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Effects of Physical Exercise on Cognition in Persons with Subjective Cognitive Decline or Mild Cognitive Impairment: A Review

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Abstract

Alzheimer's disease is the most common type of dementia that lacks a cure so prevention is an important aspect of care. Persons with subjective cognitive decline or mild cognitive impairment are more likely to be diagnosed with Alzheimer's disease later than cognitively healthy populations. The purpose of this literature review was to analyze the effects of physical exercise interventions on cognition in persons with subjective cognitive decline or mild cognitive impairment. A literature search was conducted using electronic databases from the beginning dates of the databases to September-23-2016. Of the 94 randomized controlled trials generated 6 subjective cognitive decline and 9 mild cognitive impairment studies met the eligibility criteria and were included in this review. The levels of study quality for subjective cognitive decline and mild cognitive impairment were 5 strong 1 moderate and 5 strong 4 moderate respectively. Interventions were aerobic, resistance, Tai Chi or multicomponent exercise. Overall 67% (10/15) of the studies showed that the interventions improved cognition compared to control or other interventions. There is a pressing need to conduct further research to establish the optimal dose of each modality for improving cognition in these populations.

Introduction

The rising prevalence of dementia is a global health issue. Worldwide about 47.5 million have dementia in 2016 and almost 7.7 million new cases are expected to occur every year [1]. The total annual costs associated with dementia are $226 billion in 2015 and estimated to exceed $1 trillion US dollars in 2050 in the United States [2]. Among all kinds of dementia, Alzheimer's Disease (AD) is the most common type and accounts for 60-80% of all dementias [1].

The National Institute on Aging-Alzheimer's Association (NIA-AA) introduced a model of the clinical trajectory of AD, including preclinical AD, Mild Cognitive Impairment (MCI) due to AD and AD [3,4]. Preclinical AD refers to the stage at which AD pathology is present, but results from standardized cognitive tests represent normal performance [4]. Self-perceived decline in any cognitive domain may occur in this stage called Subjective Cognitive Decline (SCD) in preclinical AD [4,5]. Even if SCD can be a reflection of subtle cognitive decline in preclinical AD cognitive decline does not reach the threshold level of MCI based on the cognitive tests [5]. However the risk of developing AD or other dementias is higher in those with SCD compared with those without SCD [6-8].

MCI is diagnosed when objective decline in cognition exists but does not meet the criteria for a diagnosis of dementia [9,10]. Core clinical characteristics include: a) Self or informant reported cognitive complaints b) Objective cognitive impairments c) Preserved general cognitive functioning d) No evidence of dementia [11]. MCI due to AD represents cognitively symptomatic but non-demented state whose primary underlying pathophysiology is AD [3]. The presence of MCI puts individuals at a higher risk of developing AD with annual estimates ranging from 10% to15% compared to 1% to 2% among cognitively normal individuals [12].

There is no specific cure for AD. Medications such as acetylcholinesterase inhibitors and *N*-methyl-d-aspartate antagonist are prescribed for persons with AD to improve cognition, but they are not disease modifying treatments [13]. Therefore delaying or slowing down the onset of AD would be important to reduce burdens to the society and patients inflicted with this illness. However, there are no current established preventive medications for AD [13,14].

In this circumstance non-pharmacological interventions have been tested to improve cognition in persons before the onset of AD. Physical exercise is one of these non-pharmacological interventions and its impact on cognition is known to be beneficial in non-demented persons [15-17]. There are biologically sound mechanisms that support the beneficial effects of physical exercise on cognition [18]. Specifically physical exercise has been shown to up-regulate several factors linked to neuro-protective mechanisms including Brain-Derived Neurotrophic Growth Factor (BDNF) Insulin-Like Growth Factor (IGF) Vascular Endothelial Growth Factor (VEGF) body composition and antioxidant defense. These changes are followed by decreased oxidative damage as well as increased neurogenesis, synaptic plasticity, dendritic spine density, cerebral perfusion and mitochondrial function of neurons. With benign effects derived from these mechanisms physical exercise can eventually have potential to improve cognition (Figure 1). Thus physical exercise can be an efficient option to diminish the risk of cognitive decline delaying the presence of AD.

Purpose

Hence research targeting persons in stages potentially before AD particularly in SCD or MCI may be recommended to slow down

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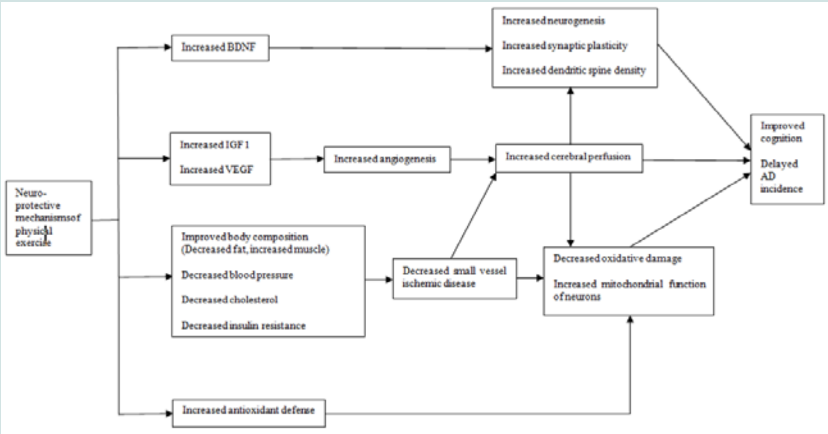

Figure 1: Theoretical model of mechanisms linkage between physical exercise and cognition. AD=Alzheimer's Disease; BDNF=Brain-Derived Neurotrophic growth factor; IGF=Insulin-Like Growth Factor; VEGF=Vascular Endothelial Growth Factor.

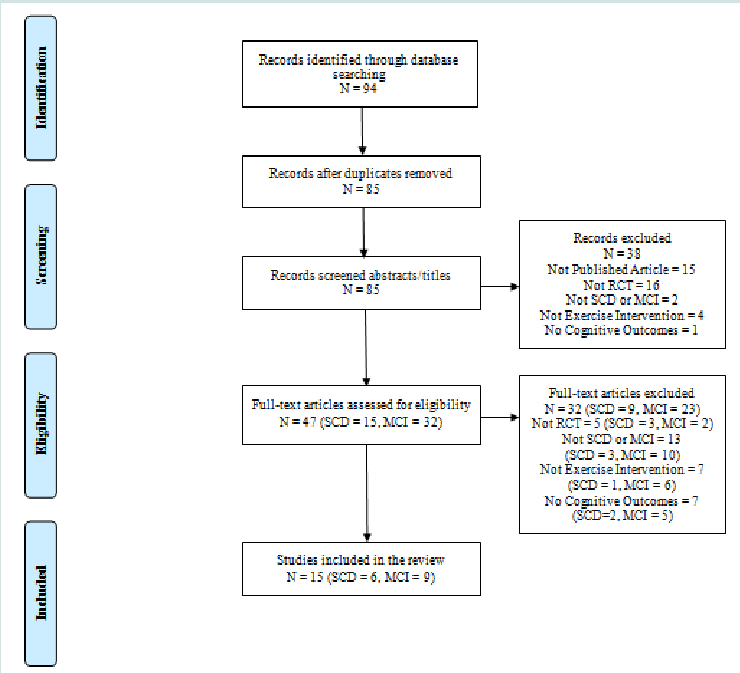

Figure 2: Flowchart of eligibility assessment.

AD progression. However the concepts of SCD and MCI have been defined in a variety of ways from study-specific clinical criteria to recommendations of the international workgroups [5,11, 19]. There have been reviews which focused on aerobic exercise effects on cognition in MCI [19,20]. In order to fill the gap with updated evidence the purpose of this review was to describe what is known about the cognitive impact of various types of physical exercise specifically on persons with SCD or MCI diagnosed with strict criteria.

Methods

Ovid MEDLINE and Ovid EMBASE databases were searched from the inception of the database through September-23-2016 by combining keywords matched to Medical Subject Headings (MeSH):"Subjective cognitive complain or subjective cognitive decline or subjective cognitive impairment or subjective memory complaint or subjective memory impairment or subjective memory decline or self-reported memory failure or mild cognitive impairment" and "exercise or exercise movement techniques or exercise therapy or sports oraerobic activity/fitness/training or resistance exercise/training or strength exercise/training or walkingor running or jogging or swimming or Pilates or yoga or Tai Chi or dance or breathing exercise or stretching or balance training or postural training" and "cognition or cognitive function". Searches were limited to human studies and published articles in all databases.

Articles were included if: 1) studies were published in English 2) studies used a Randomized Controlled Trial (RCT) design 3)

Table 1: Summary of the studies with physical exercise in SCD (n=6).

Citation, Quality	Purpose	Study Design	N	Setting	Outcomes and Measures	Results
					Aerobic exercise	
Barnes et al. 2013 Quality: Strong	Investigate the effects of 12-week aerobic exercise, stretching exercise, mental activity program and educational DVDs, three times a week on cognition	Double blinded, fully-factorial RCT with double sham (stretching and educational DVDs) as control	126 (Men 47, Women 79)	Community	**Exercise adherence rate:** 80%. **Global cognition:** A 12-week change in cognitive function based on a composite score from 6 tests below. **1. Verbal learning and memory:** RAVLT **2. Verbal fluency:** Letter and Category **3. Processing speed:** DSST **4. Executive function/mental flexibility:** TMT A and B **5. Executive function/inhibition:** EFT **6. Visuospatial function:** UFOV	**Intervention:** Individualized dance with an intensity of 60% to 75% of age-adjusted maximum heart rate. **Intervention's cognitive impact:** Global cognition. There was a significant improvement on global cognition in all 4 groups at 12 weeks (p<0.001). However, the degree of improvement was not significantly different between the aerobic and the stretching exercise (p=0.74), between the mental activity program and the educational DVDs (p=0.17), or in all 4 randomization groups (p=0.26). For individual cognitive test difference between baseline and a 12-week follow up, only visuospatial function improved more in the mental activity program than in the educational DVDs (p<0.05). No difference was observed between the aerobic and the stretching exercise in every individual test.
Maki et al. 2012 Quality: Strong	Evaluate the effects of supervised 12-week walking program, once a week on cognition, quality of life, depression, functional capacity, range of activities, social network, and motor function	Single blinded RCT with education as control	150 (Men 44, Women 106)	Community	**Exercise adherence rate:** 88% **Global cognition:** 5-Cog test **Attention:** DSST, YKSST **Executive function:** TMT **Quality of life:** SDL **Depression:** GDS **Functional capacity:** TMIG-IC **Range of activity:** LSA **Social network:** Japanese version of Lubben **Motor function:** Grip force, Balance time on one foot, TUG, Maximum walking speed for 5 meters.	**Intervention:** Group-based walking without a detail of intensity. **Intervention's cognitive impact:** Word fluency. At a 12-week follow up, word fluency, one of 5-Cog test components, improved significantly more in the walking group than in the control (F=6.833, p=0.01). There was no significant difference in other areas of cognition between the groups. Compared to the control, significant benefits in the walking group were shown in SDL (F=9.751, p=0.002), TMIG-IC (F=13.055, p<0.001), and TUG (F=10.117, p=0.002). There was no significant difference in other measures between the groups.
					Resistance exercise	
Lu et al. 2016 Quality: Strong	Explore the effects of supervised 12-week dumbbell training, three times a week on cognition and physical function.	Single blinded RCT with usual care as control	45 (Men 13, Women 32)	Community	**Exercise adherence rate:** 86%. **Global cognition:** Chinese version of ADAS-Cog **Executive function:** Chinese version of TMT B **Memory:** Chinese version of-Digit Span Test **Functional mobility:** TUG **Forward stability:** Functional Reach Test **Balance:** Activities-Specific Balance Confidence Scale	**Intervention:** Individualized dumbbell training with an intensity level tailored to the capability of each participant. **Intervention's cognitive impact:** Global cognition. At a 12-week follow up, the intervention group showed significant improvement on global cognition and functional mobility compared to the control group (ADAS-Cog mean change: -2.39 *vs.* 1.93, p=0.012/TUG mean change: -0.71 *vs.* -0.35, p=0.043). There was no difference between the groups in other cognitive and physical function.
					Aerobic or resistance exercise	
Nagamatsu et al. 2012 Quality: Strong	Examine the effects of both supervised 26-week resistance training and aerobic training, twice a week on cognition, regional patterns of functional brain plasticity, and physical function.	Single blinded RCT with balance and tone training as control	86 (Women 86)	A research center	**Exercise adherence rate:** For resistance exercise 54%, for aerobic exercise 60%. **Selective attention/conflict resolution:** Stroop Test. **Executive function:** TMT, VDT. **Associative memory:** Memorizing face-scene pairs. **Everyday problem solving ability:** EPT **Regional patterns of functional brain plasticity:** Functional MRI. **Physical function:** SPPB, 6MWT.	**Intervention:** For aerobic exercise, individualized walking with an intensity of 40% to 80% of the heart rate reserve / for resistance exercise, individualized weight machines or free weight training with an intensity of 2 sets of 6 to 8 repetitions. **Intervention's cognitive impact:** For resistance exercise, selective attention and associative memory. Compared to the balance and tone training group, the resistance training group significantly improved performance on Stroop Test [mean change from baseline to 26-week follow up: 9.13(19.88) *vs.* 1.37(15.26), p=0.04] and memorizing face-scene pairs [mean change from baseline to 26-week follow up: 0.61(0.72) *vs.* 0.23(0.66), p=0.03]. In functional MRI, the resistance training also led to improvement in the right lingual (p=0.03), occipital -fusiform gyri (p=0.02), and the right frontal pole (p=0.03), compared to the balance and tone training.

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						Compared to the control group, the aerobic training group significantly improved performance on SPPB [mean change from baseline to 26-week follow up: 1.37(1.34) *vs.* 0.70(1.77), *p*=0.03] and 6MWT [mean change from baseline to 26-week follow up: 18.73(54.63) *vs.* 4.50(34.52), *p*=0.04]. In both the resistance and the aerobic training groups, no significant effect was found on executive function and everyday problem solving ability compared to the control group.
Nagamatsu et al. 2013 Quality: Moderate	Examine the effects of both supervised 26-week resistance training and aerobic training, twice a week on verbal memory and spatial memory	Single blinded RCT with balance and tone training as control.	86 (Women 86)	A research center	**Exercise adherence rate:** For resistance exercise 54%, for aerobic exercise 60%. **Verbal memory and learning:** RAVLT **Spatial memory:** Computerized task developed for this study.	**Intervention:** For aerobic exercise, individualized walking with an intensity of 40% to 80% of the heart rate reserve / for resistance exercise, individualized weight machines or free weight training with an intensity of 2 sets of 6 to 8 repetitions. **Intervention's cognitive impact:** For aerobic exercise, verbal and spatial memory / for resistance exercise, spatial memory. Among RAVLT components, there was a significant difference in loss after interference at a 26-week follow up between the aerobic and the control group [1.58 (1.86) *vs.* 2.80 (2.58), *p*=0.04]. No other significant difference between the groups was found in verbal memory and learning. For spatial memory, both the resistance and the aerobic training improved their reaction times for memorizing the spatial location of three items more than the control at a 26-week follow up [1006.69 (189.75) *vs.* 1077.48 (223.07) / 1002.91 (195.64) *vs.* 1077.48 (223.07), *p*=0.05]. No other significant difference between the groups was found in spatial memory.
			Multicomponent exercise			
Lautenschlager et al. 2008 Quality: Strong	Determine the effects of non-supervised 24-week physical exercise on cognition, depression, and quality of life	Single blinded RCT with education as control	170 (Men 84, Women 86)	Community	**Exercise adherence rate:** 78%. **Global cognition:** ADAS-Cog, CDR-SOB **Memory:** Word list total immediate recall, Word list delayed recall. **Processing speed:** DSC subset of WAIS III. **Executive function:** VFT **Depression:** BDI **Quality of life:** SF-36	**Intervention:** Individualized walking and strength training without information on intensity. **Intervention's cognitive impact:** Global cognition and episodic memory. Throughout follow up periods at 6, 12, and 18 months, subjects in the exercise group had significantly better ADAS-Cog scores (*p*=0.04), and CDR-SOB (*p*=0.05) than those in the control group. For memory domain, delayed recall improved in the exercise group compared to the control (*p*=0.02), but immediate recall did not change significantly in both groups. For processing speed, executive function, depression, and quality of life, there was no significant change in either group.

Note: All values is mean (standard deviation) unless otherwise noted.
ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; BDI=Beck Depression Inventory; CDR-SOB=Clinical Dementia Rating-Sum of Boxes; DSC=Digit Symbol Coding; DSST=Digit Symbol Substitution Test; EFT=Eriksen Flanker Test; EPT=Everyday Problem Test; GDS=Geriatric Depression Scale; LSA=Life Space Assessment; MRI=Magnetic Resonance Imaging; RAVLT=Rey Auditory Verbal Learning Test; RCT=Randomized Controlled Trial; SCD=Subjective Cognitive Decline; SDL=Satisfaction in Daily Life; SF-36=Medical Outcomes Study 36-item Short Form; SPPB=Short Physical Performance Battery; TMIG-IC=Tokyo Metropolitan Institute of Gerontology Index of Competence; TMT=Trail Making Test; TUG=Timed Up and Go; UFOV=Useful Field of View; VDT=Verbal Digits Test; VFT=Verbal Fluency Test; WAIS-III=Wechsler Adult Intelligence Scale-III; YKSST=Yamaguchi Kanji-Symbol Substitution Test; 6MWT=6-Minute Walk Test.

Table 2: Summary of the studies with physical exercise in MCI (n=9).

Citation, Quality	Purpose	Study Design	N	Setting	Outcomes and Measures	Results
					Aerobic Exercise	
van Uffelen et al. 2008 Quality: Moderate	Examine the effects of 12-month aerobic exercise or vitamin B supplementation on cognition.	Double blinded, fully-factorial RCT with double sham (placebo activity program and placebo supplementation) as control.	152 (Men 85, Women 67)	Community	**Exercise adherence rate:** 63% **Global cognition:** MMSE **Memory:** AVLT **Executive function:** VFT **Information processing speed:** DSST **Attention:** The abridged SCWT	**Intervention:** Group-based walking with an intensity of over 3 metabolic equivalents. **Intervention's cognitive impact:** Episodic memory in men and attention in women. Within a year, neither the walking program nor the vitamin B supplementation improved cognition. However, the walking program improved memory in men (AVLT delayed recall, β=1.5, *p*=0.04) attending at least 75% of the sessions. Similarly, attention improved in women with higher attendance in the walking program (*p*=0.04).

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Baker et al. 2010 Quality: Strong	Examine the effects of 24-week supervised aerobic exercise, four times a week on cognitive performance and AD-related biomarkers in blood.	Single blinded RCT with stretching exercise as control	33 (Men 16, Women 17)	Memory disorder clinic	**Exercise adherence rate:** 94% **Executive function:** TMT, SCWT, TS, VF, SDMT **Memory:** SRT, LLT, DMST **Insulin, Cortisol, IGF-I:** Radioimmunoassay **BDNF:** ELISA	**Intervention:** Individualized treadmill walking or stationary bicycle riding with an intensity of 75% to 85% of the heart rate reserve. **Intervention's cognitive impact:** Executive function. At a 24-week follow up, results were different between women and men. For women, the aerobic exercise improved SDMT (*p*=0.04), VF (in category fluency, *p*=0.01), and SCWT (*p*=0.02). There was a trend toward improvement in TMT (*p*=0.09) in women. Also, the aerobic exercise reduced fasting plasma levels of insulin, cortisol, and BDNF in women. For men, the aerobic exercise improved TMT (*p*=.05) only. IGF-I also increased in the aerobic exercise in men. In both women and men, there were no improved memory tests.
Hildrethet al. 2015 Quality: Moderate	Examine the effects of 24-week Pioglitazone or supervised aerobic exercise on cognition.	Double blinded RCT	66 (Men 31, Women 35)	A research laboratory	**Exercise adherence rate:** 82% **Memory:** Visual Reproduction II, Logical Memory II, RAVLT **Language:** BNT, Category Fluency **Visuospatial function:** Block Design, Picture Completion **Executive function:** TMT B, DST **Other cognitive area:** ADAS-Cog, SCWT, WAIS, Clock Drawing test **Insulin sensitivity:** Whole-body GDR	**Intervention:** Individualized treadmill walking with an intensity of 50% to 85% of the maximum heart rate. **Intervention's cognitive impact:** Global cognition. Compared to the placebo group (control), GDR increased in the Pioglitazone group (mean: 0.1 *vs.* 1.7, *p*=0.002), but not in the aerobic exercise group. No treatment groups showed significant change from baseline to a 24-week follow up in any of cognitive domain measures, but ADAS-Cog improved in the aerobic exercise group compared to the placebo (mean: -1.6 *vs.* -0.3, *p*=0.05). Although change was not significant compared to the placebo, there was a trend towards improvement for Block Design in the aerobic exercise group (mean: 1.9 *vs.* 2.8, *p*=0.14). There were no significant correlations between change in GDR and cognitive performance in any group.
Resistance Exercise						
Fiatarone Singh et al. 2014 Quality: Strong	Investigate the effects of 26-week supervised cognitive training, progressive resistance training, combined cognitive and progressive resistance training, two times a week on cognition and functional independence.	Double blinded, fully-factorial RCT with double sham (educational videos and stretching) as control.	100 (Men 32, Women 68)	University clinic facility	**Exercise adherence rate:** 81% **Global cognition:** ADAS-Cog **Functional independence:** BAYER-ADL **Executive function:** WAIS-III, Category Fluency, COWAT **Memory:** List Learning Memory, BVRT, Logical Memory I and II **Attention/Speed:** SDMT	**Intervention:** Individualized weight machines or free weight training with an intensity of 15 to 18 on the Borg Scale. **Intervention's cognitive impact:** Global cognition, executive function, and visual/constructional memory. The progressive resistance training significantly improved global cognition at a 6-month (ADAS-Cog; relative effect size:-0.33, *p*<0.05), executive function at a 18-month (WAIS-III Matrices; relative effect size:-0.04, *p*=0.016), and visual/constructional memory at a 6-month follow up (BVRT; relative effect size:0.45, *p*=0.04). The cognitive training did not significantly improve any single test result at any time point, but only improved overall memory domain score at a 6-month follow up (relative effect size:0.23, *p*<0.05). Any interventions had no significant effect on functional independence and attention/speed. Moreover, The progressive resistance training 18-month benefit was 74% higher in executive domain (z-score change: 0.42 *vs.* 0.11, *p*=0.02), and 48% higher in global domain (z-score change: 0.45 *vs.* 0.23, *p*<0.05) than the combined training.
Mind-body Exercise						
Lam et al. 2011 Quality: Moderate	Examine the effects of 5-month Tai Chi on cognition.	A single blinded cluster RCT with stretching exercise as control.	389 from 38 clusters (Men 92, Women 297)	Community	**Exercise adherence rate:** Unknown **Global cognition:** CDR-SOB, Cantonese version of ADAS-Cog, MMSE **Language:** CVFT **Executive function:** TMT **Memory:** Delayed Recall Test, Digit Span Test **Attention:** Visual Span Test **Subjective cognitive complaints:** MIC **Depression:** CSDD **Neuropsychiatric symptoms:** NPI **Postural balance:** BBS	**Intervention:** Group-based 24-form simplified Tai Chi without a detail of intensity. **Intervention's cognitive impact:** Attention and global cognition. Between baseline and a 5-month follow up, MMSE, ADAS-Cog, Delayed Recall Test, TMT, CVFT, and MIC significantly improved in both groups (*p*<0.01). Improvements in BBS, Visual Span Test, and CDR-SOB were observed in the Tai Chi group only (*p*<0.05). Between the Tai Chi and the Stretching, change scores from baseline to a 5-month follow up in Visual Span Test [backward, 0.4 (1.0) *vs.* 0.08 (0.9), *p*<0.01], BBS [0.5 (2.3) *vs.* 0.1 (2.0), *p*<.05], and CDR-SOB [0.3 (0.8) *vs.* -0.2 (1.6), *p*<0.001] were significantly different.

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Lam et al. 2012 Quality: Moderate	Examine the effects of 12-month Tai Chi on cognition.	A single blinded cluster RCT with stretching exercise as control.	389 from 38 clusters (Men 92, Women 297)	Community	**Exercise adherence rate:** Unknown **Progression to dementia:** DSM-IV criteria **Global cognition:** CDR-SOB, Cantonese version of ADAS-Cog, MMSE **Language:** CVFT **Executive function:** TMT **Memory:** Delayed Recall Test, Digit Span Test **Attention:** Visual Span Test **Depression:** CSDD **Neuropsychiatric symptoms:** NPI **Postural balance:** BBS	**Intervention:** Group-based 24-form simplified Tai Chi without a detail of intensity. **Intervention's cognitive impact:** Global cognition. Group differences regarding the change from baseline to a 12-month follow up was analyzed based on ITT or completers-only (CO) analysis. The Tai Chi (T) group showed lower risk of developing dementia compared to the stretching (S) group (ITT: p=0.06, CO: p=0.04). CDR-SOB significantly improved in T compared to S (ITT: p=0.04, CO: p=0.004). For MMSE, ADAS-Cog, CVFT, Delayed Recall Test, Digit Span Test, Visual Span Test, TMT, CSDD, NPI, differences between T and S regarding the change of these parameters were not significant with ITT analysis. However, in CO analysis, T had greater improvement in Delayed Recall Test (p=0.05), and CSDD (p=0.02) compared to S. BBS improved significantly in T compared to S (ITT: p=0.05, CO: p=0.02).
Multicomponent Exercise						
Lam et al. 2015 Quality: Strong	Investigate the effect of 12-month supervised cognitive training, physical exercise, combined cognitive and physical exercise, three times a week on cognition, depression, and IADL.	A single blinded cluster RCT	555 from 44 clusters (Men 121, Women 434)	Community	**Exercise adherence rate:** 75% **Global cognition:** CDR-SOB, Cantonese version of ADAS-Cog, MMSE **Memory:** Delayed Recall Test, Digit Span Test **Language:** CVFT **Depression:** CSDD **IADL:** CDAD **Adherence:** Percentage participation of sessions per week	**Intervention:** Group-based combined stretching/static bicycle riding/Tai Chi exercise without a detail of intensity. **Intervention's cognitive impact:** Global cognition, episodic memory, and language. No changes are observed on CDR-SOB, CDAD, and MMSE in any group at the end of study. However, tests for Digit Span, ADAS-Cog, Delayed Recall, CVFT, and CSDD improved in all groups over time (p<0.05). The combined cognitive and physical exercise group resulted in better improvement on CVFT (p<0.001) compared to other groups. The overall adherence rate was 73%, considered as satisfactory.
Suzuki et al. 2012 Quality: Strong	Examine the effects of 12-month multicomponent exercise, twice a week on cognition.	A single blinded RCT with health education as control	50 (Men 27, Women 23)	Community	**Exercise adherence rate:** 79% **Global cognition:** MMSE **Logical memory function:** WMS-LM I and II **Processing speed:** DSC subset of WAIS III **Language:** LVFT, CVFT **Executive function:** SCWT I and III	**Intervention:** Group-based combined muscle strength/walking/balance exercise with an intensity of average 60% of the maximum heart rate **Intervention's cognitive impact:** Global cognition, immediate memory, and language. The exercise group showed significant improvement on MMSE (F=3.4, p=0.04), WMS-LM I (F=3.9, p=0.03), and LVFT (F=4.1, p=0.02) over time compared to the control group. However, there was no significant improvement on WMS-LM II, DSC, CVFT, and SCWT in the exercise group compared with the control group.
Suzuki et al. 2013 Quality: Strong	Examine the effects of 6-month multicomponent exercise, twice a week on cognition.	A single blinded RCT with health education as control.	100 (Men 78, Women 22)	Community	**Exercise adherence rate:** 86% **Global cognition:** MMSE, ADAS-Cog **Logical memory:** WMS-LM I and II **Brain atrophy level:** MTA-ERC atrophy level and WBC atrophy level using MRI **Biomarker:** Total cholesterol, HbA1c, BDNF, VEGF using blood samples	**Intervention:** Group-based combined muscle strength/walking/balance exercise with an intensity of average 60% of the maximum heart rate. **Intervention's cognitive impact:** Global cognition and immediate memory (in participants with amnestic MCI). For all MCI subjects, there was no difference between the groups on global cognition, logical memory, and brain atrophy level. For amnestic MCI subjects only, The exercise group showed significant improvement on MMSE (effect size: 0.31, p=0.04), WMS-LM I (effect size: 0.31, p=0.04), and WBC atrophy level (effect size: 0.29, p<0.05) over time compared to the control group. However, on ADAS-Cog, WMS-LM II, MTA-ERC atrophy level, there was no difference between the groups. For all MCI subjects, independent of age, sex, educational level, and the intervention group, low total cholesterol level and high BDNF level at baseline was associated with improvement on WMS-LM I (OR: 0.98, p=0.02), and on ADAS-Cog (OR: 1.07, p=0.01), respectively. There was no significant relationship between other biomarkers and cognitive domain.

Note: All values is mean (standard deviation) unless otherwise noted.

AD=Alzheimer's Disease; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; AVLT=Auditory Verbal Learning Test; BAYER-ADL=Bayer Activities of Daily Living; BBS=Berg Balance Scale; BDNF=Brain-derived Neurotrophic Factor; BNT=Boston Naming Test; BVRT=Benton Visual Retention Test; COWAT=Controlled Oral Word Association Test; CDAD=Chinese Disability Assessment for Dementia; CDR-SOB=Clinical Dementia Rating-Sum of Boxes; CI=Confidence Interval; CSDD=Cornell Scale for Depression in Dementia; CVFT=Category Verbal Fluency Test; DMST=Delayed Match to Sample Test; DSC=Digit Symbol Coding; DSM-IV=Diagnostic and Statistical Manual of Mental Disorder-IV; DST=Digit Symbol Test; DSST=Digit Symbol Substitution Test; ELISA=Enzyme-linked Immunosorbent Assay; GDR=Glucose Disposal Rates; HbA1c=Hemoglobin A1c; IADL=Instrumental Activities of Daily Living; IGF-I=Insulinlike Growth Factor I; ITT=Intention to Treat; LLT=List Learning Test; LVFT=Letter Verbal Fluency Test; MCI=Mild Cognitive Impairment; MIC=Memory Inventory for the Chinese; MMSE=Mini-Mental State Examination; MRI=Magnetic Resonance Imaging; MTA-ERC=Medial Temporal Areas including the Entorhinal Cortex; NPI=Neuropsychiatric Inventory; OR=Odds Ratio; RAVLT=Rey Auditory Verbal Learning Test; RCT=Randomized Controlled Trial; SCWT=Stroop Color and Word Test; SDMT=Symbol Digit Modalities Test; SRT=Story Recall Test; TMT=Trail Making Test; TS=Task Switching; VEGF=Vascular Endothelial Growth Factor; VF=Verbal Fluency; VFT=Verbal Fluency Test; WAIS-III=Wechsler Adult Intelligence Scale-III; WBC=Whole Brain Cortices; WMS-LM=Wechsler Memory Scale-Logical Memory subtest.

participants had SCD or MCI 4) studies dealt with physical exercise interventions 5) Cognition or cognitive function was measured as an outcome.

The exclusion criteria were: 1) Studies published in a language other than English 2) Review types of commentary, non-intervention study, quasi-experimental design or case study 3) Participants without SCD or MCI 4) Interventions that did not contain physical exercise 5) Outcomes other than cognition or cognitive function.

This review defined SCD using the criteria from the Subjective Cognitive Decline Initiative (SCD-I) [5]. Persons with SCD should have: 1) Self-experienced persistent decline in cognitive capacity in comparison with a previously normal status and unrelated to an acute event 2) Normal age, gender and education-adjusted performance on standardized cognitive tests, which are used to classify MCI or prodromal AD 3) No MCI, prodromal AD and dementia and 4) SCD that cannot be explained by a psychiatric condition, neurologic disease, medical disorder, medication, or substance use. According to Vega et al. there are 3 criteria which are currently recognized to diagnose MCI [11]. This review defined MCI using either of these 3 criteria from: 1) the Mayo Clinic [9,10] 2) the NIA-AA on MCI due to AD [3] or 3) the fifth edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) [21].

Global cognition or at least one domain of specific cognitive abilities (eg. executive function, learning, memory, attention and language) was assessed by standardized neurocognitive tests or other objective measures (Tables 1 and 2).The matrix system after Garrard was used to summarize the included studies [22]. Lead author's name, date, purpose, study design, sample size, setting, outcomes/measures, and results were extracted (Tables 1 and 2). The quality of studies was assessed using the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies [23]. Ratings included: strong quality (No weak ratings among 6 categories) moderate quality (One weak rating) or weak quality (two or more weak ratings). The EPHPP has 6 categories including selection bias, study design, confounders, blinding, data collection method and withdrawals. Each category is graded as 'strong', 'moderate' or 'weak'. The category ratings together gave an overall quality rating (Tables 1 and 2).

A total of 94 articles were generated and 9 duplicates were removed. Of those 85 articles 47 remained after abstracts were screened for eligibility using the inclusion and exclusion criteria by the reviewer (SA). The reviewer read those 47 full text articles to assess the eligibility. Finally a total of 15 (SCD=6, MCI=9) met the eligibility criteria and were included in this review (Figure 2).

Results

The effects of physical exercise on cognition in SCD

A total of 6 SCD studies were included in this review. Two of 6 studies were conducted in Canada (n=2) with the remaining 4 conducted in Australia (n=1) China (n=1) Japan (n=1) and the United States (n=1) [24-29]. Five of the 6 studies were rated with strong quality and 1 with moderate quality (Table 1). The mean ages in the 6 studies ranged from 69 to 75. Among the 6 studies 2 used aerobic exercise, 1 used resistance exercise, 2 used either aerobic or resistance exercise and 1 used multicomponent exercise (i.e., combined aerobic/resistance exercise) [24-29]. Five of the 6 studies used supervised exercise but 1 study did not [26]. The exercise dropout rates were 5%, 12%, 19% or 7% to 20%. The exercise adherence rates were 78%, 80%, 86%, 88% or 54% to 60% [24-29]. The reasons for dropout included illness and unwillingness to continue [24-26,29]. While factors affecting exercise adherence were not reported in all included studies 1 study provided a social cognitive theory-based intervention package which comprised information on exercise programs, rewards, goal setting, time management, barriers to activity and safe exercise in order to enhance adherence [26]. No adverse events directly related to interventions were reported in the included SCD studies.

Five of the 6 studies (83%) in SCD showed that the physical exercise intervention used significantly improved cognition compared to control or other interventions [24-28]. For aerobic exercise each dose had its own effect on cognition. For example a 3-month group-based walking without a detail of intensity (90 minutes per session, once a week) significantly improved word fluency compared to an education [28]. A 6-month individualized walking with an intensity of 40% to 80% of the heart rate reserve (60 minutes per session, 2 times a week) was efficacious for improving verbal and spatial memory compared to a balance and tone training [24]. However a 3-month individualized dance with an intensity of 60% to75% of age-adjusted maximum heart rate (60 minutes per session, 3 times a week) resulted in global cognition improvement that was equally beneficial with a stretching [29].

For resistance exercise each dose also had its own effect on cognition. For example a 6-month individualized weight machines or free weight training with an intensity of 2 sets of 6 to 8 repetitions (60 minutes per session, 2 times a week) significantly improved selective attention, associative and spatial memory compared with a balance and tone training [24,25]. 3-month individualized dumbbell training with an intensity level tailored to the capability of each participant (60 minutes per session, 3 times a week) significantly improved global cognition compared to a regular lifestyle routine [27]. For multicomponent exercise, global cognition and episodic memory were significantly improved in a 6-month individualized walking and strength training without information on intensity (50 minutes per session, 3 times a week) compared with an education [26].

Based on the results of introduced interventions aerobic exercise was effective in improving word fluency and verbal memory while resistance exercise improved selective attention and associative memory. Both aerobic and resistance exercise improved global cognition and spatial memory. Multicomponent exercise (i.e., combined aerobic/resistance exercise) was effective in improving global cognition and episodic memory.

The effects of physical exercise on cognition in MCI

A total of 9 MCI studies were included in this review. Three of 9 studies were conducted in China (n=3) with the remaining 6 conducted in Australia (n=1) Japan (n=2) the Netherlands (n=1) and the United States (n=2) [30-38]. Five of the 9 studies were rated with strong quality and 4 with moderate quality (Table 2). The mean ages in the 9 studies ranged from 65 to 78. All 9 studies used the Mayo Clinic criteria for MCI diagnosis. Among the 9 studies 3 used aerobic

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exercise, 1 used resistance exercise, 2 used 24-form simplified Tai Chi a form of mind-body exercise and 3 used multicomponent exercise (i.e., combined stretching/aerobic/mind-body exercise or combined resistance/aerobic/balance exercise [30-37]). Seven of the 9 studies used supervised exercise. The remaining 2 Tai Chi studies used supervision for 8 to 12 or 4 to 6 weeks but did not use supervision after this period [31,32]. The exercise dropout rates were 4%, 6%, 10%, 17%, 21%, 22%, 27%, 35% and 46% [30-38]. The exercise adherence rates varied from 63%,75%, 79%, 81%, 82%, 86% to 94% with 2 studies without information of adherence rate [30-37]. The reasons for dropout included illness and unwillingness to continue while 1 study reported that the adherence rate was higher in persons living with a partner [36-38]. No adverse events directly related to interventions were reported in the included MCI studies.

Five of the 9 studies (56%) in MCI showed that the physical exercise intervention used significantly improved cognition compared to control or other interventions [31-34,38]. For aerobic exercise each dose had its own effect on cognition. For example a 6-month individualized treadmill walking with anintensity of 50% to 85% of the maximum heart rate (60 minutes per session, 3 times a week) significantly improved global cognition compared with a regular lifestyle routine [38]. A 6-month individualized treadmill walking or stationary bicycle riding with an intensity of 75% to 85% of the heart rate reserve (45 to 60 minutes per session, 4 times a week) was efficacious for improving executive function compared to a stretching but the effect was more prominent in women than men [37]. In addition a 12-month group-based walking with an intensity of over 3 metabolic equivalents (60 minutes per session, 2 times a week) resulted in episodic memory improvement in men and attention improvement in women in those with better adherence [36].

For resistance exercise a 6-month individualized weight machines or free weight training with an intensity of 15 to 18 on the Borg Scale (75 minutes per session, 2 times a week) significantly improved global cognition, executive function and visual/constructional memory compared with a combined cognitive/resistance or a cognitive training [33]. For Tai Chi effects on cognition varied by a durarion of interventions. A 5-month group-based 24-form simplified Tai Chi without a detail of intensity (at least 30 minutes per session at least 3 times a week) was efficacious for improving attention and global cognition compared to a stretching whilethe same dose of a 12-month program significantly improvedglobal cognitioncompared with a stretching [31,32].

For multicomponent exercise a 12-month group-based combined stretching/static bicycle riding/Tai Chi exercise without a detail of intensity (60 minutes per session, 3 times a week) significantly improved global cognition, episodic memory and language however a combined physical/cognitive activity showed better improvement on language than a multicomponent exercise [30]. Meanwhile cognitive gains differed by a duration of interventions. For example among participants with MCI a 6-month group-basedcombined muscle strength/walking/balance exercise with an intensity of average 60% of the maximum heart rate (90 minutes per session, 2 times a week) significantly improved global cognition and immediate memory compared to a health education in participants with amnestic MCI only where as the same dose of a 12-month program for participants with amnestic MCI significantly improved global cognition, immediate memory and language compared with a health education [34,35].

Based on the results of introduced interventions aerobic exercise was effective in improving executive function, episodic memory and attention but gender or adherence rate can play a role in an efficacy of this mode. Resistance exercise improved executive function and visual/constructional memory. Tai Chi was effective in improving attention. Aerobic, resistance and Tai Chi exercise all improved global cognition. Cognitive gainsof multicomponent exercises were similar (i.e., global cognition, episodic or immediate memory and language) despite different components: combined stretching/aerobic/mind-body exercise *versus* combined resistance/aerobic/balance exercise.

Discussions

This review examined the effects of physical exercise interventions on cognition in persons with SCD or MCI. Introduced interventions were aerobic, resistance and multicomponent exercise (i.e., combined aerobic/resistance exercise) for SCD as well as aerobic, resistance, Tai Chi and multicomponent exercise (i.e., combined stretching/aerobic/mind-body or combined resistance/aerobic/balance exercise) for MCI. In these populations the findings of this review indicate that physical exercise interventions can improve cognition. Overall 67% of the studies (5 of the 6 studies in SCD and 5 of the 9 studies in MCI) indicated that the physical exercise intervention used significantly improved cognition compared to control or other interventions. Although the characteristics of samples were heterogeneous among studies, different doses of aerobic or resistance exercise had different cognitive outcomes in persons with SCD. However this finding cannot be overestimated as the dose-response relationships of aerobic or resistance exercise for SCD. An equivalent benefit on global cognition occurred between aerobic exercise and the control in 1 SCD study [29]. Difference between the groups may emerge in a different dose. A multicomponent exercise consisting of combined aerobic/resistance exercise improved global cognition and episodic memory [26]. It is possible that aerobic and/or resistance exercise may improve global cognition and/or episodic memory in the dose of this multicomponent exercise. It is noteworthy that the samples of 2 studies for SCD were only comprised of women [24,25]. Therefore an interpretation for the influence of either aerobic or resistance exercise in SCD can be restricted.

One multi component exercise and 1 aerobic exercise lack information on specific intensity [26,28]. This may make it hard to replicate interventions in the future. It is significant to see whether interventions'effects on cognition are prolonged as well as to help participants comply with exercise programs continuously. However most of the studies did not measure outcome variables beyond the end of the intervention period and only 1 study adopted a method (i.e., a theory-based approach) to facilitate exercise resulting in 78% of adherence rate [24,25,27-29]. A health behavior theory-guided approach is known to be more effective for facilitating health behavior (e.g., exercise) than a-theoretical way [39]. In this review this approach may help increase participants'adherence rate given that 2 studies without any theoretical basis showed relatively low adherence rate (i.e., 54% to 60%) [24,25].

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For MCI the current findings of improved global cognition and executive function from aerobic exercise interventions are consistent with previous reviews but this review added new evidence of the effects of modalities other than aerobic exercise [19,20]. Similar to aerobic exercise in SCD the effects of aerobic exercise on cognition in persons with MCI varied depending on each dose although it should be interpreted with caution due to hetero geneous sample characteristics among studies. A gender-specific intervention effect was shown in 1 aerobic exercise study indicating a better effect on executive function in women [37]. This sex difference in cognitive response may be derived from metabolic effects of exercise. It was indicated that aerobic exercise enhanced gluco regulation and insulin sensitivity for women but not for men [37]. However this result cannot be generalized by 1 study with a small sample size (n=33).

Tai Chi is considered to be a light to moderate intensity exercise with estimated metabolic equivalents between 1.5 and 4.0 [40]. It makes comparison of the effects across exercise modes available although no specific Tai Chi intensity was reported in the included studies. The effects of introduced multicomponent exercises on cognition (i.e., improved global cognition, episodic or immediate memory and language) might come from a single mode of intervention (i.e., aerobic, resistance or Tai Chi exercise) in the specific dose of each multicomponent exercise. However it is also possible that cognitive gains could be earned by stretching or balance exercise.

It is important to note that the samples of 4 studies were only comprised of persons with amnestic MCI [31,32,34,37]. Therefore the effects of Tai Chi aerobic and multicomponent exercise (i.e., combined resistance/aerobic/balance) on cognition cannot be applicable to non-amnestic MCI. A majority of studies in MCI did not measure cognition after the intervention period [30-32,34,37,38]. A longer follow up time may permit identification of consistent effects of intervention on cognition. Given that persons living with a partner reported higher adherence rate monitoring from people in a trustful relationship may help participants adhere to exercise [36]. In addition considering the fact that one of the reported reasons for dropout was unwillingness finding special ways such as regular reminders or motivation to target persons with MCI may be recommended because cognitive gains can be greater in participants who conform with the exercise program [36,38]. Given that persons with MCI preserve their independence of function in daily life and more than 76% of older adults aged 65 and over own cell phones in the United States, a motivational mobile text message which was effective in increasing walking count among non-demented older adults can be an useful option [3,41,42].

Strengths and limitations

This review has comprehensively examined various modes of physical exercise and their effects on cognition in persons with SCD or MCI. However this review has some limitations. First the SCD studies in this review might include MCI populations. They completely excluded dementia but did not treat MCI criteria except for 1 study which included some MCI populations [26]. Second some cognitive measures assessing the same cognitive domain differ from study to study so the results were not always directly comparable to each other even if tests were designed to measure the same cognitive domain. Third this review is limited by the scope of the literature search. It is possible that some relevant literatures are published in databases other than Ovid MEDLINE and Ovid EMBASE. Finally the literature search was only concentrated on studies published in English. Therefore certain relevant articles might be omitted.

Implications for research and practice

This review has several implications for research. To begin with more samples defined using criteria from the NIA-AA and SCD-I are required to see the effects of physical exercise on cognition in the clinical trajectory of AD [3,5]. Future studies can adopt AD-associated biomarkers to include these samples. AD-associated biomarkers for example low Cerebrospinal Fluid (CSF) Beta-amyloid protein (Aβ) level and hippocampal volume atrophy can be found in persons with SCD or MCI indicating a high likelihood of progression to AD [3, 43]. In addition, given that this review did not deal with a biological basis of how to improve cognition presented in Figure 1, incorporating biological variables is recommended to see which modality can explain a certain mechanism in these populations.

Studies for SCD or MCI also need to identify the effectiveness of interventions by gender or MCI sub-types. For intervention dose future research should not omit dose information because the effectiveness of interventions can be readily translated to practice by reporting exact exercise dose. Future studies should also reflect on this review to further test the dose-response relationship as well asthe minimally-effective or optimal dose of each modality in order to improve cognition for persons with SCD or MCI. For measures and follow up periods more research is needed to measure each cognitive domain using the same standardized tools to directly compare between studies. A longer follow up period beyond the end point of the intervention is also needed because a maintenace of positive effects on cognition could give a hint for better modality or dose.

This review has clinical implications. Although there is no consensus regarding an optimal exercise mode or dose, clinicians can refer to the findings of this review when prescribing physical exercise to persons with SCD or MCI to improve cognition. After discussing the potential benefits and risks clinicians can choose appropriate modality and dose based on each person's age, medical frailty or physical fitness. Once prescribed nurses can adopt health behavior theory-based approaches to helppersons with SCD or MCI to keep exercise schedules. Adherence can be betterfacilitated by establishing rapport between nurses and participants by requesting that caregivers remind participants about their exercise program or by using ways to motivate participants to exercise such as a motivational text message.

Conclusion

As the population with AD increases, activities to maintain or improve cognition of persons at a higher risk of developing AD will be increasingly important to delay the onset of AD. Promotion of aerobic and/or resistance exercise for SCD as well as aerobic, resistance, Tai Chi and multicomponent exercise for MCI may help toward this goal.

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