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Aerobic Exercise Effects upon Cognition in Mild Cognitive Impairment: a Systematic Review of Randomized Controlled Trials

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ABSTRACT

Several studies have shown that physical activity has positive effects on cognition in healthy older adults without cognitive complains but lesser is known about the effectiveness of aerobic exercise in patients suffering from Mild Cognitive Impairment (MCI). The aim of the present study was to systematically review the evidence from randomized controlled trials (RCTs) about the effects of aerobic exercise upon cognition in MCI patients. To this end, PubMed, Cochrane and Web of Science databases were analytically searched for RCTs including aerobic exercise interventions for MCI patients. There is evidence that aerobic exercise improves cognition in MCI patients. Overall research reported moderate effects for global cognition, logical memory, inhibitory control and divided attention. Due to methodological limitations of the investigated studies, findings should be interpreted with caution. Standardized training protocols, larger scale interventions and follow-ups may also provide better insight into the preventive effects of aerobic exercise on cognitive deterioration in MCI and its conversion into dementia.

Key words

Mild cognitive impairment • Aerobic exercise • cognition • Non-pharmacological intervention • Randomized controlled trial

Introduction

Mild Cognitive Impairment (MCI) depicts a transitional intermediate state between physiological aging and dementia and refers to a clinical syndrome with multiple profiles and different aetiologies (Petersen et al., 2014). The initial definition of MCI directly concerns the detection of underlying Alzheimer's Disease (AD). Originally, amnestic deficit was neuropsychologically thought to be a predictor of AD in MCI patients whilst more recent research stated that episodic memory damage along with executive dysfunction represents the main risk factors for MCI conversion into dementia (Cammisuli et al., 2012; Summer and Saunders, 2012). Original MCI criteria were then improved by additional clinical features, genetic background, predictors of progression and pathological outcomes leading to criteria proposed by the National Institute on Aging and the Alzheimer's Association (Albert et al., 2011) and by the Diagnostic and statistical manual of mental disorders fifth edition (DMS-V) (APA, 2013). Recently, a transitional state very similar to MCI in AD has been recognized also in Parkinson's Disease (Geurtsen et al., 2014; Cammisuli & Timpano, 2017; Hoogland et al., 2017). Cognitive impairment is common in non-demented PD patients in different extent and it is associated with an increasing risk to develop Parkinson's Disease Dementia (Litvan et al., 2012). There is growing evidence that non-pharmacological interventions help in preserving personal and instrumental autonomy, reducing neuropsychiatric symptoms and improving quality of life in AD

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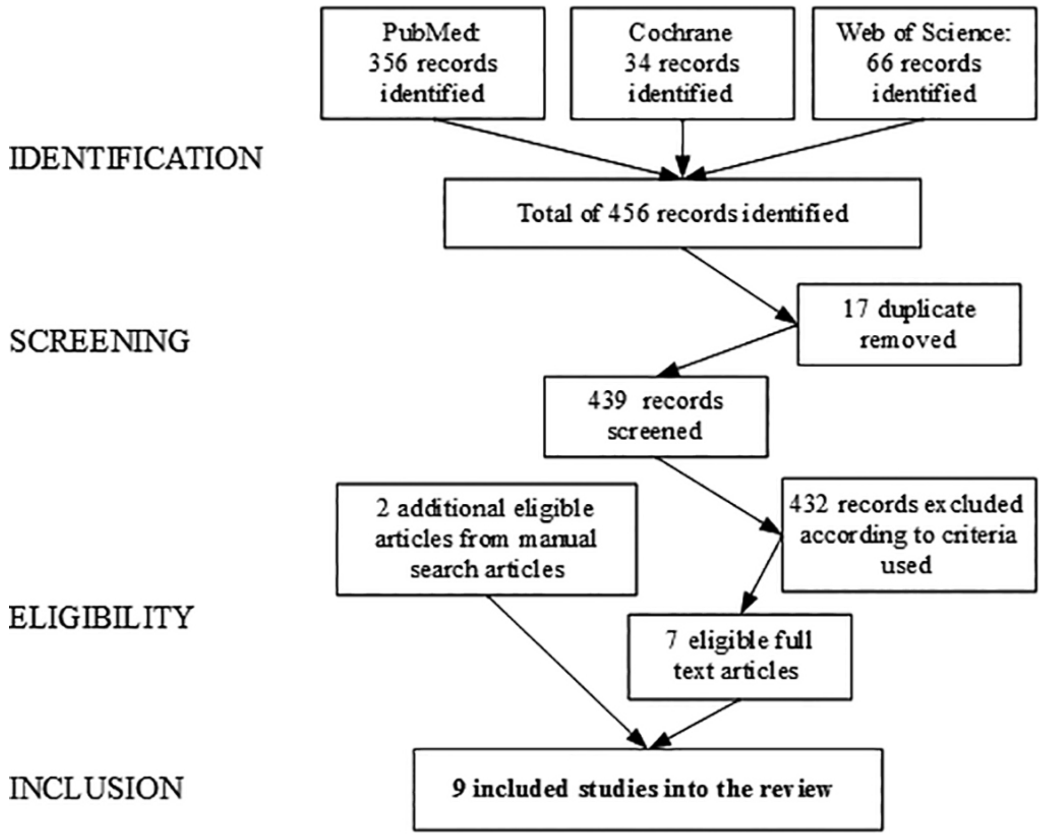

Fig. 1. - Flow diagram: studies selection criteria.

patients (Graessel et al., 2011; Tsolaki, 2016; Cipriani et al., 2016; Cammisuli et al., 2016). Cognitive training for MCI and mild AD has been found to be effective in ameliorating patients' residual cognitive abilities and reducing caregivers' burden (Cammisuli et al., 2011; Bergamaschi et al., 2013). Moreover, an evolving literature has shown significant benefits of physical exercise, specifically aerobic one, in attenuating cognitive impairment and reducing dementia progression (Ahlskog et al., 2011).

Cognitive functionality of MCI patients can take advantage from regular physical exercise, in particular for executive functioning sustaining patients' personal and instrumental autonomy of daily living (Farina et al., 2014). Aerobic activity is a physical exercise of low to high intensity that depends mainly on the aerobic energy generating process, referring to the use of oxygen to adequately meet energy demands during exercise. Generally, it involves any exercise that increases heart rate and keeps it higher than basal one for extended periods of time. Aerobic exercises like walking, running, swimming, aquarobics, cycling, rowing, etc., improve vascular health, reduce blood pressure, arterial stiffness, oxidative stress, systemic inflammation and enhance endothelial function (Forbes et al., 2013).

MCI patients present with brain alterations preceding many times before the onset of overt AD (De Carli et al, 2007; Pike et al., 2007). A large amount of experimental studies showed potential mechanisms to account for cognition improvement due to exercise including effects on neuronal survivability and function, neuroinflammation, vascularization, neuroendocrine response to stress and brain amyloid burden, and on physiological processes, such as glucoregulation and cardiovascular system (Baker et al., 2010). In humans, brain imaging studies suggested that aerobic fitness in heathy elderly is associated with reduced age-related atrophy and increased perfusion in brain areas sustaining executive functions and memory that resulted as vulnerable to aging effects (Baker et al., 2010).

Previous meta-analyses of RCTs showed that physical exercise in healthy adults is associated to cognitive improvement, larger hippocampal volumes, attenuation of age-related grey matter

Tab. 1. - Evaluation of selection criteria of included studies.

Study	1	2	3	4	5
Scherder et al., 2005	+	+ / -	-	+ / -	-
Lautenschlager et al., 2008	-	+	+	+	+
van Uffelen et al., 2009	-	+	+	+	+
Baker et al., 2010	+	+	-	+	+
Valera et al., 2012	+ / -	+ / -	+	+ / -	+
Suzuki et al., 2012	+	+	+	+	+
Suzuki et al., 2013	+	+	+	+	+
Nagamatsu et al., 2013	-	+	+	+	+
Davis et al., 2013	-	-	+	+	+

Note: (1) The diagnosis of Mild Cognitive Impairment is based on validated criteria: Petersen et al. (1999); Winblad et al. (2004), Petersen (2004), Albert et al. (2011), APA (2013); (2) Inclusion and exclusion criteria are specifically described; (3) The study has sufficient statistical power (n ≥ 25 per group); (4) Intervention, measurements and outcome measurements are correctly described; (5) Complication, dropouts and patients' adherence taken into account.

Tab. 2. - Quality assessment of the included RCT studies.

Study	Selection bias	Study design	Confounders	Blinding	Data collection	Withdrawal	Overall
Scherder et al., 2005	* * *	* *	* *	* * *	* * *	*	* *
Lautenschlager et al., 2008	* * *	* * *	* * *	* * *	* * *	* *	* * *
van Uffelen et al., 2009	* * *	* * *	* * *	* * *	* * *	* * *	* * *
Baker et al., 2010	* * *	* * *	* * *	* *	* * *	* *	* * *
Valera et al., 2012	* * *	* * *	*	* *	*	*	* *
Suzuki et al., 2012	* * *	* * *	* *	*	* * *	*	* *
Suzuki et al., 2013	* * *	* * *	*	* *	* * *	*	* *
Nagamatsu et al., 2013	*	* * *	*	* *	* * *	* * *	* *
Davis et al., 2013	*	* * *	*	*	*	* *	*

Note: * = Weak quality; * * = Moderate quality; * * * = High quality.

volume loss, and improved connectivity of brain networks (Ahlskog et al., 2011). The aim of this study was to systematically review the evidence from randomized controlled trials (RCTs) about the specific effects of aerobic exercise on cognition in MCI patients and to suggest prescriptions for a routinely healthy lifestyle to follow.

Methods

PubMed (general search without any restriction), Cochrane Library (search 'All text') and Web of Science (search as 'Topic') databases were systematically examined for RCTs using the following terms in: "mild cognitive impairment" AND "aerobic exercise" AND "cognition". The search was performed on December 2016 and repeated on March 2017. Additional titles were manually searched in relevant bibliographies of previous studies on the investigated topic (Smith et al., 2010; Ahlskog et al., 2011; Gates et al., 2013; Öhman et al., 2014; Zheng et al., 2016).

The studies from the literature search were selected from initial search if the met the following criteria: (1) patients with MCI; (2) aerobic exercise as one of the main interventions (multicomponent interventions were potentially eligible for inclusion if they included aerobic exercise as principal practice; indeed, combined programs of different physical exercises may induce specific brain changes); (3) randomized controlled trial as study design; (4) any validate neuropsychological test of cognition reported at baseline and at follow-up.

Exclusion criteria included: (1) studies recruiting individuals with neurological diseases different from MCI (i.e., Alzheimer's disease or other dementias, stroke, multiple sclerosis, traumatic brain injury, Parkinson's Disease, focal brain disorders, etc.) individuals with subjective cognitive decline, subjects with age-related cognitive decline or unspecified memory complaints, psychiatric diseases and other comorbid medical conditions (e.g., mild cognitive impairment and diabetes mellitus); (2) aerobic exercise as sport practice (e.g., Thai Chi, handball, etc.); (3) manuscripts written in other languages than English. This screening finally yielded 9 studies to be evaluated (Figure 1).

Three independent reviewers (D.M.C., A.I., and C.P.) evaluated the included studies for methodological quality (Table 1). Disagreement was discussed until a consensus was definitively reached. Methodological quality of the selected manuscripts was checked by criteria for RCTs used by Cochrane (Forbes et al. 2008). To ascertain the validity of eligible randomized trials, a pair of reviewers (D.M.C. and F.F.) working independently and with adequate reliability assessed the risk of bias in relation to selection, study design, confounders, blinding, data collection and withdrawal using the Quality Assessment Tool for Quantitative Studies (Thomas et al., 2004) (Table 2).

Results

Overall, the quality of included trials was moderate. Results from nine studies selected are summarized in Table 3. Eight studies used Mini Mental State Examination (MMSE) (Folstein et al., 1975) to examine the effect of aerobic exercise on global cognition whilst only one study used Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) (Rosen et al. 1984). Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) came up beside these global screening instruments in two studies. MMSE is widely used in clinical practice but it is less informative than MoCA, so that it has a limited power due to poorer psychometric properties. Nevertheless, three studies reported improvement in global cognition after intervention by the MMSE.

We noted that only some specific executive sub-domains improved after an aerobic intervention. Researchers usually moved to evaluate few cognitive functions associated to dorsolateral prefrontal cortex and anterior cingulate cortex by fluency tests, Stroop test and dual-task conditions (i.e., TMT), that have been observed to be poor in MCI patients (Cammisuli et al., 2013). Starting from this assumption, we have to limit results to improvements in inhibitory control and divided attention only. However, our research replicates previous findings on healthy elderly subjects undergone physical trainings (Colcombe and Kramer, 2003; Hillman et al., 2008; Pruneti et al., 2017) but they are little surprising in relation to memory enhancement. Indeed, three selected studies (Suzuki et al., 2012, 2013; Nagamatsu et al., 2013) reported that aerobic exercise may boost long-term memory under a free recall condition. Again, this could be due to the role of executive functions in organizing and making meaningful verbal material after experimenter's test presentation of prose story that allows long and cohesive responses of the examinees (cfr. Cammisuli and Timpano Sportiello, 2016).

Summary

On the basis of the present findings, we prudently state that MCI patients benefit from aerobic exercise but we cannot conclude that aerobic exercise promotes a selective effect upon cognition, due to the lack of investigation on visuospatial and constructive skills, language, spatial and temporal orientation. Beyond a brain neuroprotective effects, regular aerobic exercise may attenuate cognitive decline via mitigation of cerebrovascular risk factors and should be considered a respectable strategy for preventing a more severe cognitive deterioration in MCI patients. Regular participation in moderate-intensity aerobic training (which typically implies exercise sufficient to elevate heart rate or Vo_2 to approximately 60% of the maximum for 50/60 minutes 3 day a week) may improve cognition. Physical exercise brings improvements in cognitive functions accompanied by structural and functional changes of brain regions in MCI, especially as lower rates of brain atrophy and higher hippocampal efficiency (Huang et al., 2016). In this regard, aerobic exercise might modify risk factors and pathological mechanisms associated with cognitive deterioration and delay dementia onset. Measuring the effectiveness of exercise on cognition is often challenging because of intrinsic nature of MCI, in which a percentage of patients may remain stable over time or revert to a normal cognitive state.

Tab. 3. - Summary of main results of selected studies.

Study	Participants	Groups	Intervention	Aerobic exercise	Cognitive assessment	Follow-up	Main findings pertaining intervention groups
Scherder et al., 2005	43 MCI Sex: M:5; F:38 Age: 76-94	Intervention groups: A. Walking group B. Hand and face exercise group Controls: Normal activity group	3d/wk 30 min. per session for 2month	Walking (moderate-intensity)	MMSE VLMT WMS-R: Digit Span RBMT: Face Recognition and Picture Recognition Category naming TMT	None	Significant improvements in tasks appealing executive functions
Lautenschlager et al., 2008	170 probable MCI Sex: M:84; F:86 Age: 50 yrs. or more	Intervention group: Physical activity group Controls: Education and usual care group	3d/wk 50 minutes per session for 6 months	Walking (moderate-intensity)	ADAS-Cog CERAD WAIS-III D-KEFS	12 and 18 months after intervention	Improvement in global cognitive function after intervention
van Uffelen et al., 2008	152 probable MCI Sex: M:85; F:67 Age: 70-80	Intervention group: Walking programme group Controls: Placebo activity programme	2d/wk 60 minutes per session 1 year	Walking (moderate-intensity)	MMSE AVLT VFT DSST SCWT-A	None	Improvement in memory for men and memory and attention for women
Baker et al., 2010	33 MCI Sex: M:16; F:17 Age: 55-85	Intervention group: High-intensity aerobic exercise Controls: Stretching group	4d/wk 45-60 min. per session for 6 months	75% to 85% of heart rate reserve using a treadmill, stationary bicycle, or elliptical trainer	MMSE Symbol-Digit Modalities Verbal Fluency Stroop Test TMT, Task Switching Story Recall List Learning	None	Executive functions and divided attention improvement
Valera et al., 2011	48 MCI Sex: M:21 F:27 Age: 78.3±9.5	Interventions groups: A. Moderate-intensity aerobic exercise; B. High-intensity aerobic exercise Controls: Recreational therapy	3d/wk 30 minutes per session 6 months	40% to 60% heart rate reserve, cycling	MMSE-Spanish version	Yes (3rd month)	Slight improvement of global cognition for aerobic groups

Tab. 3. - Summary of main results of selected studies.

Study	Participants	Groups	Intervention	Aerobic exercise	Cognitive assessment	Follow-up	Main findings pertaining intervention groups
Suzuki et al., 2012	50 MCI Sex: M:27; F: 23	Intervention group: Multicomponent exercise group Controls: Education control group	2d/wk 90 min. per session 12 months	Endurance walking (60% heart rate)	MMSE WMS-R: Logical Memory LVFT DSC Stoop Test	None	Improvements in global cognition, logical memory (immediate recall) and verbal fluency
Suzuki et al., 2013	100 MCI Sex: M:55; F:45 Age: 75.4±7.1	Intervention group: Multicomponent exercise group Controls: Education control group	2d/wk 90 min. per session 6 months	Endurance walking (60% heart rate)	MMSE ADAS-Cog WMS-R: Logical Memory	None	Amnestic MCI benefits in logical memory and general cognitive function. Reduced cortical atrophy.
Nagamatsu et al., 2013	86 probable MCI Sex: only female Age: 70-80	Intervention groups: A. Resistance training; B. Aerobic training Controls: Balance and tone training	2d/wk 60 min. per session 26 weeks	Walking (40% heart rate reserve)	MMSE MoCA Stroop Test TMT Digit Span Everyday Problems Test	Yes (a not-specified "midpoint" follow-up is reported in the article)	Verbal memory and learning improvement. Spatial memory was related to overall physical performance
Davis et al., 2013	86 probable MCI Sex: female Age: 70-80 yrs.	Intervention groups: 1.Resistance training 2.Aerobic training Controls: Balance and tone control group	Outdoor walking programme (40% heart rate reserve)	2d/wk 60 min. per session 6 months	MMSE MoCA Stroop Test	None	No significant improvement for aerobic training group compared to the rest in the Stroop test

Note: MMSE = Mini Mental State Examination; VLMT = Verbal Learning and Memory Test; WMS-R: Wechsler Memory Scale-Revised; RBMT = Rivermead Behavioural Memory Test; TMT = Trail Making Test; ADAS-cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale; CERAD = Cognitive Battery of the Consortium to Establish a Registry for Alzheimer Disease; D-KEFS = Delis-Kaplan Executive Function System; MoCA = Montreal Cognitive Assessment; LVFT = Letter Verbal Fluency Test; CVFT = Category Verbal Fluency Test; DSC = Digit Symbol Cording; Auditory Verbal Learning Test; VFT = Verbal Fluency Test; DSST = Digit Symbol Substitution Test; SCWT-A= Abridged Stroop Colour Word Test.

Initial findings from RCTs investigating the role of aerobic exercise upon cognition in MCI are quite promising. They allow to preliminary advice MCI patients, particularly those who are sedentary, to initiate daily aerobic exercise (cfr. Pruneti, 2014; Pruneti et al. 2014). Regular aerobic exercise gradually increased to achieve 60% of maximum heart rate or peak oxygen consumption per unit time (Vo_2) and performed at least 150 minutes weekly seems to be reasonable for a good regimen. This is very similar to American College of Sport Medicine and American Heart Association Recommendations reporting a "moderate-intensity aerobic physical activity for a minimum of 30 minutes on five days each week" (Nelson et al., 2007; Pruneti et al., 2011). Regular physical exercise also improves posture and reaction time, coordination and motor performance and enhances subjective well-being (Gajewsky and Falkenstein, 2016).

However, the limitations of the included studies in our review suggest to interpret results cautiously, due to several methodological problems in defining MCI, blinding, samples size, few and heterogeneous neuropsychological tests adopted to measure the effects of aerobic exercise upon cognition, changes on neurocognitive measures at follow-up (effect size strength) and their clinical significance in relation to a potential progressive cognitive deterioration.

Standardized training protocols with arms allowing the comparison among healthy elderly individuals, MCI, and early AD patients undergoing aerobic training, larger scale interventions and medium/long-term follow-ups to evaluate maintenance effects may provide better insight into the critical role of aerobic exercise on cognitive deterioration in MCI patients. Additional research is need to address specific health care needs of MCI patients (i.e., psychoeducational interventions for patients and relatives about the importance of weekly physical exercise), cost-effectiveness of different physical trainings (i.e., aerobic trainings *versus* other physical trainings) and interaction with complementary interventions, such as vitamin supplementation and cognitive training.

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