Exercise and Cognitive Functions in People with Mild to Moderate Alzheimer's Disease: A Systematic Review

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Abstract

Background: Alzheimer's disease is a neurodegenerative disease, a progressive brain disorder that slowly declines cognitive functions. Furthermore, a higher incidence rate and prevalence have been reported in older adults. Several studies have been reported that exercise might be an intervention to delay cognitive decline in older people.

Objective: To determine a type of exercise that appropriate on cognition in people with mild to moderate severity of Alzheimer's disease

Methods: The literature searches focused on PubMed, Cochrane Library, PEDro, and ScienceDirect from 1978 to December 2017. The inclusion criteria were randomized control trials studies, non-randomized control trials studies that examined the effect of exercise on cognitive function in people with mild to moderate severity of Alzheimer's disease (AD), and all journal articles were published in English languages. In addition, the reviewers independently screened the trials for eligibility criteria. Data extraction from each of the studies was completed in detail by one reviewer and accuracy was checked by another reviewer.

Results: Of the 6344 studies, only six studies were included in the review. The level of quality was poor to good level with an average PEDro scale was 5.4. It has been found that different types of exercise such as balance exercise, endurance or aerobic exercise, resistance or strengthening exercise, affected on cognition in people with AD. However, a number of clinical studies reported that combined exercise had high effectiveness in delaying cognitive impairment in people with AD. However, two studies reported that there was no significant difference between groups and between before and after training whereas four studies showed significant difference in cognition between before and after training.

Conclusions: Combined exercise may be appropriate to delay the cognitive function in people with Alzheimer's disease.

Keywords: Alzheimer, exercise, combined exercise, cognitive function, systematic review

การออกกำลังกายและการรู้คิดในผู้ป่วยอัลไซเมอร์ที่มีความรุนแรงระดับเล็กน้อยถึงปานกลาง: การทบทวนวรรณกรรมอย่างมีระบบ

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บทคัดย่อ

ความสำคัญของปัญหา: โรคอัลไซเมอร์เป็นโรคที่มีความเสื่อมถอยของสมองลงอย่างช้า ๆ ในเรื่องของความสามารถด้านการรู้คิด ปัจจุบันมีความชุกของโรคที่เพิ่มมากขึ้นในกลุ่มผู้สูงอายุ การศึกษามากมายได้มีการรายงานถึงผลของการออกกำลังกายสามารถชะลอความเสื่อมของการรู้คิดในผู้สูงอายุปกติได้

วัตถุประสงค์: เพื่อศึกษารูปแบบของการออกกำลังกายที่เหมาะสมต่อการรู้คิดในกลุ่มผู้ป่วยอัลไซเมอร์ที่มีความรุนแรงระดับเล็กน้อยถึงปานกลาง

วิธีดำเนินการศึกษา: ทำการสืบค้นงานวิจัยจาก 4 ฐานข้อมูล ซึ่งประกอบไปด้วย PubMed, Cochrane Library, PEDro และScienceDirect โดยสืบค้นจากฐานข้อมูลตั้งแต่ พ.ศ.2521 จนถึงเดือน ธันวาคม พ.ศ.2560 เกณฑ์ในการคัดเข้าประกอบด้วย จะต้องเป็นการศึกษาแบบการทดลอง โดยทุกการศึกษาจะต้องตีพิมพ์ด้วยภาษาอังกฤษ ศึกษาในกลุ่มผู้ป่วยอัลไซเมอร์ที่มีความรุนแรงระดับเล็กน้อยถึงปานกลางและทำการศึกษาเกี่ยวกับผลของการ ออกกำลังกายต่อการรู้คิด ซึ่งการคัดเลือกการศึกษาในครั้งนี้ จะมีผู้คัดเลือก 2 ราย ทำการประเมินและคัดเลือกอย่างอิสระตามเกณฑ์การคัดเข้าที่ได้มีการกำหนดไว้

ผลการศึกษา: จากการคัดเลือกทั้งหมด 6,344 เรื่อง มีเพียง 6 เรื่องที่ผ่านการคัดเลือกเข้าการศึกษา ในครั้งนี้ สำหรับคุณภาพของการศึกษาทั้งหมดอยู่ในระดับแย่ถึงระดับดี โดยค่าเฉลี่ยของคะแนน PEDro อยู่ที่ 5.4 และจากการศึกษาพบว่าการออกกำลังกายที่ส่งผลดีต่อการเปลี่ยนแปลงด้านการรู้คิดในผู้ป่วยอัลไซเมอร์มีหลายรูปแบบที่แตกต่างกัน ในปัจจุบันพบว่ามีการศึกษาจำนวนมากที่ทำการศึกษาผลของการออกกำลังกายแบบผสมผสาน และผลการศึกษาพบว่าสามารถช่วยชะลอความเสื่อมของการรู้คิดในผู้ป่วยอัลไซเมอร์ได้ แต่อย่างไรก็ตามจากการศึกษาทั้งหมด 6 เรื่อง พบว่าการศึกษา 2 เรื่องไม่มีการเปลี่ยนแปลงอย่างมีนัยสำคัญทางสถิติเมื่อมีการเปรียบเทียบระหว่างกลุ่มและระหว่างก่อนและหลังทำการฝึกและ 4 เรื่องที่มีการเปลี่ยนแปลงอย่างมีนัยสำคัญทางสถิติเมื่อมีการเปรียบเทียบระหว่างก่อนและหลังทำการฝึก

สรุป: การออกกำลังกายในรูปแบบ ผสมผสานเป็นรูปแบบที่เหมาะสมต่อการชะลอความเสื่อมของการรู้คิดในผู้ป่วยอัลไซเมอร์

Background

Recently, several studies have reported that numbers of older people are increasing. It has been estimated that the total number of older people will be more than tripled from the year 2000 to 2050 [1]. Older adults are more prone to be at risk of many problems from degeneration. One of the problems is deterioration of brain; in other words, dementia is the top of disease in older adults. It is a common degenerative neurological disorder in old age. Symptoms of degenerative neurological disorders are cognitive impairment, physical decline, and behavioral changes [2]. Alzheimer's disease (AD) is the most subtype of dementia, accounting for up to 60%-80% of all dementia cases. AD is a progressive brain disorder that slowly declines cognitive abilities. Several evidences indicated that there was correlation among genetic, environmental risk factors and AD. The prevalence of AD was 26.6 million in 2006 and it is estimated that it will increase four times by 2050 [3]. AD has been categorized into 3 stages: early, middle, and late stage. The most important symptoms of AD are declines in performance on cognitive tasks; for example, attention deficits, working memory, problem solving, and executive function [4, 5]. Cognitive decline is the primary problem in Alzheimer's patients. In addition, AD may affect communication skills, movement skills, balance, muscle strength, and personality [4]. To date, the method to treat patients with AD consists of pharmacological and non-pharmacological treatments [6]. Pharmacological treatment has been found to exert a lot of benefits , such as improvement and maintenance of cognitive functions, decrease disturbed behaviors, and maintain functional ability [7]. However, there are some limitations regarding their side effects such as vomiting, anorexia, and nausea. In addition, pharmacological treatment is expensive [8]. In contrast to the pharmacological treatment, non-pharmacological treatments such as cognitive behavioral therapy, music therapy, and exercise appear to be useful to treat AD. Previous studies have shown that exercise effectively delayed cognitive decline [9, 10]. It could increase cerebral blood flow, oxygen supply, other essential supplies within brain, improved synthesis of neurotransmitters [11] and reduced brain tissue loss with ageing [12]. Currently, a growing evidence has shown the relationship between exercise and cognition. There are many types of exercise that could be able to delay the cognitive decline. Previous studies suggested that aerobic exercises can delay cognitive decline [13]. The mechanism that aerobic exercise delays cognitive decline, is to increase hippocampus volume translation to improve cognitive function [14]. Aerobic exercise not only improves cognition, but also improves mobility; walking speed and number of steps [15], improves mental health and decreases negative emotions [16]. There are many different types of aerobic exercise to delay the cognitive decline, for example cycling, walking, treadmill training, home-based exercise, music based. It has been reported that programs of physical activity can improve cognitive function in older adults with cognitive impairment [17]. However, it is unclear regarding the characteristics of exercise intervention program to improve cognitive function in people with mild to moderate stages of AD. Therefore, this review focused on effect of exercise interventions on cognition in patients with mild to moderate AD. The aim of this systematic review was to determine exercise program and cognitive functions in people with mild or moderate stages of AD.

Methods

Type of studies

All selected studies that reported the effect of exercise on cognitive function in different study designs e.g., control trial study; randomized controlled trials (RCTs) and non-randomized controlled were included. Type of outcome measurement was cognition. Cognition or mental activities are how people acquire, store, retrieve, and use knowledge. In this study, the performance

of cognition is defined as eight domains of mental processes: perception, language, memory, imagery, concept formation, problem solving, decision making, and reasoning [18].

Inclusion and exclusion criteria

The inclusion criteria of participants were as follows: all participants were diagnosed with AD with mild to moderate AD by using the criteria for the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association. The age of participants was 60 years or older with both males and females. All studies had to be published in English language. The exclusion criteria were as follows: pharmacological studies in patients with AD, animal studies, and studies in the other types of dementia, such as vascular dementia, mixed dementia, and frontotemporal dementia.

Search strategy

The literature review focused on PubMed, Cochrane Library, PEDro, and Science direct. The following search terms were used: exercise, physical, training, Alzheimer's, dementia, cognitive, and cognition. A systematic review was searched from the year 1978 to December 2017. The key words used to search in computerized databases include of cognition, cognitive function, memory, executive function, executive control, executive controls, exercise, physical, physical exercise, Alzheimer, dementia, Alzheimer Sclerosis, Alzheimer Dementia. These key words were combined. The reviewer also contracted authors study if there were insufficient information.

Data extraction

Data extraction form of each study was completed in detail by one reviewer and checked for accuracy by another reviewer. Check lists used by two reviewers contained a number of inclusion criteria of studies, data synthesis and documentation of conflict of interest. However, disagreements regarding were resolved by discussion. Cohen's kappa coefficient was used to measure inter-rater agreement for qualitative (categorical) items from two reviewers and accounts the possibility of the agreement occurring by chance. The table of data extraction consisted of PEDro scale, number of participants, intervention, setting, schedule, and cognitive measures. (Table 1)

Quality assessment of clinical trial evidence

The PEDro scales were used to assess the quality of clinical trials. It consists of 10 items: random allocation, concealed allocation, similarity at baseline, subject blinding, therapist blinding, assessor blinding, > 85% follow up for at least one key outcome, intention-to treat analysis, between-group statistical comparison for at least one key outcome, and point and variability measurement for at least one key outcome [19]. Level of PEDro scores are 4 levels; the scoring 9-10 on the PEDro scale is considered to be of "excellent" methodologically quality, scoring 6-8 is defined as good quality , scoring 4-5 is fair quality, and below 4 is a poor quality [20].

Data synthesis

Data synthesis was displayed in table 1. The table provided PEDro score, number of participants in each group, mean age, exercise program, intensity, outcomes and summary of results.

Table 1:

Present about Characteristics of studies type of exercise on cognition in people with mild to moderate severity Alzheimer's disease.

Title	Pedro scale	Sample			Age (Mean)	Setting	Exercise		Intensity	Outcome	Results
		Control	Exercise	Other			Exercise group	Control group			
1. Hoffmann K. et al. ,2015	7/10	100	100	-	70.5	Memory clinic	**Two phases** **1. Adaptation (4 weeks)** **1.1 Build-up strength** of lower extremity (2 times/week) **1.2 Exercise program** (1 time/week) 1.2.1 Warm-up 10 min Balance training 1.2.2 Aerobic exercise Bicycle ergometer, Treadmill training (10 min/bout, 3 bouts, 2-5 min rest between) [Intensity:50-60%of HRR, or 12-14 on Borg Scale] 1.2.3 Cool-down 10 min low load exercise Quadriceps muscle, Hamstring, and stretching **2. Moderate-high training** (12 weeks) same as Adaptation phase, but [Intensity:70-80%of HRR, or 15-17 on Borg Scale]	usual care	60 min/ time, 3 times/ week, 4 months	**Primary outcome:** - The Symbol Digit Modalities Test (SDMT) **Secondary outcome**: - Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) - The Stroop Color and Word Test (Stroop) - Verbal fluency test - Mini mental state examination (MMSE)	No significant different on cognitive test between exercise and control group, and between before and after exercise

Table 1:

Present about Characteristics of studies type of exercise on cognition in people with mild to moderate severity Alzheimer's disease. (Con.)

Title	Pedro scale	Sample			Age (Mean)	Setting	Exercise		Intensity	Outcome	Results
		Control	Exercise	Other			Exercise group	Control group			
2. Yang S. et al., 2015	5/10	25	25	-	71.5	Rehab-clinic	**Two phases** **First week** Aerobic exercise (40 min) - Warm-up 5 min - Cycling training with moderate, 70% of maximum heart rate (MHR) (the exercise load was 0. 5kg.M-1 kg.M) 30 min - Reorganization movement 5 min **One week later** Aerobic exercise (50 min) - Warm-up 5 min - Cycling training with moderate, 70% of maximum heart rate (MHR) (the exercise load was 1kg.M) 40 min - Reorganization-movement 5 min ***The training progress was supervised by therapist.**	health education	40 min/day, 3 days/ week, 3 months	- Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog) - Mini mental state. examination (MMSE)	- Minimum Mental State Examination score was significantly increased - The Alzheimer's Disease Assessment Scale-cognition score was significantly decreased in aerobic group before and after 3 months

Table 1:

Present about Characteristics of studies type of exercise on cognition in people with mild to moderate severity Alzheimer's disease. (Con.)

Title	Pedro scale	Sample			Age (Mean)	Setting	Exercise		Intensity	Outcome	Results
		Control	Exercise	Other			Exercise group	Control group			
3. Vreugdenhil A. et al., 2012	6/10	20	20	-	74.1	Individual home	**Aerobic exercise** : walking **Balance exercise and strength exercise** : Daily home-based exercises : Home Support Exercise Program (HSEP) consists of 10 exercises; marching on the spot to walking from room to room; wall push-ups; lifting up on toes; toe tapping; seat walk; getting up from a chair; leg lifts to the front, back, and sides; reaching up and to the front and sides; calf stretching; and hamstring stretching.	usual care	60 min/day, 5 days/ week, 4 months.	- Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog) - Mini mental state examination (MMSE)	Exercise group was significant increased MMSE and decreased ADAS-Cog

Table 1:

Present about Characteristics of studies type of exercise on cognition in people with mild to moderate severity Alzheimer's disease. (Con.)

Title	Pedro scale	Sample			Age (Mean)	Setting	Exercise		Intensity	Outcome	Results
		Control	Exercise	Other			Exercise group	Control group			
4. FGM Coelho et al., 2013	4/10	78	13	14		Rehab center	**Multimodal exercise** : Strength/resistance training : Aerobic training (walking, activities with balls, games and running (65% to 75% of MHR) : Flexibility training : Balance training : Agility training : Concomitantly cognitive activities requiring focused attention, planned organization of the answers, abstraction, motor sequencing, judgment, self-control behavior and mental flexibility.	Daily routine	60 min/ time, 3 times/week, 4 months	- Frontal Assessment Battery, - The Clock Drawing Test - The Symbol Search Subtest	- Intervention group significantly increased the scores in frontal cognitive variables, Frontal assessment Battery and Symbol Search Subtest after training - The control group decreased the scores in the Clock Drawing Test after training

Table 1:

Present about Characteristics of studies type of exercise on cognition in people with mild to moderate severity Alzheimer's disease. (Con.)

Title	Pedro scale	Sample			Age (Mean)	Setting	Exercise		Intensity	Outcome	Results
		Control	Exercise	Other			Exercise group	Control group			
5. Larissa P. et al., 2013	5/10	70	16	14		Rehab center	- Aerobic exercises - Muscle strengthening - Flexibility exercises - Balance exercises 5 minutes of warm-up, 20 minutes of aerobic work to capacity, and 35 minutes to perform the dual-task activities (motor and cognitive tasks). Sessions included weight training, agility, and flexibility and balance training, with simultaneous stimulation of attention, language, and executive functions.	usual care	60 min/ time, 3 times/week, 4 months	- Montreal Cognitive Assessment - The Clock Drawing Test - The Frontal Assessment Battery - The Symbol Search Subtest	Intervention group participants showed a significant increase in frontal cognitive function after training

Table 1:

Present about Characteristics of studies type of exercise on cognition in people with mild to moderate severity Alzheimer's disease. (Con.)

Title	Pedro scale	Sample			Age (Mean)	Setting	Exercise		Intensity	Outcome	Results
		Control	Exercise	Other			Exercise group	Control group			
6. Carla M. et al., 2012	5/10	78.3	12	15		Rehab center	**Five parts** 1. warm-up, 2. pre-exercise stretching, 3. exercise session, 4. cool-down, 5. post-exercise stretching - **Flexibility exercise** (stretching) using bars, - **Strength exercise** Muscular resistance (using elastic ribbons specific exercises for large muscle groups and with series of 15/20 repetitions according to the volume overload) walking (moderate intensity)	usual care	60 min/ time, 3 times/week, 6 months	The Mini-Mental State Examination (MMSE)	The control group showed functional , neuropsychiatric deterioration in the comparisons between pre- and post-intervention times and between groups

Table 1:

Present about Characteristics of studies type of exercise on cognition in people with mild to moderate severity Alzheimer's disease. (Con.)

Title	Pedro scale	Sample			Age (Mean)	Setting	Exercise		Intensity	Outcome	Results
		Control	Exercise	Other			Exercise group	Control group			
							- **Motor coordination** (i.e. rhythmic activities, sequences to be completed) - **Balance exercise** (i.e. games and recreational motor activities with emphasis on changes in center of gravity and direction, single-leg stance, and unexpected disturbances - **Aerobic exercise**				

FGM Coelho et al., 2013 Concomitantly cognitive activities, for example, participants were instructed to carry out a motor task (bouncing ball, walking, exercise with weights) and, at the same time, carry out a cognitive task, such as generating words according to semantic criteria (such as animal names, names of fruits, personal names, names of flowers and figures) or reacting to sensory stimuli (whistle song) and verbal commands

Results

Six-thousand and three hundred forty-four articles were initially identified from four databases; PubMed, Cochrane Library, PEDro, and Sciencedirect. The articles that were not relevant title, duplicate publication, not control trial, animal, not exercise, and not English language were excluded. Therefore, 68 articles were remained. Forty-six articles were excluded because there were not-control trial; study protocol articles, systematic review, review, not relevant studies, and no full text available. Furthermore, study protocol articles (n=11) were excluded because these articles were study protocols, non-cognitive measurement such as daily living activity performance, balance and mobility, functional ability, depression, and brain intensity. Hence, a only six studies were included in this review. Cohen's kappa coefficient was used to measure agreement of the studies. The kappa score of 0.75 is defined as a good agreement (Figure 1). The average PEDro scale was 5.4. These studies were fair quality. The study selection process was presented in Figure 2.

Reviewer 1 / Reviewer 2	Factors affecting	Exclude	Total
Include	6	1	7
Exclude	1	9	10
Total	7	10	17

Figure 1: Reliability/Reproducibility process by use Kappa

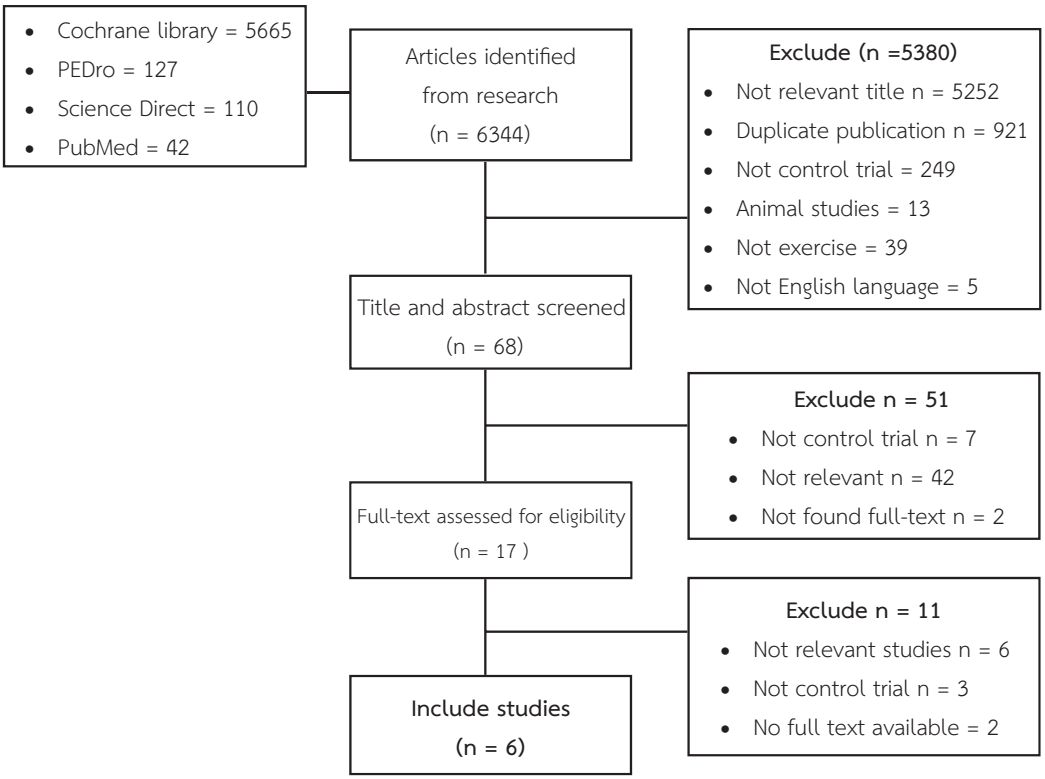

Figure 2: Trial identification and inclusion

It has been found that the effectiveness of exercise on cognition in patient with AD were different types of exercise, for example strengthening exercise, endurance or aerobic exercise, balance exercise, and cognition training. Of six studies, two studies reported that there was no significant difference in cognition between groups and between before and after training [21, 22] whereas the other four studies showed significant difference in cognition between before and after training. Similar protocols were used in four studies including of multimodal exercise program; strength or resistance training, aerobic training, balance training, and flexibility training. Three of four studies showed significant difference in cognition before and after exercise training whereas the other one study did not show any significant difference in cognition. Studies by FGM Coelho et al. (2013) and Larissa P. et al. (2013) used the same program for cognitive training, for example, concomitantly cognitive activities requiring attention, planned organization of the answers, abstraction, motor sequencing, judgment, self-control behavior and mental flexibility. By these interventions, there was a significantly increased in the scores of frontal cognition. On the other hand, the study of Carla M. et al. (2012) which did not show cognitive training program [23] expressed a positive result on the effect of exercise intervention on cognition but the result was not significantly different. Vreugdenhil A. et al. (2012) studied the effect of aerobic exercise combined with balance and strengthening exercise. The program included of walking exercise with home support exercise program. The home support exercise program consisted of 10 exercises (e.g., marching on the spot to walking from room to room; wall push-ups; lifting up on toes; toe tapping; seat walk; getting up from a chair; leg lifts to the front, back, and sides; reaching up and to the front and sides; calf stretching; and hamstring stretching). This study examined the effect of combination exercise program on Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog). This assesses several domains of cognition (i.e., verbal memory, executive function, orientation, constructional praxis). During four-month follow-up, there was significantly increased in MMSE and decreased in ADAS-Cog. They suggested that the combined exercise can improve cognition. In addition, the other two studies in our review, one study showed significantly different in cognition whereas no significant difference was shown in the other study. Hoffmann K. et al. (2015) examined the effect of moderate to high intensity of aerobic exercise program on cognitive functions. The program composed of two phases; adaptation phase, and moderate to high intensity training phase. Adaptation phase consisted of building up strength of lower extremities, balance training, and aerobic training for one month. In the next three months, moderate to high intensity training phase (70-80% of maximal heart rate (MHR)) by bicycle ergometer and treadmill training were performed. They reported that there was no significant difference in cognitive functions between groups and between before and after trainings [21]. Similarly, Yang et al. (2015) reported that the effect of aerobic exercise; cycling training with moderate intensity with 70% of MHR in mild to moderate AD. The result showed that there was significantly different on ADAS-cog test between before and after trainings for three months in exercise group [24].

It can be concluded that a combination of exercise or multimodal exercise program was an appropriate exercise for mild to moderate AD. However, the frequency, intensity, and duration (FIT) of combined exercise in each study were different. The minimum frequency of exercise was three days per week [25, 26]. The range of exercise intensity was from 65% to 75% of MHR [25]. In addition, time and duration of exercise were sixty minutes per session for four months.

Discussion

A main purpose of this systematic review was to report the effect of exercise on cognition of mild or moderate AD. Two studies examined effect of moderate to high intensity of aerobic

exercise on cognition [21]. Only study by Yang et al[24] reported that there was significant difference on cognition [24] whereas the another study was without difference [21]. The difference of experimental results might be due to differences in exercise intensity and exercise program. In addition, four from six studies had similar protocols of exercise program which composed of multimodal exercise program. The results of multimodal exercise program that composed of cognitive training program were positive effect on cognition. Although previous study suggested that aerobic exercise could improve cognition [24], previous studies favored to use combined exercises more than one type of exercise. Increased age is associated with degenerative systems. Older people with AD involves cognitive decline and also changes in muscle strength, flexibility, balance, and cardiovascular endurance. These changes supported the findings that combination exercise can improve health-related physical fitness and cognitive function. Previous studies presented effects of combined exercise on frontal cognitive function in patients with AD[21, 23]. The frontal cognitive functions significantly improved abstraction, organization, motor sequencing, behavior self-control and attention [25]. The combination exercise is the multi-task activities and one of the multiple-task is cognitive activities. The cognitive activities are associated with several frontal areas, so it can improve several domains of cognition. The possible mechanisms of multi-task activities that affect the frontal cognitive functions may occur from the combination of the tasks which demand attention and abstraction. The possible mechanisms that physical exercise improve cognitive performance might be due to an improvement of neurotransmitters synthesis and cerebral blood flow [27, 28]. Increased brain-derived neurotrophic factors was positive effect on brain neuroplasticity [29]. Previous study found that exercises induced brain-derived neurotrophic factors in the frontal cortex, hippocampus, and cerebellum [30]. Therefore, combination of exercise types tended to be more effective than any single exercise in patients with AD. However, FIT principle of combination exercise was still unclear. This review concluded that the appropriate FIT principle of combination exercise program was three days per week, 65% to 75% of MHR, 60 minutes per session and four months of duration. The American College of Sports Medicine (ACSM) in 9th edition recommends that the intensity of exercise should be 40% to 85% of heart rate reserve (HRR) or maximal oxygen uptake reserve (VO_2R), and 3-5 times per week for 20-60 minutes a day with large muscle groups [31]. According to the FIT principle for older people, older adults should engage in cardiovascular exercise. Intensity of exercise should be prescribed by assessing overall health status of the individual and should be started with low intensity exercise.

Conflicts of interest:

The authors declare no conflict of interest.

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