Physical Activity and Dementia

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Physical activity (PA) has emerged as an alternative nonpharmacological approach to effectively address the effects of dementia. This is mainly because regular PA improves the strength of cells and tissues to respond to oxidative stress, vascularization, and energy metabolism and also allows neurotropic effects through neurotrophic factor (BDNF) concentrations, which contribute to brain plasticity, memory improvement, neurogenesis, and synaptic plasticity [15]. These processes attenuate for the loss of brain tissue while the brain is ageing [14].

Keywords: physical activity ; cognitive function ; dementia

1. Introduction

Recent findings indicate that the population has been rapidly ageing during the last century due to improvements in health care, increase in life expectancy, and decrease in fertility rates [1]. As people age, body organs, tissues, and cells undergo change. Histological studies have shown that ageing affects the central nervous system (CNS) since it experiences neuroanatomical alterations, including an overall reduction in brain activity [2][3]. Therefore, changes and damage in the CNS are worrisome, due to its decisive role in controlling and coordinating essential functions of the body, including cognitive functions [4]. The physiological characteristics of dementia, an umbrella term for multiple neurodegenerative diseases [5], has been linked to the severe degeneration of brain cells and synapses in certain areas of the CNS, including the temporal, parietal and frontal cortices [6]. Damage in these areas manifests itself through memory and learning deficits [6]. In addition, dementia affects emotional regulation, social functioning, and activities of daily living [5].

The causes of dementia onset are not fully understood, but notably, the mechanism underlying dementia is associated with abnormal protein deposits that coexist with neurovasculature at different stages of the disease, which affect the functioning of the brain [7]. Depending on the type of dementia, different protein accumulations are observed. For instance, alpha-synuclein protein is linked to Lewy body dementia, whereas beta-amyloid and tau proteins are both related to Alzheimer's disease (AD), the most common form of dementia. Inadequate blood flow can lead to vascular dementia [7]. Other non-modifiable factors linked to dementia include age, sex, inflammation, and comorbidity, and genetic, environmental, and lifestyle factors [8]. Particularly in recent years, substantial epidemiological studies have provided evidence for lifestyle-related risk factors that trigger the development of dementia [9][10][11]. In light of this, the Lancet Commission presented a model describing nine modifiable risk factors (e.g., physical inactivity) that may contribute as much as 35% to the risk of dementia across the lifespan. Thus, by modifying these risk factors, one has a higher chance of preventing or delaying dementia progression [12].

In this way, PA plays a crucial role in the healthcare system. Including preventive and care strategies for dementia that promote resilience and healthy lifestyles, such as PA, may delay the onset and progression of dementia [12]. PA is understood "as any bodily movement produced by skeletal muscles that require energy expenditure above and beyond resting energy expenditure (one metabolic equivalent = 1 MET) and it can be undertaken in many different ways: walking, cycling, sports and active forms of recreation" [13]. Additionally, PA can be classified into different intensity levels: light (1.6–2.9 MET), moderate (3–5.9 MET) and vigorous (≥6 MET), each of which are based on the subjective intensity perception of an individual. Thus, this classification denotes, through MET values, the energy expenditure and/or the amount of oxygen consumed while sitting or performing a PA [14].

Although the positive effects of exercise on cognition in older adults have been researched, the influence of PA on cognitive function of PwD is still not well understood [15]. Scientific intervention studies have emerged to provide evidence for the efficacy of PA as a cognitive reserve-enhancing factor and to assess its potential in delaying cognitive decline in PwD. In two recent meta-analyses, [16][17] considering evidence up to 2018, one showed that 13 RCTs with 673 subjects diagnosed with AD presented statistically significant improvements in cognition after participating in PA interventions (SMD = 1.12 CI: 0.66~1.59) [16]. The second meta-analysis [17] involved 13 RCTs with 659 subjects with AD and reported that PA had a positive effect on cognitive function among persons with AD (p = 0.003). Overall, previous reviews have reported that PA might positively affect the cognition of PwD given its potential to delay cognitive impairment. However, these studies revealed inconclusive results associated with methodological issues and heterogeneity. Such conclusions are in line with other reviews published in recent years [18][19].

Therefore, in order to obtain more conclusive results, multiple reviews [16][17][18][19][20] have emphasized that new trials should address methodological barriers by including larger sample sizes [16][17][18][19] and other strategies as follows: providing standardized intervention characteristics [16][19]; providing more information about randomization processes, blinding, attrition rates, and adverse events [20]; conducting different measurements throughout the intervention period [18]; implementing long-term follow-up measures [16][17][18]; using improved and more sensitive cognitive measures [18]; targeting the type of the disease [19]; targeting stage of the disease [17]; separately assessing subjects with Alzheimer's disease and vascular dementia [19]; including different types of PA [18]; and ensuring that the control group does not perform the same amount of PA as the experimental group [18].

2. Physical Activity Interventions in People with Dementia

Overall, the meta-analysis found that PA interventions had a medium-size effect on the cognitive function of PwD. This indicates general positive effects of PA on cognition in PwD. However, the included trials presented a high percentage of heterogeneity (I^2 = 86%, $p \leq 0.0001$) as they showed differences in the number of participants, intervention settings, cognitive measurement tools, follow-up periods, PA dose-responses, and reported outcomes. Therefore, these differences between the studies' methodologies limited the possibility of solid conclusions about the effects of PA on the cognition of PwD. These findings were consistent with a review by Forbes et al. [20], which showed considerable heterogeneity (I^2 value 80%) and thus inconclusive results.

Even though these results resemble those obtained by Forbes et al. [20], if we look at the newly added trials implemented in recent years, a slight difference is revealed. In particular, six recent trials [21][22][23][24][25][26] showed more powerful designs since they included larger sample sizes. In this way, this finding enables us to see small developments and progress in this particular field of research, including more solid methodological designs and higher statistical power in the most recent studies. Therefore, the results presented in these trials might lead to more precise conclusions about the effects of PA on the cognition of PwD.

Various features of PA interventions could play a crucial role in mediating the effects of PA on cognition, such as PA modalities, dose responses, and intensity. Based on the type of exercise and intensity, changes in the brain's structure have been obtained [27].

For instance, interventions implemented three types of *PA modalities*: (1) only PA training (cardiovascular or strengthening), (2) combined PA training (cardiovascular and strengthening), and (3) combined PA with cognitive training. According to Bossers et al. [28], combining aerobic PA with resistant training led to improvements in executive functions and memory functions. Thus, the study recommended combining both modalities to stimulate cognitive improvements in both. Öhman et al. [29] attributed improvements in executive functions to dual-tasking (e.g., talking while walking, singing while dancing) and other combined PAs performed at home (strength, balance, and endurance exercises). This study suggested that combined training may enhance the frontal lobe, which is the brain area in charge of executive functions. These results are consistent with one systematic review implemented by Lauenroth et al. [30], who claimed that multimodal PA interventions that consider cardiovascular training combined with resistance training and cognitive tasks resulted in better and more significant outcomes than individual PA training. Moreover, this type of intervention has contributed to improving frontal cognitive functions, global cognition, working memory, episodic memory, executive function, and processing speed [31].

Additionally, studies presented variations in their *PA dose responses*. Their session durations ranged between fifteen and one hundred and twenty minutes; their frequency per week fluctuated between two and seven times, and their total length took between less than three months and longer than twelve months. Particularly, studies in which longer periods of PA were undertaken were more likely to display positive effects. For example, Öhmann et al. [26] implemented a 12-month PA program, which led to positive effects on executive functions among community-dwelling PwD. Moreover, Hoffmann et al. [25] affirmed that PA seems to affect executive function (mental speed and attention) when implemented for at least six months. In the same way, Toot et al. [22] confirmed that for cognition effects, the interventions' duration seems to play a decisive role. Thus, a four-month program was not enough time to induce cognitive changes. Likewise, Kassermeijer et al. [21] did not show significant effects due to exergaming training. According to the authors, a possible explanation for these results was that people probably needed more time to master the challenges from this type of program, and this RCT implemented a short intervention period of 12 weeks. These results were aligned with one meta-analysis outcome [32] and with one study, which proved that six to twelve months of PA increased cognitive scores and affected brain structure [27].

Regarding *PA intensities* of trial interventions, the majority implemented moderate, followed by light and vigorous PA intensities. However, there is no consensus among studies as to which intensity level might be ideal. Karssemeijer et al. [21] stated no significant effects on executive functions, working memory or episodic memory after implementing a light intensity combined cognitive and PA intervention among community-dwelling persons with mild dementia. In contrast, The Dementia and PA trial [23], which had the largest sample size of the included studies, applied a moderate-to-high intensity PA program; however, these PA intensities also did not result in positive outcomes. Thus, Lamb et al. [23] specified that an exercise program of moderate-to-high intensity improved physical fitness but did not slow cognitive deterioration. Furthermore, participants who took part in the PA arm and had a high intervention attendance displayed worse cognitive decline than the control group. Therefore, according to these authors, there is a possibility that PA may have worsened cognitive impairment. In particular, these negative effects were associated with inflammation and inadequate oxygen supply to certain cortical areas. In this way, this study suggested that high-intensity aerobic and strength exercise should not be used as a method for addressing cognitive deterioration, and future research should examine other forms of PA among dementia patients. Likewise, Toots et al. [22] indicated that high-intensity training did not result in significant differences in global cognition or executive functions. These results are in line with one systematic review [32] that specified that PwD are fragile patients, and excessive and vigorous intensities of PA should be avoided to prevent other health complications. Moreover, monitoring a steady heart rate of 60% of the maximum heart rate might prevent excess complications and burden among patients. In addition, this range might be enough to activate neurobiological responses that benefit the brain functioning of PwD [32]. Further research is needed to clarify the role of intensity in mediating PA effects.

Another relevant aspect for effective PA interventions described in trials was *PA engagement and adherence to* programs due to high numbers of withdrawals in the trials. Thus, studies stated that bad adherence to their program was associated with a lack of motivation [33][34], low emphasis on PA in geriatric facilities, and a lack of knowledge regarding the benefits of PA [30]. Moreover, a high number of persons declined to participate in one study due to a lack of attractiveness of PA, particularly women [23]. Furthermore, one RCT stated that only one specific segment of institutionalized patients joined the study because they were already motivated to perform PA [24]. A current review showed that for healthy adults aged 80 years and older, it was necessary to initiate and adhere to PA to identify its health benefits, overcome physical-activity-associated fear, recognize and prioritize individual PA preferences, receive social support, and minimize environmental barriers [35]. However, considering that PwD present low functional activity and cognitive functioning, it is probable that variables mediating their PA engagement are different compared to those reported by healthy adults [36]. Recent literature lacks evidence on PA participation and adherence-related factors in PwD [37].

Thus, it can be observed that different factors, such as *PA modalities*, *dose responses*, *intensities*, and *engagement and adherence*, play an important role in facilitating effects on cognition in PwD. However, due to the variety of methodologies, contents and results reported in the included studies, the effects of PA on the cognition of PwD remain unclear. Additional evidence is needed, particularly concerning ideal PA modalities, dose-response intensity, and adherence.

3. Conclusions

The evidence for the benefits of PA for PwD remains unclear. Furthermore, the selected studies contained stronger methodological aspects compared to reviews conducted in previous years. In addition, considering that certain prerequisites may affect PA programs, further research is needed. In particular, ideal PA modalities, duration, adherence to interventions, and exercise intensity monitoring should be considered.

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