Review article

Impact of physical activity on cognitive function of older adults with mild cognitive impairment

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Impacto del ejercicio físico en las funciones cognitivas de adultos mayores con deterioro cognitivo leve

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Abstract
Aging is associated with changes that can affect cognitive functions. Mild cognitive impairment is recognized as an intermediate state between normal aging and dementia. The latter is a multifactorial condition related to metabolic, vascular, neurological, and inflammatory factors, such as hypertension, diabetes, dyslipidemia, obesity, or Parkinson's disease. Its progression compromises autonomy, increases care costs, and generates a significant burden for the family and the health system, which requires preventive strategies. A search was performed in PubMed, Hinari, Scielo, Google Scholar, and EBSCO, using Boolean operators and keywords such as "cognitive dysfunction", "cognition", "physical exercise", and "aging". We included literature review articles, systematic reviews with meta-analysis, and case-control studies, published in English, Spanish, and Portuguese between 2020 and 2024. The objective of this review was to identify the influence of physical exercise on cognition in older adults with mild cognitive impairment. The findings show that physical exercise constitutes a promising non-pharmacological alternative, with heterogeneous effects on different cognitive functions. Although improvement is reported in certain domains, there is still a need for comparative studies that integrate comorbidities and other interventions to establish more solid conclusion.

Keywords
Cognitive Dysfunction, Aging, Cognition, Exercise.

Resumen
El envejecimiento se asocia con cambios que pueden afectar las funciones cognitivas. El deterioro cognitivo leve se reconoce como un estado intermedio entre el envejecimiento normal y la demencia. Esta última es una condición multifactorial relacionada con factores metabólicos, vasculares, neurológicos e inflamatorios, como hipertensión, diabetes, dislipidemia, obesidad o enfermedad de Parkinson. Su progresión compromete la autonomía, incrementa los costos de atención y genera una carga significativa para la familia y el sistema de salud, lo que exige estrategias preventivas. Se realizó una búsqueda en PubMed, Hinari, Scielo, Google Académico y EBSCO, se utilizaron operadores booleanos y palabras clave como «disfunción cognitiva», «cognición», «ejercicio físico» y «envejecimiento». Se incluyeron artículos de revisión bibliográfica, revisiones sistemáticas con metaanálisis, y estudios de casos y controles, publicados en inglés, español y portugués entre 2020 y 2024. El objetivo de esta revisión fue identificar la influencia del ejercicio físico en la cognición de adultos mayores con deterioro cognitivo leve. Los hallazgos muestran que el ejercicio físico constituye una alternativa no farmacológica prometedora, con efectos heterogéneos en distintas funciones cognitivas. Aunque se reporta mejoría en ciertos dominios, persiste la necesidad de estudios comparativos que integren comorbilidades y otras intervenciones para establecer conclusiones más sólidas.

Palabras clave
Disfunción Cognitiva, Cognición, Envejecimiento, Ejercicio Físico.

Introduction

Mild cognitive impairment (MCI) is an entity that has been recognized as a transitional state between normal and expected cognitive function in the elderly population and dementia.[i] MCI is defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) as a minor neurocognitive disorder and must include evidence of moderate cognitive impairment compared to the previous state in one or more domains, based on concern by the individual themselves, a known informant, or the clinician, and that this moderate impairment can be evidenced in a standardized neuropsychological test. In addition, it must include that this impairment does not affect the person's activities of daily living and does not occur simultaneously with a confusional syndrome or other mental disorder.[ii]

The onset of MCI is divided into three age groups: early onset (<65 years), average onset (65-75 years), and late onset (>75 years), age has shown to be an important factor in the onset of MCI, with a higher prevalence in adults over 75 years of age,[iii] an age group that includes the "fourth age," a term referring to those 80 years of age or older.[iv]

MCI encompasses the deterioration of cognitive functions such as memory, orientation, language, thinking, sensory perception, affect, judgment, reasoning, gnosis, and praxis, leading to increased care efforts for families and society.[v] The World Health Organization defines dementia as "the result of various diseases and injuries that affect the brain." In 2021, it was estimated that the number of people living with dementia reached 57 million worldwide, with more than 60 % living in low- and middle-income countries.[vi]

The risk of MCI progressing to established dementia in people over 65 is 14.5 % in the two years following diagnosis.[vii] This is one of the leading causes of death and one of the major causes of dependency and disability in older adults.[viii]

The Global Burden of Disease Study has reported that in 2019, there were approximately 57.4 million people worldwide with dementia, and they estimate that there will be more than 152 million in 2050.[ix] These figures are similar to those in the 2015 World Alzheimer's Report, which stated that more than 46 million people live with dementia, and that this figure will almost double every 20 years, reaching 75 million in 2030 and 131.5 million in 2050.[x] Therefore, it is necessary to seek strategies for the prevention of MCI and to prevent dementia from progressing.

In recent years, the population pyramid has inverted due to increased life expectancy, leading to a rise in the elderly population. Therefore, public health must identify and implement timely therapies in patients with probable MCI to improve symptoms and modify the progression of the disease.

Because MCI is a multifactorial disease, there is no specific pharmacological treatment or intervention that can modify MCI. Therefore, management must be multimodal, including symptomatic pharmacological treatment, changes in nutrition, and lifestyle modifications, taking into account physical, social, and mental activity.[xi]

Physical exercise interventions are effective in improving cognitive function in older adults, regardless of their initial cognitive status. Both aerobic and anaerobic physical exercise improve cognitive function in adults over 50 years of age.[xii]

For this review, we conducted a search in PubMed, Hinari, SciELO, Google Scholar, and EBSCO databases. Boolean operators "AND" and "OR" were used, and keywords such as "cognitive dysfunction," "cognition," "physical exercise," and "aging" were included. We included articles from literature reviews, systematic reviews with meta-analyses, and case-control studies in English, Spanish, and Portuguese published between 2020 and 2024. The purpose of this narrative review was to identify the influence of physical exercise on the cognitive functions of older adults with mild cognitive impairment.

Discussion

Mild cognitive impairment and its associated symptoms

The brain is composed of four main lobes: the frontal lobe (motor function, language [Broca's area], and cognitive functions), the parietal lobe (interpretation of vision, hearing, motor, sensory, and memory functions), temporal lobe (part of the social brain, it is in this area that information from retained memories and emotions is processed, in addition to containing Wernicke's area), and occipital lobe (the visual cortex that interprets visual information).[xiii]

Different brain structures are related to the memory process, among which the hippocampus stands out as being responsible for consolidating memory (working and episodic memory), the amygdala adds emotional components to memory (pain, fear, pleasure), which allows to differentiate between positive and negative memories, and the prefrontal cortex helps remember something that has already happened and recognize the steps that were taken.[xiv]

MCI is a syndrome characterized by memory loss and it is the transition period between normal cognitive decline associated with aging and dementia.[xv] Petersen (1999) was one of the first to establish diagnostic criteria for MCI, followed by Winbland (2004) (Table 1).

The main problem with the criteria proposed by Petersen *et al.*, is that only memory is taken into account as a cognitive function; therefore, the diagnosis of MCI is only established with memory impairment.[xvi]

Using Winbland's criteria, MCI can be classified as a heterogeneous entity, divided into subtypes: amnesic and non-amnesic.

In the amnesic type, memory is mainly affected compared to other cognitive functions, and there is a higher risk of transition to Alzheimer's disease. In contrast, in the non-amnesic type, other cognitive

Table 1. Comparative chart between the diagnostic criteria for mild cognitive impairment according to Petersen and Winbland.

Differences in the proposed criteria	Petersen (1999)	Winbland (2004)
Memory (Petersen) versus other cognitive areas (Winbland)	Memory impairment recognized by the patient	There may be impairment in other cognitive areas besides memory
Recognition of impairment	Objective evidence of cognitive impairment	Cognitive impairment is recognized by the patient or by a close caregiver/ family member
Identification of MCI (Mild Cognitive Impairment)	Does not meet criteria for dementia diagnosis	MCI is an entity that does not meet the criteria for a normal person, nor for dementia
Cognitive function	General cognitive function is normal	-
Performance of daily activities	Normal performance of daily activities	-

Source: Review and update of the criteria for objective cognitive impairment and its implication in mild cognitive impairment and dementia; [xix]; and review of the diagnostic criteria for mild cognitive impairment: new predictive markers of Alzheimer's disease.[xvii]

functions are more affected than memory, and there is a higher risk of transition to other non-Alzheimer's dementias (vascular dementia, Lewy body dementia, and frontotemporal dementia).[xv,xviii]

In a study conducted by Öksüz *et al.*, in Turkey on a population of 140 people with MCI, it was found that the rate of progression from amnesic MCI to dementia is higher than that of non-amnesic MCI (53.9 % vs. 35.5 %).[xx] Recognizing the subtype of cognitive impairment is important because, when the amnesic variant is detected, there is a greater possibility of initiating therapeutic strategies to prevent it from progressing to Alzheimer's-type dementia.[xxi] Regarding risk factors for the onset of MCI, Han *et al.*, conducted a cross-sectional study between October 2016 and June 2017 with a population of people over 65 years of age from three communities in China, where they found that age, high blood pressure, educational level, female sex, and low-density lipoprotein cholesterol levels were the main factors related to MCI ($p < 0.05$), and found no significant differences related to body mass index, marital status, smoking history, or high-density lipoprotein cholesterol ($p > 0.05$).[xxii]

According to Senda *et al.*, the Addenbrooke's Cognitive Examination-III (ACE-III) test proved to be more sensitive ($p < 0.01$) and comprehensive than other screening scales, such as the Mini- Ace, Mini-Mental State Examination, and Montreal Cognitive Assessment, for detecting MCI.[xxiii] Among the ways to determine the progression of amnesic MCI to Alzheimer's-type dementia, the use of biomarkers has been proposed, which can be divided into three categories: imaging-based biomarkers, cerebrospinal fluid-based biomarkers, and plasma-based biomarkers.

Of the diagnostic methods, plasma-based biomarkers are worth mentioning. According to a study by Grande *et al.*, the plasma biomarker p-tau 217 demonstrated high accuracy (AUC of 0.94) in differentiating amyloid deposit disease, comparable to standard methods using cerebrospinal fluid and positron emission tomography. This makes it a promising and less invasive option for the early detection of dementia and Alzheimer's disease.[xxiv]

The most commonly used biomarkers today are beta-amyloid proteins (AB42 and AB42/AB40) and phosphorylated tau protein (p-tau 181 and p-tau 217).[xxv]

In a study conducted by Aurtenetxe *et al.*, in Spain, a population of 40 people over the age of 65 was divided into two groups: one healthy control group and one with MCI, at the San Carlos Hospital. They used an imaging biomarker, T1 MRI, which showed a reduction in hippocampal volume in people with MCI compared to the healthy control group.[xxvi]

There are multiple pharmacological treatments for Alzheimer's-type dementia, but there are no data on drugs approved by the FDA for MCI. The management of MCI is based on controlling cardiovascular risk factors (hypertension, diabetes *mellitus*, obesity, hyperlipidemia), adequately controlling the diet, promoting physical exercise and cognitive training, and routine monitoring every 6-12 months.[xxvii]

Physical exercise and its effect on memory

Memory is a complex cognitive process that involves: encoding, where the brain interprets perceived information; consolidation, where selected information is stabilized for long periods; retention, where information is modified and stored permanently; and retrieval, where information is reactivated through specific pathways for reuse. [xxviii]

The order in which information is retained is: sensory, which is information perceived by the senses; short-term memory, also known as active or working memory, which is information used at a given moment; and long-term memory, which it is retained and retrieved over long periods of time, divided into episodic (memory of experiences) and semantic (memory of concepts and facts).[xxix,xxx,xxxi]

Alaniz-Gómez *et al.*, mention that semantic memory is responsible for the number of words in one's personal vocabulary, general knowledge of what one has seen, heard, etc., propagated by semantic networks.[xxxii] Quaranta *et al.*, found that there were statistically significant differences ($p < 0.01$) in semantic memory scores between individuals who progressed rapidly from MCI to some type of dementia (mean score on the Rey Auditory Verbal Learning Test [RAVLT] for delayed recall = 0.7) and those who did not progress, with the latter having better scores (mean score for delayed recall = 2.0). This shows that the greater the memory impairment, the greater the degree of conversion to Alzheimer's-type dementia.[xxxiii]

Thus, memory impairment, specifically long-term memory, is the main determinant of Alzheimer's-type dementia. Therefore, single-domain amnesic MCI and multi-domain amnesic MCI have a higher predictive value for progression, predominantly the latter, compared to non-amnesic MCI.[xxxiv]

Patients with amnesic MCI have an average annual risk of 10-17 % of progressing to Alzheimer's-type dementia, which is why it has gained relevance. There is a hypothesis that early identification and intervention could reduce the percentage of progression to Alzheimer's-type dementia.[xxxv]

For this reason, efforts have been made to develop pharmacological and non-pharmacological interventions to prevent such deterioration in the earliest stages. One of the non-pharmacological interventions is physical exercise, which has demonstrated potential in improving overall cognition, memory, executive functions, and increasing brain volume. [xxxvi]

In addition, it is theorized that the effect of physical exercise on memory is related to the prevention of cardiovascular risks, the increasing the functional neuronal connectivity, and the increase in brain-derived neurotrophic factor, which stimulates cell growth and maintains the neurons.[xxxvii]

Brain-derived neurotrophic factor allows for neuronal growth and maturation through the regulation of synaptic transmission and neuronal plasticity in adults. Low levels of this growth factor are thought to lead to tau protein phosphorylation, AB protein accumulation, neuroinflammation, and neuronal apoptosis, so that high levels may reduce the risk of progression to Alzheimer's disease.[xxxviii]

Another theory states that physical exercise improves memory through neuroplasticity mechanisms and molecular factors. Among the molecular factors, an increased endothelial growth factor and brain-derived neurotrophic factor, where found to, result in physiological responses that ultimately improve coding processes and memory consolidation.[xxxix]

Chun-Kit *et al.*, described that physical exercise, in which they included aerobic exercise and resistance exercise, is capable of improving overall cognition (SMD = 0.45, 95 % CI 0.15- 0.76). However, it was not possible to identify a clear effect on memory (SMD = 0.15, 95 % CI 0.04 - 0.34).[xl] On the other hand, Nagamatsu *et al.*, describe a statistically significant effect on working memory ($p < 0.05$), which is one of the first cognitive functions to deteriorate.[xli]

However, Chow *et al.*, observed that groups receiving the physical activity intervention for more than two months showed greater improvement in memory SMD = 0.71) compared to those with an intervention lasting up to two months (SMD = 0.28). Therefore, it is important to consider that, in addition to the type of physical activity, the duration of said activity is also one of the variables to be taken into account.[xlii]

In a study conducted by Hernández *et al.*, the effects of cognitive rehabilitation (CR) and natural stimulation were compared in 128 patients over the age of 54 with MCI and hypertension. CR proved to be the most effective intervention, achieving significant improvements in attention, memory, and verbal fluency ($p \leq 0.01$). In terms of physical activity, no significant gains were reported for the cognitive functions evaluated. This suggests that structured interventions are especially beneficial for patients with greater initial impairment, supporting the theory of remaining cognitive reserve.[xliii]

Cognitive reserve reflects the adaptive and flexible ability to use cognitive processes

and neural connections to compensate for partial cognitive function losses.[xliv] A systematic review and meta-analysis on cognitive reserve in MCI and Alzheimer's disease found that people with high cognitive reserve (determined by high educational level, highly complex jobs, or participation in intellectually stimulating activities throughout life) are associated with a 47 % reduction in the relative risk of progression to dementia.[xlv]

Similarly, Vanegas-Sanabria *et al.*, suggest that multimodal interventions are necessary to achieve a significant impact on overall cognitive functions. If there is a decline in executive functions, individual physical exercise intervention would not yield good results due to patients' inability to perform physical exercise.[xlvi]

Modification of executive functions through physical exercise

Executive functions (EF) are defined as abilities that enable the formulation of goals, planning to achieve them, and subsequently adopting specific behavior in response to that mental process. These functions are necessary for individuals to adapt to various situations in life. The domains of executive functions include organization, inhibitory control, mental flexibility, hypothesis generation, planning, abstract thinking, and working memory.[xlvii]

Aging brings about changes in normal human cognitive functioning, including executive functions. These functions are mediated by the prefrontal lobe, which is considered vulnerable to the effects of age, resulting in impaired autonomy, decision-making, planning, and scheduling of daily activities.[xlviii]

The study by Ojeda *et al.*, which used a sample of 34 older adults between the ages of 60 and 90 from the city of Puerto Montt, evaluated the cognitive level of the participants and their EF performance and found a high correlation (correlation coefficient: 0.611 [$p < 0.01$], directly proportional between cognitive status and EF. However, no significant difference was found when performing the Neuropsi or Wais IV tests ($p \geq 0.10$) between the group without cognitive impairment and the group with MCIin FE performance; only when comparing the without impairment group with the severe cognitive impairment group ($p < 0.05$).[xlix]

In contrast to the above, it has been reported that MCI leads to impairment in executive functions, as well as a decrease in immediate episodic memory. Likewise, there are declines in spontaneous language and verbal fluency. In patients with multidomain amnesic MCI, memory impairment affects planning and conflict resolution. This shows that the clinical picture of MCI involves a decline in executive functions in older adults.[l]

Due to decreased mental flexibility, reduced precision, slowness in changing activities, and impaired practical reasoning, the quality of life of older adults is directly impacted. This leads to maladjustment in their daily lives and autonomy, resulting in exclusionary behavior by society.[li]

In the search for methods to preserve or reduce the deterioration of executive functions, the role of physical exercise has been investigated, despite the conflicting information on its specific impact on MCI. However, Naya *et al.*, analyzed 42 randomized clinical trials and meta-analyses, concluding that several studies evidenciate the positive effect of regular exercise on cognition, executive function, verbal memory, and a reduced risk of progression from MCI to established dementia.[lii]

Venegas *et al.*, reported that multicomponent exercise and aerobic exercise can cause changes in cognition in MCI and dementia. There is a positive and moderate effect on patients' overall cognition, which is greater when multicomponent exercise is combined with anaerobic exercise.[xlvi]

In a meta-analysis conducted by Cheng *et al.*, a meta-analysis review protocol was carried out, taking into account various types of physical exercise (aerobic, anaerobic, Thai chi and yoga). Moreover, in the various domains of EF in elderly patients with MCI, finding, a slight to moderate improvement in three domains of EF (inhibitory control, working memory, and mental flexibility) with statistical significance ($p < 0.05$) in three domains of EF (inhibitory control, working memory, and mental flexibility), with aerobic exercise, yoga, and Thai Chi having the greatest effect on these domains.[liii]

Ren *et al.*, found that, of the various types of physical exercise performed in China in people over 65 with MCI, Thai Chi and Qigong have shown an improvement in symptoms in two domains of EF, namely working memory ($p < 0.05$) and mental flexibility ($p < 0.01$), with no significant differences in inhibitory control ($p \geq 0.10$) and planning ($p \geq 0.10$).[liv]

In the systematic review conducted by Zhidong *et al.*, a significant effect of exercise ($p < 0.01$) on working memory in older adults was found. Of the 51 effects included in the meta-analyses, the total effect size was 0.29 ($p < 0.01$), showing a statistically significant difference in working memory between the groups that underwent physical activity and the control group (without physical activity).[lv]

It should be noted that, to evaluate MCI, a single study variable cannot be used, as it is a disease involving multiple aspects related to its development, such as comorbidities, pharmacotherapy, gender, educational level, and diet, among others. As a result, the main limitation of this literature review is its specific focus on physical exercise, one of many variables that modify MCI; therefore, its scope is limited, and studies that consider the relationship of multiple variables in the treatment of MCI are recommended.

Conclusion

MCI is an intermediate state between the normal cognitive functions of healthy older adults and the impaired cognitive functions of older adults with dementia. Its diagnosis and timely intervention would translate into the use of different preventive and therapeutic measures to prevent it from progressing to dementia. Physical exercise, especially multicomponent exercise combined with aerobic exercise, is a promising strategy whose benefits include a positive effect on some cognitive functions, such as executive function (inhibitory control, working memory, and mental flexibility) and an increase in growth factors, such as brain-derived neurotrophic factor, which may be an important component in preventing the progression to dementia. However, due to heterogeneity in the results of different studies, physical activity alone cannot be recommended as a therapeutic measure for improving memory. However, it can be considered as an additional therapy to other interventions, such as cognitive rehabilitation therapies. In addition, it should be noted that the triggers of this disease are multifactorial, so each approach must be individualized.

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