informação. Se achar que algo está incorreto ou que não está claro, não hesite em solicitar mais informações. Se concorda com a proposta que lhe foi feita, queira assinar este documento.

Título do estudo: Contributos de um programa de exercício físico multicomponente para indivíduos com diagnóstico de demência.

Enquadramento: O presente estudo realiza-se no âmbito do Programa Doutoral em Atividade Física e Saúde pela Faculdade de Desporto da Universidade do Porto – *Centro de Investigação em Atividade Física, Saúde e Lazer*, e tem por objetivo investigar os efeitos da prática de exercício físico na demência e o seu impacto ao nível físico, cognitivo e psicossocial. Este projeto é realizado sob a orientação dos Profs. Doutores Maria Joana Carvalho e Óscar Ribeiro.

Explicação do estudo: O programa de exercício físico decorre de setembro de 2018 a junho de 2019, com uma frequência de dois dias por semana. As sessões de treino irão decorrer em contexto comunitário, e cada uma terá a duração aproximada de 1h. Pretende-se estudar os efeitos do exercício físico ao nível da saúde física e mental dos participantes no programa (grupo de intervenção), assim como dos sujeitos que colaboram com a mesma investigação, mas não participam no treino semanal (grupo de controlo), através da aplicação de vários instrumentos de avaliação aos indivíduos com diagnóstico de demência, e respetivos cuidadores.

Confidencialidade e anonimato: Garante-se a confidencialidade dos dados recolhidos e o uso exclusivo dos mesmos apenas para fins de investigação (artigos científicos, conferências, seminários, congressos, *posters)*, assim como o anonimato dos participantes. Os dados serão conservados durante o prazo de concretização do projeto e por um período adicional necessário ao tratamento e divulgação dos dados.

Categorias dos dados que serão recolhidos *(se não consentir a recolha de dados de uma ou mais categorias, por favor, assinale):*

Pessoa com diagnóstico de Demência:
-Questionário de Anamnese
-Avaliação da Composição Corporal pela Medida de DEXA
-Avaliação da Força de Preensão Manual
- Avaliação da Aptidão Física e Medidas Antropométricas
-Avaliação da Intensidade das Sessões de Treino
-Avaliação do Nível de Atividade Física
-Avaliação Ingestão Alimentar
-Avaliação do Risco de Queda
-Avaliação do Consumo de Oxigénio
-Avaliação da Pressão Arterial
-Avaliação da Função Cognitiva
-Avaliação do Estadio da Demência
-Avaliação da Qualidade de Vida
-Avaliação da Qualidade do Sono
-Recolha de sangue, urina e saliva

Muito obrigada pela sua colaboração!

Flávia Alexandra Borges Machado

contacto telefónico: 964 050 967

Responsável: Maria Joana Carvalho

contacto telefónico: 220 425 291

[5] http://portal.arsnorte.min-saude.pt/portal/page/portal/ARSNorte/Comiss%C3%A3o%20de%20%C3%89tica/Ficheiros/Declaracao_Helsinquia_2008.pdf

[6] http://dre.pt/pdf1sdip/2001/01/002A00/00140036.pdf

[7] https://www.cnpd.pt/bin/rgpd/rgpd.htm

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Declaro ter lido e compreendido este documento, bem como as informações verbais que me foram fornecidas pelas pessoas que acima assinam. Foi-me garantida a possibilidade de, em qualquer altura, recusar participar neste estudo sem qualquer tipo de consequências, e o direito de solicitar o acesso aos meus dados pessoais e de apresentar reclamação a uma autoridade de controlo. Enquanto titular dos dados é-me reconhecido o direito de portabilidade e, por esse motivo, poderei solicitar ao responsável pelo tratamento os dados pessoais que me dizem respeito, num formato estruturado e fácil interpretação. Desta forma, aceito participar neste estudo e permito a utilização dos dados que de forma voluntária forneço, confiando em que apenas serão utilizados para esta investigação e nas garantias de confidencialidade e anonimato que me são dadas pela investigadora.

Assinatura: … … … … … … … …... … … … … ... … … … … … … Data: …… /…… /………..

SE NÃO FOR O PRÓPRIO A ASSINAR POR IDADE OU INCAPACIDADE
NOME: …
BI/CD Nº: .... DATA OU VALIDADE ….. /..… /….....
GRAU DE PARENTESCO OU TIPO DE REPRESENTAÇÃO: ....
ASSINATURA …

Consentimento Informado, Livre e Esclarecido para participação em investigação – Cuidador

De acordo com a Declaração de Helsínquia[8], Convenção de Oviedo[9] e o Regulamento Geral de Proteção de Dados[10]

Por favor, leia com atenção a seguinte informação. Se achar que algo está incorreto ou que não está claro, não hesite em solicitar mais informações. Se concorda com a proposta que lhe foi feita, queira assinar este documento.

Título do estudo: Contributos de um programa de exercício físico multicomponente para indivíduos com diagnóstico de demência.

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Confidencialidade e anonimato: Garante-se a confidencialidade dos dados recolhidos e o uso exclusivo dos mesmos apenas para fins de investigação (artigos científicos, conferências, seminários, congressos, *posters)*, assim como o anonimato dos participantes. Os dados serão conservados durante o prazo de concretização do projeto e por um período adicional necessário ao tratamento e divulgação dos dados.

Categorias dos dados que serão recolhidos *(se não consentir a recolha de dados de uma ou mais categorias, por favor, assinale):*

Cuidador da Pessoa com Diagnóstico de Demência:

-Questionário de Anamnese *(quando aplicável)*
-Avaliação da Sobrecarga do Cuidador *(quando aplicável)*
-Avaliação da Qualidade de Vida do Idoso com Demência
-Avaliação dos Sintomas Comportamentais e Psicológicos Neuropsiquiátricos
-Avaliação da Funcionalidade nas Atividades de Vida Diária

Muito obrigada pela sua colaboração!

Flávia Alexandra Borges Machado
contacto telefónico: 964 050 967

Responsável: Maria Joana Carvalho
contacto telefónico: 220 425 291

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[8] http://portal.arsnorte.min-saude.pt/portal/page/portal/ARSNorte/Comiss%C3%A3o%20de%20%C3%89tica/Ficheiros/Declaracao_Helsinquia_2008.pdf

[9] http://dre.pt/pdf1sdip/2001/01/002A00/00140036.pdf

[10] https://www.cnpd.pt/bin/rgpd/rgpd.htm

-o-o-o-o-o-o-o-o-o-o-o-o-o-o-o-o-o-o-o-

Declaro ter lido e compreendido este documento, bem como as informações verbais que me foram fornecidas pelas pessoas que acima assinam. Foi-me garantida a possibilidade de, em qualquer altura, recusar participar neste estudo sem qualquer tipo de consequências, e o direito de solicitar o acesso aos meus dados pessoais e de apresentar reclamação a uma autoridade de controlo. Enquanto titular dos dados é-me reconhecido o direito de portabilidade e, por esse motivo, poderei solicitar ao responsável pelo tratamento, os dados pessoais que me dizem respeito num formato estruturado e fácil interpretação. Desta forma, aceito participar neste estudo e permito a utilização dos dados que de forma voluntária forneço, confiando em que apenas serão utilizados para esta investigação e nas garantias de confidencialidade e anonimato que me são dadas pela investigadora.

Assinatura: … … … … … … … …... … … … … ... … … … … … … Data: …… /…… /………..

DOCUMENTO É COMPOSTO DE 2 PÁGINAS E FEITO EM DUPLICADO: UMA VIA PARA A INVESTIGADORA, OUTRA PARA A PESSOA QUE CONSENTE

Consentimento Informado, Livre e Esclarecido para Gravação de Imagens em Fotografia ou Vídeo – Participante

A presente declaração confirma que a investigadora explicou à pessoa que consente o propósito e procedimentos utilizados na gravação de imagens em fotografia e/ou vídeo, tendo sido dada à mesma a oportunidade colocar todas as questões necessárias. Os materiais recolhidos serão utilizados unicamente para âmbitos de investigação e divulgação em congressos/seminários/ações de formação, entre outros. Garante-se a ocultação de outros dados de identificação da pessoa, e se expressamente indicar não será exibida a sua face. É igualmente garantido que a presente autorização pode ser retirada, a todo o momento, sem que isso cause qualquer prejuízo.

Por favor, indique o seu parecer selecionando uma das seguintes opções:

☐ Não Autorizo

☐ Autorizo Gravação de Imagens em Fotografia e Vídeo *(a face pode ser exibida)*

☐ Autorizo apenas Fotografia *(a face pode ser exibida)*

☐ Autorizo apenas Vídeo *(a face pode ser exibida)*

☐ Autorizo Fotografia e/ou Vídeo apenas se **não** for exibida a face

Por favor, leia com atenção todo o conteúdo deste documento. Não hesite em solicitar mais informações se não estiver completamente esclarecido(a). Verifique se todas as informações estão corretas. Se tudo estiver conforme, então assine este documento.

Declaro que concordo com o que foi proposto e explicado pela investigadora que assina este documento, tendo podido fazer todas as perguntas sobre o assunto.

Assinatura: … … … … … … … …... … … … … ... … … … … Data: …… /…… /………..

SE NÃO FOR O PRÓPRIO A ASSINAR POR IDADE OU INCAPACIDADE

NOME: …

BI/CD Nº: .... DATA OU VALIDADE ….. /..… /…....

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

ASSINATURA …

ESTE DOCUMENTO É COMPOSTO DE 2 PÁGINAS E FEITO EM DUPLICADO: UMA VIA PARA A INVESTIGADORA, OUTRA PARA A PESSOA QUE CONSENTE

Consentimento Informado, Livre e Esclarecido para Gravação de Imagens em Fotografia ou Vídeo – Cuidador

A presente declaração confirma que a investigadora explicou à pessoa que consente o propósito e procedimentos utilizados na gravação de imagens em fotografia e/ou vídeo, tendo sido dada à mesma a oportunidade colocar todas as questões necessárias. Os materiais recolhidos serão utilizados unicamente para âmbitos de investigação e divulgação em congressos/seminários/ações de formação, entre outros. Garante-se a ocultação de outros dados de identificação da pessoa, e se expressamente indicar não será exibida a sua face. É igualmente garantido que a presente autorização pode ser retirada, a todo o momento, sem que isso cause qualquer prejuízo.

Por favor, indique o seu parecer selecionando uma das seguintes opções:

☐ Não Autorizo

☐ Autorizo Gravação de Imagens em Fotografia e Vídeo *(a face pode ser exibida)*

☐ Autorizo apenas Fotografia *(a face pode ser exibida)*

☐ Autorizo apenas Vídeo *(a face pode ser exibida)*

☐ Autorizo Fotografia e/ou Vídeo apenas se **não** for exibida a face

Por favor, leia com atenção todo o conteúdo deste documento. Não hesite em solicitar mais informações se não estiver completamente esclarecido(a). Verifique se todas as informações estão corretas. Se tudo estiver conforme, então assine este documento.

Declaro que concordo com o que foi proposto e explicado pela investigadora que assina este documento, tendo podido fazer todas as perguntas sobre o assunto.

Assinatura: … … … … … … … …... … … … … ... … … … … Data: …… /…… /………..

SE NÃO FOR O PRÓPRIO A ASSINAR POR IDADE OU INCAPACIDADE

NOME: …

BI/CD Nº: .... DATA OU VALIDADE ….. /..… /…....

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

ASSINATURA …

ESTE DOCUMENTO É COMPOSTO DE 2 PÁGINAS E FEITO EM DUPLICADO: UMA VIA PARA A INVESTIGADORA, OUTRA PARA A PESSOA QUE CONSENTE