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What we need to know about exercise, neurodegenerative disease and ageing? A Systematic Review

O que precisamos de saber sobre exercício, doenças neurodegenerativas e envelhecimento? Uma revisão sistemática

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TITULO DO ARTIGO

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TITLE PAPER

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RESUMO

Enquadramento – As doenças neurodegenerativas são caracterizadas por um conjunto de patologias crónicas e irreversíveis do sistema nervoso. Até ao momento não foram realizadas revisões de literatura que relacionem o exercício, as doença neurodegenerativas e o envelhecimento. Assim, o objetivo desta revisão sistemática foi analisar a literatura actual sobre os efeitos e associações entre o exercício físico em quatro doenças neurodegenerativas: Alzheimer, Parkinson, Huntington e Demência Vascular.

Métodos – Utilizou-se a metodología PRISMA e o desenho PICOS para a pesquisa de artigos relevantes em língua inglesa, publicados entre abril de 2016 a setembro de 2021. A pesquisa incluiu descritores relevantes para o tipo de exercício, as doenças neurodegenerativas e o envelhecimento.

Results – A pesquisa bibliográfica resultou em 5.883 artigos (WoS=1.048; PubMed=1.392 e SCOPUS=3.132); 10 artigos de texto integral foram revistos após os procedimentos de seleção. As doenças neurodegenerativas reportadas foram a doença de Alzheimer (n = 2), Huntington (n = 2), Parkinson (n = 2), e a demência vascular (n = 4).

Conclusão – Artigos revistos propunham vários mecanismos neurofisiológicos para explicar os efeitos do exercício sobre o cérebro e o sistema nervoso: (1) aumento da função neuro transmissora; (2) aumento da proteção contra os efeitos nocivos das espécies reativas oxidativas; (3) potenciar a neurogénese; (4) redireccionamento do fluxo sanguíneo cerebral; (5) aumento da produção de óxido nítrico; e (6) aumento da plasticidade cerebral.

Palavras-chave: doenças neurodegenerativas, exercício físico; atividade física; envelhecimento.

ABSTRACT

Background: Neurodegenerative diseases are characterized by a set of chronic and irreversible pathologies of the nervous system. As well as know, no literature reviews have been conducted to link exercise, neurodegenerative disease and ageing. Therefore, the aim of this systematic review was to analyse the current literature about the effects and associations amongst exercise on four neurodegenerative diseases: Alzheimer, Parkinson, Huntington and Vascular Dementia.

Methods: Following the preferred reporting item for systematic reviews and meta-analyses (PRISMA) and population-intervention-comparators-outcomes (PICOS) design, a systematic search of relevant English-language articles was performed from April 2016 to September 2021. The search included descriptors relevant to exercise mode, neurodegenerative diseases and ageing.

Results: The literature search returned 5,883 articles (WoS=1,048; PubMed=1,392 and SCOPUS=3,132); 10 full-text articles were reviewed after screening procedures. The neurodegenerative diseases reported were Alzheimer's disease (n = 2), Huntington's disease (n = 2), Parkinson's disease (n = 2), and Vascular Dementia (n = 4).

Conclusion: Reviewed articles proposed several neurophysiological mechanisms to explain the exercise effects on the brain and nervous system: (1) increased neurotransmitter function; (2) increased protection against the damaging effects of oxidative reactive Species; (3) potentiate neurogenesis; (4) redirection of cerebral blood flow; (5) increased nitric oxide production; and (6) increased brain plasticity.

Keywords: neurodegenerative diseases, physical exercise; physical activity; ageing.

INTRODUCTION

Neurodegenerative Disease is characterized by a set of pathologies which affect the basic units of the nervous system, the neurons. These diseases have common characteristics such as the fact that they are chronic and associated with progressive and irreversible cell destruction (Ropper et al., 2019). These types of diseases are generally incurable and debilitating and, due to these characteristics, patients mainly suffer from a marked loss of cognitive, motor, physiological and, consequently, social skills (Cahill, 2020; Fu et al., 2018). There are numerous neurodegenerative diseases, the most frequent being Alzheimer's disease, Parkinson's disease and Huntington's disease, which do not all affect the same region of the brain (Oddone & Imbriani, 2015). Also, vascular dementia is a cognitive and functional impairment in the cerebrovascular brain injury associated with ageing process (Aggarwal et al., 2007; Desmond, 2004; Smith, 2017). A mood and behavioural changes is observable on neurological examination in the four neurodegenerative diseases (Mendez, 2019).

According to the World Health Organization (2017), 10 million Europeans and approximately 36 million citizens worldwide suffered from some type of dementia. The same study predicts that by 2040 the incidence of neurodegenerative diseases will increase, becoming the most frequent cause of death in the elderly (Cahill, 2020). The financial costs associated with this group of diseases are very high, exceeding the cost of others, such as cancer and heart disease (Braga et al., 2018; World Health Organization, 2017). European society is increasingly ageing, both due to the increase in average life expectancy and the decrease in the birth rate. These factors are cited for the high prevalence of these diseases (Cahill, 2020; Oddone & Imbriani, 2015). Aggarwal et al. (2007) referred vascular dementia is the second most common form of dementia in the United States after Alzheimer's disease. In contrast, Schapira (1999) reported Parkinson's disease as the commonest neurodegenerative disease after Alzheimer's disease. Huntington disease also has a high prevalence in the elderly (Frese et al., 2017).

Current researches reported that benefits of aerobic exercise, combined exercise and resistance exercise in people diagnosed with neurodegenerative disease (Cahill, 2020; Fu et al., 2018). However, these studies did not focus on the associations between physical exercise mode, neurodegenerative disease and ageing. Therefore, the primary purpose of this systematic review was to analyse the current literature about the effects of exercise on four neurodegenerative diseases, specifically Alzheimer, Parkinson, Huntington and Vascular Dementia. Additionally, we aimed to verify the associations between exercise, neurodegenerative disease and ageing.

MATERIAL AND METHODS

2.1. Literature Search Strategy

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines and the population-intervention-comparators-outcomes (PICOS) design were followed to conduct this systematic review (Moher et al., 2009). The literature search was based on three databases: PubMed/Medline, Web of Science (Core Collection: Citation Indexes) and SCOPUS/ScienceDirect. The eligibility criteria were assured by a PICOS approach and the following search strategy was defined: (1) population: elders and seniors individuals; (2) intervention: current research about motor performance decline, postural control and cognitive process, exercise and cognitive function; exercise programs; (3) comparison: differences between normative and ageing values; (4) outcomes: association between exercise, neurodegenerative disease and ageing; and (5) study design: experimental/quasi-experimental cross-sectional and longitudinal trials (e.g., crossover, controlled trial and randomised controlled trial). According to the search strategy, studies April 2016 to September 2021 were included for relevant publications using keywords with a Boolean phrase (Table 1)

Table 1 – Baseline characteristics of the sample

Search Term		Keywords
Population	**1**	*("elderly" OR "older" OR "seniors" OR "ageing")*
Neurodegenerative diseases	**2**	(("Alzheimer" OR "Huntington" OR "Parkinson" OR OR "dementia" OR "Neurodegeneration"))
Exercise programs	**3**	("exercise" OR "physical activity" OR "motor activity" OR "physical fitness")
Boolean phrase	**4**	(1 AND 2 AND 3)

2.2. Selection Criteria

The included studies in the present review followed these inclusion criteria: (1) studies with screening procedures based on four neurodegenerative disease: motor performance decline (topic 1), postural control and cognitive process (topic 2), exercise and cognitive function (topic 3); exercise programs (topic 4); (2) cross-sectorial or longitudinal cohort, case-control, and/or randomized controlled trials; (3) studies in humans with Sport Science and as Scope; (4) original article published in a peer-review journal; (5) full-text available in English; and (6) article reported data collection, study design, procedures, and outcomes. The exclusion criteria were articles with bad quality screening by Downs Black checklist (Downs & Black, 1998); individuals aged ≤65 years; individuals without the diagnosis of Alzheimer's disease, Parkinson's disease, Huntington's disease and Vascular Dementia; reviews, abstract/papers conference, surveys, opinion pieces, commentaries, books, periodicals, editorials, case studies, non-peer-reviewed text, or master's/doctoral thesis.

2.3. Quality Assessment

The methodological quality was assessed using Dows and Black checklist for assessing the methodological quality of randomized and nonrandomized healthcare interventions (Downs & Black, 1998). This checklist was used in previous reviews due their accuracy in the cross-sectional and longitudinal studies (Teixeira et al., 2021a, 2021b). Each item is scored as "1" (yes) or 0" (no/unable to determine), and the scores for each item to provide the total quality score. The selection of full texts was based on a selection to determine the selection criteria: inclusion or exclusion. Dataset from the reviewed articles were organized according to: reference (year), participants (number, age and sex), experimental design, methodological tasks/instruments, statistics procedures, findings, conclusions and quality assessment (QS). Sample characterization was reported as mean ± standard deviation, CI, and effect size (ES) wherever possible.

Disagreements were resolved through discussion between two authors, or via a third researcher if required. Each author performed the classification independently with subsequent inter-observer reliability analysis: kappa index (0.93) and confidence interval (CI): 0.92–0.95). In the evaluation of methodological quality, the mean quality score was 90.14 (min: 0.65, max: 0.89).

RESULTS

The literature search returned 5,883 articles (WoS=1,048; PubMed=1,392 and SCOPUS=3,132); 10 full-text articles were reviewed after screening procedures. From the reviewed studies, motor performance decline was reported in three studies (n = 3), postural control and cognitive process in three studies (n = 3), exercise and cognitive function in three studies (n = 3), and exercise programs were explained in three studies (n = 1). The neurodegenerative diseases were Alzheimer's disease (n = 2), Huntington's disease (n = 2), Parkinson's disease (n = 2), and Vascular Dementia (n = 4) (Figure 1).

The reviewed articles were published between 2016–21 The present review analysed a total of 2 624 participants (min: 22, max: 1 635). Table 1 showed the main findings by the studies included in this review. Four neurodegenerative diseases were reported (Table 1).

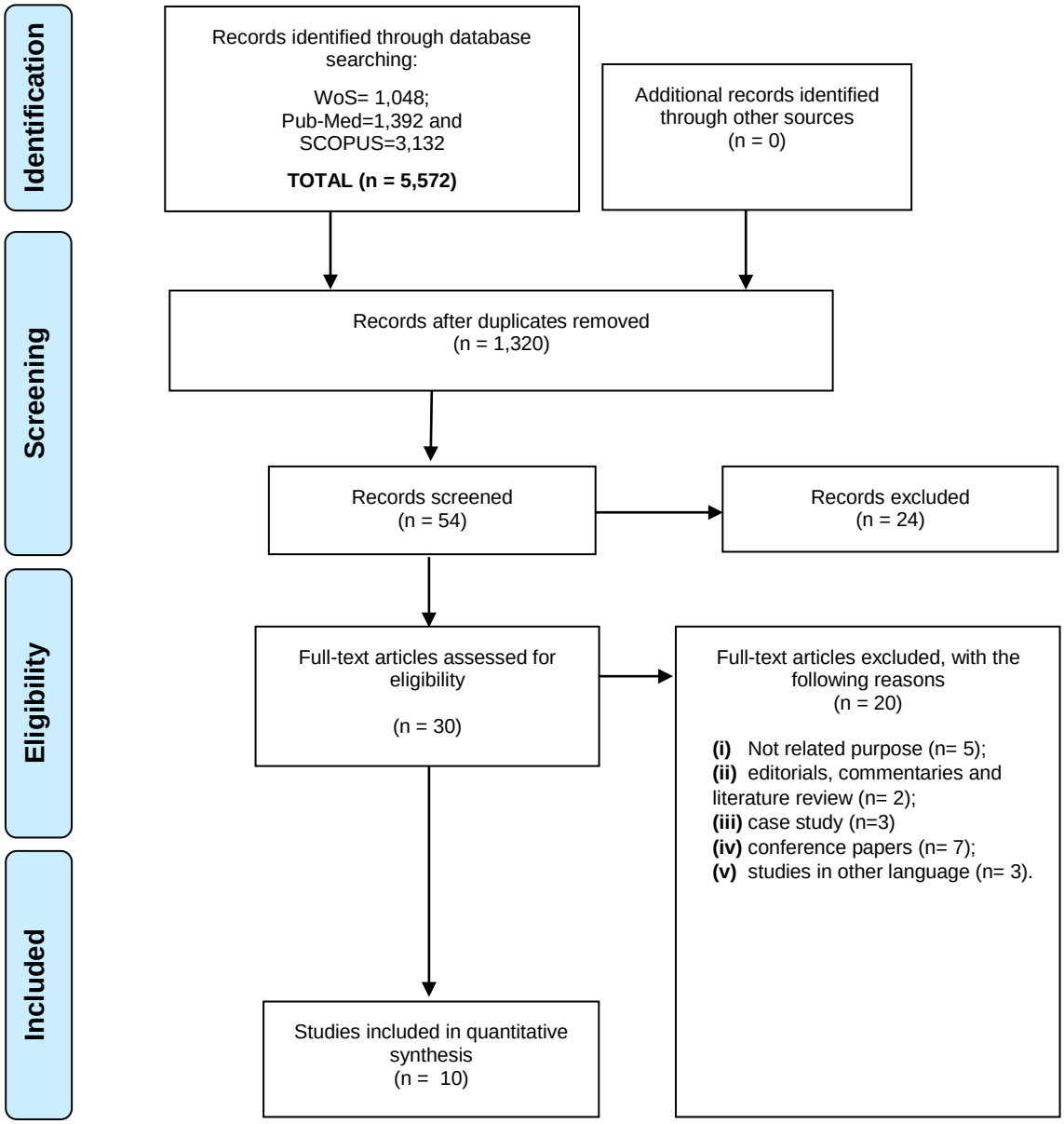

Figure 1 - PRISMA flow diagram

Table 2- Summary sampling representativeness, methodological procedures, outcomes and quality assessment about reviwed articles.

Pathology	Definition	References
Alzheimer's disease (AD)	Alzheimer's disease is a progressive, neurodegenerative disease that represents a growing global health crisis. Two major forms of the disease exist: early onset (familial) and late onset (sporadic). Early onset Alzheimer's is rare, accounting for less than 5% of disease burden. It is inherited in Mendelian dominant fashion and is caused by mutations in three genes (APP, PSEN1, and PSEN2). Late onset Alzheimer's is common among individuals over 65 years of age. Heritability of this form of the disease is high (79%), but the ethology is driven by a combination of genetic and environmental factors. A large number of genes have been implicated in the development of late onset Alzheimer's	(Borges et al., 2018; Bossers et al., 2015 ; Guadagni et al., 2020 ; Hauer et al., 2012 ; Mendez, 2019)
Huntington's disease (HD)	Huntington disease is a relentlessly progressive neurodegenerative disorder with symptoms across a wide range of neurological domains, including cognitive and motor dysfunction. There is still no causative treatment for HD but environmental factors such as passive lifestyle may modulate disease onset and progression.	(Ferraz et al., 2018; Frese et al., 2017; Mason & Barker, 2009; Wild et al., 2013)
Parkinson's disease (PD)	Parkinson's disease is the commonest neurodegenerative disease after Alzheimer's disease, with an estimated incidence of 20/100 000 and a prevalence of 150/100 000. It is characterised clinically by asymmetric onset of bradykinesia, rigidity, and, usually, resting tremor. The cause of the most common clinical features is the death of dopaminergic neurones in the substantia nigra of the midbrain. Lewy bodies are present in a proportion of surviving neurones. At the pathological level there is overlap with other neurodegenerative disorders including Alzheimer's disease, and this has been used to support the view that these diseases may share some common pathogenetic mechanisms.	(Frese et al., 2017; Quinn et al., 2016 ; Schapira, 1999)
Vascular Dementia (VD)	Vascular dementia is a term used to describe a constellation of cognitive and functional impairment that can be viewed as a subset of the larger syndrome of vascular cognitive impairment associated with cerebrovascular brain injury. Vascular dementia is a common disorder among the elderly, although it can also occur in younger persons. Comprising 20% of all cases of dementia in the United States, vascular dementia is the second most common form of dementia after Alzheimer's disease. Patients with vascular dementia often exhibit mood and behavioral changes and may have focal neurological signs on neurological examination.	(Desmond, 2004; Hansson et al., 2018; Sampaio et al., 2019; Smith, 2017; Aggarwal et al., 2007)

AD – Alzheimer's disease; HD – Huntington's disease; PD – Parkinson's disease; VD –Vascular Dementia;

Reference (y)	Participants	Experimental Approach	Aims	Tasks/Instruments Statistical Analysis	Findings	Conclusions
Borges et al. (2018)	Older adult sample (67.0 ± 7.29 years): control group (n=30); experimental group (n=30).	Simple randomized clinical	To evaluate the postural balance, cognition and functional autonomy of older adults with dementia, who are long-stay inpatients, subjected to ballroom dancing.	Ballroom dance program consisted of 50-minute sessions (three times a week, on alternate days, for a period of 12 weeks). Protocol of functional autonomy for activities of daily living to the: - **assessment cognition**: mini-mental state examination; - **analysis of postural balance**: stabilometric and postural platforms.	Mini-mental state examination, the control group presented a 24.27 mean, and the experimental 22.75. Functional autonomy for activities of daily living - experimental: 54.47 ± 7.24 ($p < 0.0001$) x control: 61.77 ± 8.47 ($p = 0.011$). Postural balance - experimental: X = 3.16 ± 3.44 ($p = 0.02$) x control X = 6.30 ± 7.62 ($p = 0.04$).	Ballroom dancing can be recommended for older adults to provide improvement in their balance and motor performance of the activities of daily living.
Bossers et al. (2015)	109 patients with dementia (age 85.5 ± 5.1 years), Combined gp (n=37) Aerobic gp (n=37) Social gp (n = 36)	Randomized controlled trial	To compare training effects of combined aerobic and strength training versus aerobic-only training on cognitive and motor function in institutionalized patients with dementia. To explore whether improved motor function mediates improved cognitive function.	Using a 9-week, parallel, three-group, single-blind, randomized, controlled trial with a follow-up assessment at week 18. Each 9-week intervention consisted of 36, 30-minute sessions. -**Combined group** received and completed two strength and two walking sessions per week; - **Aerobic group** completed four walking sessions; **Social group** completed four social visits per week.	Baseline corrected post-test scores in the combined versus the social group were higher for global cognition, visual memory, verbal memory, executive function, walking endurance, leg muscle strength, and balance. Aerobic versus social group scores were higher for executive function. Follow-up effects reversed toward baseline values. Motor improvement did not significantly mediate cognitive improvement.	Compared with a non-exercise control group, a combination of aerobic and strength training is more effective than aerobic-only training in slowing cognitive and motor decline in patients with dementia. No mediating effects between improvements in cognitive function via improved motor function were found. Future research into the underlying mechanistic associations is needed.
Ferraz et al. (2018)	Elderly individuals (≥ 60 years of age; n=62) with idiopathic PD .	Randomized controlled trial	To compare the effects of functional training, bicycle exercise, and exergaming on walking capacity of elderly with PD.	The primary outcome measure was the 6-minute walk test (6MWT); secondary outcome measures were the 10-m walk test (10MWT), sitting-rising test (SRT), body mass index, PD Questionnaire-39, WHODAS 2.0, and 15-item Geriatric Depression Scale. - **Functional training group** (n=22); **bicycle exercise group** (n=20), **Kinect Adventures group** (Microsoft, Redmond, WA) (n=20).	All groups showed significant improvements in 6MWT (G1 p=0.008; G2 p=0.001; G3 p=0.005), SRT (G1 $p < 0.001$; G2 $p = 0.001$; G3 p=0.003), and WHODAS 2.0 (G1 PZ.018; G2 PZ.019; G3 PZ.041). Only G3 improved gait speed in 10MWT ($p = 0.11$). G1 ($p = 0.014$) and G3 (p=0.004) improved quality of life. No difference was found between groups.	Eight weeks of exergaming can improve the walking capacity of elderly patients with PD. Exergame training had similar outcomes compared with functional training and bicycle exercise. The three physical exercise modalities presented significant improvements on walking capacity, ability to stand up and sit, and functionality of the participants.
Frese et al. (2017)	Twelve male HD patients (mean ± SD, 54.8 ± 7.1 years) and twelve male controls (49.1 ± 6.8 years)	Randomized controlled trial	To investigate whether endurance training (ET) stabilizes the progression of motor and cognitive dysfunction and ameliorates cardiovascular function in HD patients.	6 weeks of endurance training. Before and after the training intervention, clinical assessments, exercise physiological tests, and a body composition measurement were conducted. To examine the natural course of the disease, HD patients were additionally assessed	During the ET period, there was a motor deficit stabilization as indicated by the Unified Huntington's Disease Rating Scale motor section score in HD patients (baseline: 18.6 ± 9.2, pre-training: 26.0 ± 13.7, post-training: 26.8 ± 16.4). Peak oxygen uptake (VO_2peak) significantly increased in HD patients (ΔVO_2peak = 0.33 ± 0.28) and controls	This study confirm that HD patients are amenable to a specific exercise-induced therapeutic strategy indicated by an increased cardiovascular function and a stabilization of motor function.

				6 months prior to ET.	(ΔVO_2peak = 0.29 ± 0.41).	
Guadagni et al., (2020)	206 healthy low-active middle-aged and older adults (mean ± SD age 65.9 ± 6.4 years)	Randomized controlled trial	To test the hypothesis that aerobic exercise is associated with improvements in cognition and cerebrovascular regulation.	Supervised 6-month aerobic exercise intervention and assessed them before and after the intervention. Neuropsychological tests were used to assess cognition before and after the intervention. Transcranial Doppler ultrasound was used to measure cerebral blood flow velocity. Cerebrovascular regulation was assessed at rest, during euoxic hypercapnia, and in response to submaximal exercise.	The intervention was associated with improvements in some cognitive domains, cardiorespiratory fitness, and cerebrovascular regulation. Changes in executive functions were negatively associated with changes in cerebrovascular resistance index (CVRi) during submaximal exercise (β = -0.205, p = 0.013), while fluency improvements were positively associated with changes in CVRi during hypercapnia (β = 0.106, p = 0.03).	The 6-month aerobic exercise intervention was associated with improvements in some cognitive domains and cerebrovascular regulation. Secondary analyses showed a novel association between changes in cognition and changes in cerebrovascular regulation during euoxic hypercapnia and in response to submaximal exercise.
Hansson et al. (2019)	Community dwelling dyads (n = 210) of individuals with AD	Randomized controlled trial	To examine whether a regular, long-term exercise program performed by individuals with AD at home or as group-based exercise at an adult day care center has beneficial effects on cognition.	Two types of intervention comprising customized home-based exercise (HE) and group-based exercise (GE), each twice a week for 1 year, were compared with a control group (CG) receiving usual community care. Cognitive function was measured using the Clock Drawing Test (CDT), Verbal Fluency (VF), Clinical Dementia Rating (CDR), and Mini-Mental State Examination (MMSE) at baseline and 3, 6, and 12 months of follow-up.	Executive function, measured using CDT, improved in the HE group, and changes in the score were significantly better than those of the CG at 12 months (adjusted for age, sex, and CDR, P = .03). All groups deteriorated in VF and MMSE score during the intervention, and no significant differences between the groups were detected at 12-month follow-up when analyses were adjusted for age, sex, and CDR.	Regular, long-term, customized HE improved the executive function of community-dwelling older people with memory disorders, but the effects were mild and were not observed in other domains of cognition.
Hauer et al. (2012)	Older with dementia (82.0 ± 6.5 years): - intervention(n=62); - control (n=60).	Randomized controlled trial	To determine whether a specific, standardized training regimen can improve muscle strength and physical functioning in people with dementia.	Supervised, progressive resistance and functional group training for 3-month intervention and 3-month follow-up: - one-repetition maximum in a leg press device for **maximal strength**; - five-chair-stand test for **functional performance**.	Training significantly improved both primary outcomes (percentage change from baseline: maximal strength, intervention group (IG): +51.5 ± 41.5 kg vs control group (CG): -1.0 ± 28.9 kg, P < .001; functional performance, IG: -25.9 ± 15.1 seconds vs CG: +11.3 ± 60.4 seconds, P < .001). Physical activity increased significantly during the intervention (P < .001).	The intensive, dementia-adjusted training was feasible and substantially improved motor performance in frail older people with dementia and may represent a model for structured rehabilitation or outpatient training.

Wild et al. (2013)	Eighteen patients with PD (ages 53-88, 10 women; Hoehn and Yahr stage I-II) and 18 older adults (ages 61-84; 10 women)	Observational cohort	To investigate the effect of dual-tasking on cognitive performance and gait parameters in patients with idiopathic Parkinson's disease (PD) without dementia. The impact of cognitive task complexity on cognition and walking was also examined	Two neuropsychological measures of **executive function/attention** (the Stroop Test and Wisconsin Card Sorting Test). Cognitive performance and gait parameters related to functional mobility of stride were measured under single (cognitive task only) and dual-task (cognitive task during walking) conditions.	Gait parameters of patients differed significantly from controls at single and dual-task conditions, indicating that patients gave priority to gait while cognitive performance suffered. Dual-task cognitive costs of patients increased with task complexity, reaching significantly higher values then controls in the arithmetic task, which was correlated with scores on executive function/attention (Stroop Color-Word Page).	Baseline motor functioning and task executive/attentional load affect the performance of cognitive tasks of PD patients while walking. These findings provide insight into the functional strategies used by PD patients in the initial phases of the disease to manage dual-task interference.
Quinn et al. (2016)	314 adults were assessed for eligibility: 248 did not meet inclusion criteria, 34 declined, and 32 were recruited and randomized.	Randomized controlled trial	This study aimed to evaluate the feasibility and benefit of a structured exercise intervention in people with Huntington's Disease (HD).	This study was conducted at 6 sites, and participants were randomized into either exercise or control (usual care) groups, and were assessed at baseline, 13 and 26 weeks. The intervention was a 12 week, three times per week progressive exercise program, including aerobic (stationary cycling) and upper and lower body strengthening exercise with tapered 1:1 support for 20 of 36 sessions.	The intervention group had better fitness (predicted VO_2max difference: 492.3 ml min^{-1}, 95% CI: [97.1, 887.6]), lower UHDRS mMS (difference 2.9 points, 95% [-5.42, -0.32]) and lower weight at Week 13 (difference 2.25 kg, 95% CI: [-4.47, -0.03]).	This study demonstrates that a short term exercise intervention is safe and feasible. Individuals with HD may benefit from structured exercise, and intensity, monitoring and support may be key factors in optimizing response. Larger scale trials are now required to fully elucidate the extended clinical potential of exercise in HD.
Sampaio et al. (2019)	Thirty-seven institutionalized elders (84.05 ± 5.58 years) clinically diagnosed with AD (mild and moderate stages) were divided into two groups: Experimental Group (EG, n = 19); - Control Group (CG, n = 18)	Randomized controlled trial	This study examined the effect of a Multicomponent Training (MT) intervention on cognitive function, functional fitness and anthropometric variables in institutionalized patients with Alzheimer's disease (AD).	The EG participated in a 6-month supervised MT program (aerobic, muscular resistance, flexibility and postural exercises) of 45–55 minutes/session, twice/week. Cognitive function (MMSE), physical fitness (Senior Fitness Test) and anthropometric variables (Body Mass Index and Waist Circumference), were assessed before (M1), after three months (M2) and after six months (M3) of the experimental protocol.	A two-way ANOVA, with repeated measures, revealed significant group and time interactions on cognitive function, chair stand, arm curl, 2-min step, 8-foot up-and-go (UG), chair sit-and-reach (CSR) and back scratch tests as well as waist circumference. Accordingly, for those variables a different response in each group was evident over the time, supported by a significantly better EG performance in chair stand, arm curl, 2-min step, UG, CSR and back scratch tests from M1 to M3, and a significant increase in MMSE from M1 to M2. The CG's performance decreased over time (M1 to M3) in chair stand, arm curl, 2-min step, UG, CSR, back scratch and MMSE.	Results suggest that MT programs may be an important non-pharmacological strategy to improve physical and cognitive functions in institutionalized AD patients.

10MWT – 10-m walk test; 6MWT – 6-minute walk test; AD – Alzheimer's disease; CDR –Clinical Dementia Rating; CDT – Clock Drawing Test; CG – control group; CSR – chair sit-and-reach; ET – endurance training; GE – group-based exercise; HD – Huntington's disease; HE – home-based exercise; IG – intervention group; MMSE – Mini-Mental State Examination; MT – Multicomponent Training; PD – Parkinson's disease; SRT – sitting-rising test; UG – foot up-and-go; VD –Vascular Dementia; VF – Verbal Fluency; VO_2 – maximum oxygen update; WHODAS 2.0 – World Health Organization Disability Assessment Schedule 2.0; ΔVO_2peak – interval of maximum oxygen update.

DISCUSSION

Neurodegenerative diseases are progressive disorders that affect the central nervous system and worsen gradually (Wild et al., 2013). Increasing evidence shows that syndrome is interrelated with many neurodegenerative diseases, such as Alzheimer's, Parkinson's and Huntington's (Ferraz et al., 2018; Hansson et al., 2019; Quinn et al., 2016). Although some results are inconsistent or not replicable in the literature, the targeting of metabolic syndrome is still critical, since dysfunctional metabolism is associated with all neurodegenerative diseases (Ferraz et al., 2018; Guadagni et al., 2020).

Most genetic causes of neurodegenerative diseases in are due to neurometabolic disorders. There are over 200 disorders, including aminoacidopathies, creatine disorders, mitochondrial cytopathies, peroxisomal disorders and lysosomal storage disorders (Wild et al., 2013). There are several ways in which neurometabolic disorders can be classified such as; pathophysiology, age of onset and disease progression whether acute or chronic (Sampaio et al., 2019). Diagnosis of neurometabolic disorders is challenging as the neurological features may not be very distinctive (Teixeira et al., 2021a). In addition, some neurometabolic disorders progress very slowly and therefore may be recognised as cerebral palsy or isolated developmental delay (Hansson et al., 2019; Sampaio et al., 2019). An observational cohort was included in this systematic review, reporting two neuropsychological measures of executive function/attention (the Stroop Test and Wisconsin Card Sorting Test) in under single (cognitive task only) and dual-task (cognitive task during walking) conditions (Wild et al., 2013). The article respected the inclusion and exclusion criteria for the design of the review, however comparisons with randomized controlled trials should be observed with caution. Nevertheless, the methodological quality of the included studies was very high (mean quality score was 90.14) with a high level of evidence as randomized controlled trials (n=9). Of those, one was a simple controlled trial design

Studies suggest that physical activity reduces the risk of dementia and Alzheimer's disease by 28% and 45% respectively. For example, Ferraz et al. (2018) showed a linear reduction in the risk of dementia with increasing daily walking distance. Data from the Nurse's Health Study showed that walking for a minimum of 1.5 h per week is associated with better cognitive performance (Wild et al., 2013). The Parkinson's Disease status remained the same, showing no progression of the disease (Hauer et al., 2012). However, psychosocial and external factors seem to directly influence the stability and maintenance of motor and cognitive gains, as well as quality of life (Borges et al., 2018; Bossers et al., 2015). Thus, physiotherapy can be an important ally to delay the progression of the disease in all stages (Frese et al, 2017; Hauer et al., 2012).

This systematic review presented some limitations that should be considered as: (i) the terminology used in the literature varies greatly between authors; and (iii) methodological constraints about screening procedures; (iv) smallest study samples represented a limitation for external validity of the data collection; (v) only full-text articles available in English; this was a language limitation in the literature search strategy. Future systematic reviews must also include a meta-analysis approaches and a wider range of publication languages. Also, neurodegenerative disease should be further evaluated by integrating a more extensive literature review.

CONCLUSIONS

main conclusion of this systematic review was focused on the several neurophysiological mechanisms proposed for the effect of exercise on the brain, and the most studied are: (1) increased neurotransmitter function; (2) increased protection against the damaging effects of oxidative reactive Species; (3) potentiate neurogenesis; (4) redirection of cerebral blood flow; (5) increased nitric oxide production; and (6) increased brain plasticity.

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