ORIGINAL RESEARCH

Aerobic Fitness and Cognition Changes After Exercise Training in Alzheimer's Disease

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ABSTRACT

Background: Alzheimer's disease (AD) currently affects 5.4 million Americans and is the sixth leading cause of death in the United States. The mechanism of exercise-induced brain adaptations are not fully understood, but enhanced aerobic fitness has been postulated as an essential physiological mechanism and is beginning to be studied. The purpose of this analysis was to examine the relationship between changes in aerobic fitness and cognition following 6 months of aerobic exercise training in older adults with AD.

Methods: Twenty-seven community-dwelling older adults with mild to moderate AD completed a 6-month, 3 times per week, moderate-vigorous intensity cycling exercise program in 2 identical studies using a single-group repeated-measures designs. AD symptoms were measured with the AD Assessment Scale–cognitive subscale (ADAS-cog), while aerobic fitness was assessed by the intermittent shuttle walk test (ISWT) at baseline and 6 months. Pearson's correlation coefficient tests and linear regression were used to assess the relationship between changes in aerobic fitness and cognition.

Results: Adjusted for age, the 6-month change in ISWT distance had an inverse relationship with the 6-month change in ADAS-Cog ($r = –0.49$; $P = .01$), indicating that enhanced aerobic fitness was associated with improved cognitive changes. Linear regression was statistically significant when adjusted by age ($F([2,14] = 5.33$, $P = .01$, $R^2 = .31$).

Conclusion: Enhanced aerobic fitness may attenuate cognitive decline in persons with mild to moderate AD. *Journal of Clinical Exercise Physiology*. 2017;6(2):22–28.

Keywords: executive function, aging, physical activity, cycling, memory loss

INTRODUCTION

Alzheimer's disease (AD) is an epidemic public health problem that currently affects 5.4 million Americans and is the sixth leading cause of death in the United States (1). Cognitive impairment is the primary feature of AD, which results in reduced capacity to perform activities of daily living from a previously higher level as well as manifestations of psychological and behavioral symptoms and loss of independence (2). The structural and functional brain alterations associated with AD are multifactorial and complex. Key histologic findings in AD are the formation of extracellular β-amyloid plaques (Aβ) and intracellular neurofibrillatory tangles, which favor the formation and accumulation of damaging reactive oxygen species and proinflammatory cytokines (3). The resulting proinflammatory environment promotes neural mitochondrial dysfunction (4) and inadequate brain perfusion (5), which propagates a destructive cycle characterized by accelerated neural apoptosis and

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degeneration as well as reduced neurotrophin biosynthesis (6).

The complexity of AD pathophysiology is a contributing factor to the paucity of effective treatment options designed to reduce or reverse cognitive decline. However, aerobic exercise training has been shown in several randomized controlled trials to be a potentially effective behavioral intervention to reduce the rate of brain deterioration and cognitive decline through a multitude of physiologically sound mechanisms of action (7,8). Moderate to vigorous intensity aerobic exercise training has antioxidant (9) and anti-inflammatory effects (10), and likewise improves measures of arterial (11) and mitochondrial function (12). Each is a likely synergistic component to healthy human brain aging. In rat models of AD, aerobic exercise training improves cerebral perfusion (13) and metabolism (14), resulting in the reduction in Aβ load (15), up-regulation of neurotrophins (14), and hippocampal neurogenesis and volume (16). The cardiovascular fitness hypothesis further suggests that enhanced cardiovascular or aerobic fitness, which is often measured by peak oxygen consumption (VO_2P), induced by aerobic exercise training is essential for realizing these various brain benefits (17,18) and mediates the effect of aerobic exercises on both cognition and neuroprotective mechanisms (19). However, studies examining the relationships between aerobic fitness and cognition in AD are limited.

Therefore, the purpose of this study was to examine the relationship between changes in aerobic fitness and cognition following 6 months of aerobic exercise training in community-dwelling older adults with AD. We hypothesized that improvements in aerobic fitness following 6 months of aerobic exercise training would be associated with favorable cognitive changes.

METHODS

Design

This study was a secondary data analysis of 2 pilot studies that were conducted from 2007 to 2009 and 2009 to 2011, respectively. Each study used a single-group, repeated-measures design to test the feasibility and effects of a 6-month, individualized, moderate-vigorous intensity cycling intervention on cognition in older adults with AD. Aerobic fitness and cognition were assessed by trained research assistants (RAs) who were blinded to the study aims at baseline, 3 months, and 6 months (20,21). All study protocols were approved by the University of Minnesota's Institutional Review Board.

Analysis Sample

Recruitment strategies have been fully described elsewhere and included newspaper advertisements, referrals by community partners, study flyer distributions, and educational seminars (20). Participants were qualified using the following inclusion criteria: having an AD diagnosis confirmed by a physician, community dwelling (not nursing homes), over the age of 60 years with demonstrated competency in English, and receipt of medical clearance for the cycling intervention from the primary care provider and from a cardiologist for those with a known cardiac history. Participants were excluded if their Mini-Mental State Examination (MMSE) score was <12; if they had psychiatric disorders, such as schizophrenia or significant depressive symptoms; if they had contraindications for aerobic exercise as outlined by the American College of Sports Medicine (ACSM) (22); or if they could not perform cycling exercise. Those currently taking AD medications were included if medication use was stable and had been initiated at least 6 months prior to enrollment in the study.

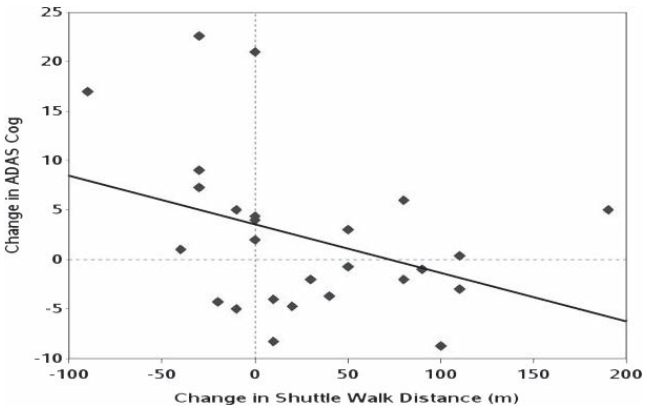

FIGURE 1. Association between change in Incremental Shuttle Walk Test (ISWT) distance and AD Assessment Scale cognition subscale (ADAS-Cog) following 6 months of supervised aerobic exercise training. Change in ADAS-Cog was inversely correlated with change in ISWT distance following 6 months of aerobic exercise training. A higher score on the ADAS-Cog suggests greater cognitive impairment. Individuals who increased their walking capacity showed attenuated cognitive decline.

Procedures

Respondents to our recruitment were screened using a 3-step procedure: (1) phone screen to elicit the presence of AD diagnosis, health history, and exercise contraindication; (2) in-person interview to assess the potential participant's consenting ability, obtain informed consent or surrogate consent/participant assent, administer the MMSE, and conduct a brief physical assessment; and (3) obtain medical verification from a participant's primary care provider and cardiologist if significant cardiac history was indicated by the participant or caregiver. Participants with medical clearance were enrolled in the studies and underwent baseline data collection at the University of Minnesota's Clinical and Translational Science Institute.

The 6-month Cycling Intervention

After completing baseline data collection, participants began their 6-month cycling intervention at a local YMCA gym or a senior facility that was close to the participant's home. Both studies employed a 3 day per week, individualized, moderate-vigorous intensity cycling protocol that progressively increased intensity over sessions from 40% up to 75% of heart rate reserve (HRR). HRR was defined as the

difference between the resting heart rate following 10 minutes of seated rest and the highest heart rate recorded in the Incremental Shuttle Walk Test (ISWT). The duration of cycling was progressively increased by 5-minute increments from 10 to 15 minutes initially to 45 minutes per session over time. In each exercise session, a comfortable cycling rate was chosen by each participant (40–60 revolutions per minute), while cycling resistance was controlled by the exercise interventionist to help the participants reach the prescribed exercise intensity. The participants wore a Polar F7 heart rate monitor (Polar Electro Finland Oy, Kempele, Finland) for continuous heart rate monitoring, and their rating of perceived exertion (RPE) (23) was assessed every 5 minutes. Before and after cycling, the participants completed a warm-up that consisted of 5 minutes of range of motion activities, 5 minutes of low-intensity cycling (<40% HRR). Following exercise they performed 5 minutes of low-intensity cycling to cool down to gradually lower the heart rate (<40% HRR). The cycling dose began at 40% to 55% of HRR (or comparable RPE) for 10–15 minutes initially. The intensity and session duration were increased alternatively by 5% of HRR or 5-minute increments over the sessions. Progressions were allowed after the participants completed a prescribed dose 3 times in a row and continued until they could cycle for 45 minutes at 65% to 75% of HRR or a comparable RPE. Heart rate and RPE were documented in the last 15 seconds of each 5-minute interval, and the proper use of the RPE was continuously reinforced. The exercise interventionists further monitored blood pressure every 10–15 minutes, assessed overexertion signs and symptoms, and administered the talk test (24) (the ability to talk without losing breath) to adjust cycling dose accordingly to ensure participants' safety. All cycling interventions were performed on either a Precor (Woodinville, WA) or Livestrong R1x (Cottage Grove, WI) recumbent stationary cycle (21,25).

Outcomes Measures

Cardiovascular fitness and cognition were assessed at baseline, 3 months, and 6 months by trained RAs who interacted with the participants only for data collection. Aerobic fitness was measured using the ISWT. The VO_2P achieved on the ISWT exhibits a strong correlation with that achieved in the laboratory-based, gold standard cardiopulmonary exercise test (CPX) performed on a treadmill ($r = 0.88$) (26) or on a cycle ergometer ($r = 0.91$) (27). Therefore, the ISWT was considered an appropriate test for assessing aerobic fitness in our population (28). The ISWT was performed according to the original protocol proposed by Singh and colleagues (29). Participants were required to walk along a level, 10-m course at a previously determined speed dictated by signals from an audio recording. The participant had to make each shuttle (1 way from one marker to another marker) prior to the next beep. The walking speed was progressively increased at 1-minute intervals, for a total of 12 stages, with a minimum walking speed of 1.2 miles per hour, up to a maximum of 5.3 miles per hour. A triple beep sounded to alert participants that they needed to walk faster. Since older adults with AD may have trouble multitasking and remembering test instructions, the RAs also gave verbal instruction by saying ''stop'' when participants arrived at the marker before the beep, ''go'' when the single beep for walking sounded, and ''go and walk faster now'' when the triple beep sounded, indicating faster pace required. The test was terminated if the participant failed to complete the shuttle in the allowed time. Participants were permitted to use a walker or cane during the test. The total number of completed shuttles was recorded to derive the distance walked in meters, shortest time for completing a shuttle in seconds, and highest speed during a shuttle (meters per second) based on the shuttle walk's normative data table (29).

Cognition was measured using the AD Assessment Scale cognitive subscale (ADAS-cog) (30). The ADAS-cog is administered over 15 minutes and assesses 11 cognitive domains: orientation, word recall, word recognition, remembering test instructions on word recognition, naming objects and fingers, expressive language, comprehension of spoken language, word finding difficulty, commands, ideational praxis, and construction praxis. The ADAS-cog score ranges from 0 to 70 with higher scores indicating worse global cognition. The ADAS has good interrater ($r = 0.65$ to 0.99) and test-retest reliability ($r = 0.51$ to 1.0)(30).

Data Management and Analysis

Continuous variables were summarized as means and standard deviations; categorical variables were summarized as frequency and percent and were used to describe the sample. Paired *t* tests were used to examine differences between baseline and follow-up measurements for ISWT and ADAS-cog. An alpha level <0.05 was considered statistically significant. Pearson bivariate correlation was used to assess the simple association between variables for the entire sample, and linear regression was used to assess relationships between variables while controlling for covariates in order to determine strengths and differences in predictors. All analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

Participant Characteristics

Sample demographics are displayed in Table 1. The study sample consisted of predominantly men, and they were classified as having mild to moderate AD. The age of the participants ranged from 65 to 91 years with average years of education ranging from 8 to 24 years.

Participant Adherence to Exercise Training

Of the 32 participants enrolled, 27 (85%) completed the 6-month cycling program. The adherence rate for the first pilot study was 95.8%; that is, participants completed an average of 70 of the possible 72 training sessions. The second pilot-study participants attended 83% of their prescribed sessions (an average of 65 of the possible 72 training sessions).

TABLE 1. Study demographics. Data are mean+/-SD or n (%).

Variable	Values
Age (y)	79.3 (6.9)
Gender (male)	17 (63)
Education (y)	15.2 (3.5)
Baseline ADAS-cog	18.0 (5.8)
Baseline MMSE	20.6 (4.1)
Baseline ISWT distance (m)	180 (117)

ADAS-cog = Alzheimer's Disease Assessment Scale cognitive subscale; MMSE = Mini Mental State Examination; ISWT = Incremental Shuttle Walking Test; SD, standard deviation

Changes in ISWT distance and ADAS-Cog Scores from Aerobic Exercise

The ISWT results at baseline, 3 months, and 6 months, along with mean differences, are shown in Table 2. The average ISWT distance increased by 13 m (7%) at 3 months and 26 m (14%) at 6 months of cycling training. The change from baseline to 3 months was not significant while the change at 6 months was significant ($P = .03$). The ISWT velocity did not change significantly compared with baseline for both 3 and 6 months. The ISWT number of shuttles performed (i.e., walking from one marker to the next) did not significantly change from baseline to 3 months, but it did improve by 2.6 shuttles between baseline and 6 months ($P = .03$). The ADAS-cog results are also reported in Table 2. There was a decrease in ADAS-cog score of –0.2 (5.6) after 3 months of exercise training. The ADAS-cog scores increased by 2.5 (5.0) points between 3 and 6 months. All changes in ADAS-cog scores were nonsignificant.

Association Between 6-Month Changes in Cardiovascular Fitness and Cognition

Adjusted for age, the 6-month change in ISWT distance was inversely related with the 3- and 6-month change in ADAS-Cog (Table 3), indicating that enhanced aerobic fitness was associated with more favorable cognitive changes. Age-adjusted linear regression showed that for each additional meter walked in the ISWT at 6 months, a participant's ADAS cog score improved by 0.64 points (Figure 1).

DISCUSSION

The results of this analysis suggest that 6 months of supervised, moderate-vigorous intensity cycling exercise resulted in a significant increase in aerobic fitness, as measured by an increase in ISWT distance, in community-dwelling older adults with mild/moderate AD. As reported previously (21,31), there was very little change in ADAS-cog scores following 6 months of moderate-vigorous intensity cycling. A possible confounder is that AD causes ongoing decline in cognition over time and may have impacted any effects of exercise training. The 6-month ADAS-cog change score computed in this analysis was 2.3 (7.9), which is lower than

TABLE 2. Cognitive and aerobic fitness changes over 6 months[a].

Tests	Baseline	3 m	Baseline to 3 m Change (*P*)	6 m	Baseline to 6 m Change (*P*)
ISWT distance (m)	180 (117)	193 (130)	.17	206 (150)	.03
ISWT MWV ($m \cdot s^{-1}$)	1.05 (0.35)	1.10 (0.35)	.10	1.10 (0.37)	.14
ISWT shuttles (no.)	18.0 (11.7)	19.3 (13.0)	.17	20.6 (15.0)	.03
ADAS-cog	18.0 (5.8)	17.8 (7.6)	.87	20.3 (9.7)	.14

ADAS-cog = Alzheimer's Disease Assessment Scale cognitive subscale; ISWT = Incremental Shuttle Walk Test; MWV = maximal walking velocity achieved on ISWT

[a]Baseline, 3 month, and 6 month data expressed as mean (standard deviation). *P* values reflect changes in data from baseline to 3 months and from baseline to 6 months.

TABLE 3. Pearson partial correlation coefficients for selected variables.

Variable	Baseline Cognition	Cognition Change		
		3 Mo	6 Mo	3–6 Mo
Baseline ISWT distance	–0.35	–0.13	0.00	0.15
ISWT distance change 3 mo	0.11	–0.30	–0.22	–0.00
ISWT distance change 6 mo	–0.11	–0.47[a]	–0.49[b]	–0.23
ISWT distance change 3–6 mo	–0.20	–0.23	–0.31	–0.23

ISWT = Incremental Shuttle Walk Test

[a]$P < .05$.

[b]$P = .01$.

historical averages and did not approach the minimally clinically relevant 4-point increase (i.e., deterioration) on the ADAS-cog previously observed in clinical trials of patients with mild AD (32).

The change in ADAS-cog of 2.3 also in our analysis was less than what is typically seen in older adults with AD during a 6-month time frame. The AD Neuroimaging Initiative showed an average 6-month ADAS-cog change of 3.1–3.8 points in older adults with mild AD undergoing clinically significant worsening (33). Historical averages reported in randomized controlled trials investigating the efficacy of AD drugs have shown a 2.4–3.9 point increase in ADAS-cog scores over 6 months (34). Furthermore, in individuals with mild to moderate AD who have participated in clinical trials and have been randomized to placebo groups (n = 536), the 6-month reported mean change was 3.14 (34). The findings from this study, when compared with historical averages, suggest that aerobic exercise might indeed have a role in slowing cognitive decline in AD. However, the novel finding from this study was that improvements in aerobic fitness, as measured by distance accumulated during the ISWT following the cycling exercise training program, were associated with improvements in cognitive functioning.

Our findings are consistent with several studies that have examined the link between aerobic fitness and cognition. Randomized controlled trials investigating the efficacy of aerobic exercise training in participants with AD have resulted in positive alterations in executive function (7,8). Additionally, multiple longitudinal studies have reported a significant relationship between lower amounts of self-reported leisure-time physical activity and reductions in cognition (35,36).

Some of the most compelling evidence of an aerobic fitness mediator in cognitive functioning during aging has been recently provided. Wendell and colleagues (37) found a significant longitudinal association between baseline VO_2P and the trajectory of performance on multiple measures of cognitive screening, and they emphasized the importance of behavioral interventions designed at improving aerobic fitness for concurrently optimizing cognitive aging over time. Our findings that participants who improved their aerobic fitness experienced favorable changes in cognition also give support for these findings and the cardiovascular fitness hypothesis postulating that aerobic fitness is a physiological mechanism for aerobic exercise's effect on cognition (17,18).

The significant improvement we report for ISWT distance was likely due to an improvement in aerobic fitness and not a learning effect. Although there is documentation of a learning effect on symptom-limited graded exercise tests, such as in patients with claudication (38), we are unaware of a similar learning effect in individuals with AD. Given the extent of cognitive impairment in a person with AD, it's highly unlikely that a learning effect would have influenced the performance on ISWT. Particularly, we are unaware of any significant learning effect that takes place over such a wide time frame between ISWT's in individuals with mild to moderate AD.

Although statistically there was a significant improvement in ISWT distance, there were also nonresponders to the aerobic exercise training program. Currently, the minimal clinically important difference for the ISWT distance in participants with AD or other cognitive impairments has not been established. Previous research involving participants with cardiovascular and obstructive lung disorders suggest that a minimal clinically important difference for ISWT distance ranges from 47 to 70 m (39,40). Participants in the current study did not demonstrate this much improvement in ISWT distance; however, the mean age of study participants in our study was 10–15 years older than in the studies of Singh (40) and Houchen-Wolloff and colleagues (39). The exact cause of the lack of improvement in ISWT distance of some participants is unknown; however, it is unlikely due to the exercise prescription used in the studies or protocol adherence. For optimal cardiorespiratory improvements, the ACSM exercise recommendations for older adults is moderate-vigorous aerobic exercise performed 3–5 days per week (41), and this was used in each of the pilot studies contributing subjects for this analysis. Adherence to the exercise prescription is an important factor in determining the success of the intervention for improving physical function and aerobic fitness (42,43), and each of the pilot studies demonstrated high adherence pertaining to attendance and meeting the prescribed exercise intensity and duration targets of each training session.

The heterogeneity of aerobic fitness response (assessed by VO_2 max) to regular exercise is well documented in exercise physiology (44). Past exercise training studies (45), including those involving older adults (46), that utilized similar exercise prescriptions (i.e., intensity and duration) as our studies have shown improvements in VO_2 max of 24% to 25%, with a range of 0 to 58%. The heterogeneity is not significantly attributed to differences in age and sex but has a strong heredity component (44). To our knowledge the heterogenicity of aerobic fitness changes, as assessed by ISWT, attributed to regular exercise in older adults both with and without AD is unknown. However, given the strong correlation between the VO_2P estimated by ISWT performance with measured CPX performed on a treadmill or cycle ergometer (26,27), it is logical to assume that the same heterogenicity noted during VO_2 max testing following exercise training would apply for the ISWT.

There are limitations of this analysis. Although the VO_2P achieved on the ISWT has a strong correlation with VO_2P achieved on CPX (26,27), the CPX using indirect calorimetry is considered the gold standard for measuring cardiovascular fitness and aerobic capacity. However, it should be noted that the ISWT may offer greater clinical utility than CPX as it is more cost effective and less time consuming. Secondly, socialization during exercise, the small sample size, lack of a control group, and the use of a single neuropsychological battery, rather than multiple, extensive neuropsychological questionnaires, could be viewed as study limitations. Pertaining to the former, socialization is known to improve mood; however, there is no evidence to

suggest that socialization significantly improves any indicators of aerobic fitness or improves cognition in people with AD. Lastly, medications were tracked for part of the screening process and any changes were documented subsequently. However, those with AD cannot reliably recall their medication history or even what medications they had or had not taken prior to coming to the exercise sessions. Given the known inaccuracies in medications reporting, medication history or changes were not included in this paper.

There are several strengths to the pilot studies used, which are described in detail elsewhere (21,31). Briefly, the most important is that the individualized, progressive, moderate-vigorous intensity cycling protocol resulted in a high session adherence and tolerability and improved aerobic fitness. The choice of using a cycle ergometer for aerobic exercise training instead of a treadmill was because safety was our foremost concern for the participants. The cycles were powered by participants and easy for them to get on and off, which reduced fall risk, a prevalent problem in the study population. People with AD often forget what they are doing or may suddenly decide to stop exercising in the middle of a session, which may also predispose participants to falls during treadmill exercise. The cycling mode reduces worry or anxiety that are associated with a treadmill due to inexperience (47). This cycling exercise program provided a cross-transfer effect, which is an important finding as it shows that a safe and tolerable, nonambulatory aerobic exercise training modality can improve walking ability in a population known to be at a higher risk of falls. Finally, the sample in the study represented the entire spectrum of both mild and moderate AD with MMSE scores ranging from 13 to 24.

In summary, our analysis suggests that moderate-vigorous intensity cycling exercise training improves ISWT distance in those with mild/moderate AD. This improvement was associated with an attenuated decline in ADAS-Cog scores compared with 6-month historical averages. These findings, as well as the biological mechanisms of exercise-induced neuroprotection in those with AD, need to be further established in large-scale randomized controlled trials. This is currently being investigated in a large National Institutes of Health sponsored study (The FIT-AD Trial, NCT01954550) (48).

REFERENCES

1. 2016 Alzheimer's Disease Facts and Figures [Internet]. Alzheimer's Association. Available from: m/alz.org/facts-and-figures.asp#Quick.
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington DC: American Psychiatric Association; 2013.
3. Zhao Y, Zhao B. Oxidative stress and the pathogenesis of Alzheimer's disease. Oxid Med Cell Longev. 2013;2013: 316523.
4. Castellani R, Hirai K, Aliev G, Drew KL, Nunomura A, Takeda A, A, Cash AD, Obrenovich ME, Perry G, Smith MA. Role of mitochondrial dysfunction in Alzheimer's disease. J Neurosci Res. 2002 Nov 1;70(3):357-60.
5. Kalaria RN, Pax AB. Increased collagen content of cerebral microvessels in Alzheimer's disease. Brain Res. 1995;705 (1-2):349-52.
6. Butterfield DA, Drake J, Pocernich C, Castegna A. Evidence of oxidative damage in Alzheimer's disease brain: central role for amyloid beta-peptide. Trends Mol Med. 2001;7(12): 548-54.
7. Kemoun G, Thibaud M, Roumagne N, Carette P, Albinet C, Toussaint L, Paccalin M, Dugue B. Effects of a physical training programme on cognitive function and walking efficiency in elderly persons with dementia. Dement Geriatr Cogn Disord. 2010;29(2):109-14.
8. Venturelli M, Scarsini R, Schena F. Six-month walking program changes cognitive and ADL performance in patients with Alzheimer. Am J Alzheimers Dis Other Demen. 2011;26(5):381-8.
9. Ji LL, Gomez-Cabrera MC, Vina J. Exercise and hormesis: activation of cellular antioxidant signaling pathway. Ann N Y Acad Sci. 2006;1067:425-35.
10. Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. J Appl Physiol. 2005;98(4):1154-62.
11. Kingwell BA, Sherrard B, Jennings GL, Dart AM. Four weeks of cycle training increases basal production of nitric oxide from the forearm. Am J Physiol. 1997;272(3 Pt 2):H1070-7.
12. Jornayvaz FR, Shulman GI. Regulation of mitochondrial biogenesis. Essays Biochem. 2010;47:69-84.
13. Swain RA, Harris AB, Wiener EC, Dutka MV, Morris HD, Theien BE, Konda S, Engberg K, Lauterbur PC, Greenough WT. Prolonged exercise induces angiogenesis and increases cerebral blood volume in primary motor cortex of the rat. Neuroscience. 2003;117(4):1037-46.
14. Dao AT, Zagaar MA, Levine AT, Alkadhi KA. Comparison of the effect of exercise on late-phase LTP of the dentate gyrus and CA1 of Alzheimer's disease model. Mol Neurobiol. 2016;53(10): 6859–6868.
15. Wolf SA, Kronenberg G, Lehmann K, Blankenship A, Overall R, Staufenbiel M, Kempermann G. Cognitive and physical activity differently modulate disease progression in the amyloid precursor protein (APP)-23 model of Alzheimer's disease. Biol Psychiatry. 2006 15;60(12):1314-23.
16. Pereira AC, Huddleston DE, Brickman AM, Sosunov AA, Hen R, McKhann GM, Sloan R, Gage FH, Brown TR, Small SA. An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. Proc Natl Acad Sci U S A. 2007; 104(13):5638-43.
17. Barnes DE, Yaffe K, Satariano WA, Tager IB. A longitudinal study of cardiorespiratory fitness and cognitive function in healthy older adults. J Am Geriatr Soc. 2003;51(4):459-65.
18. North TC, McCullagh P, Tran ZV. Effect of exercise on depression. Exerc Sport Sci Rev. 1990;18:379-415.
19. Colcombe SJ, Kramer AF, Erickson KI, Scalf P, McAuley E, Cohen NJ, Webb A, Jerome GJ, Marquez DX, Elavsky S. Cardiovascular fitness, cortical plasticity, and aging. Proc Natl Acad Sci U S A. 2004;101(9):3316-21.

20. Yu F. Improving recruitment, retention, and adherence to 6-month cycling in Alzheimer's disease. Geriatr Nurs. 2013;34(3):181-6.
21. Yu F, Thomas W, Nelson NW, Bronas UG, Dysken M, Wyman JF. Impact of 6-month aerobic exercise on Alzheimer's symptoms. J Appl Gerontol. 2015;34(4):484-500.
22. American College of Sports Medicine. ACSM's guidelines for exercise testing and prescription. Thompson WR, Gordon NF, Pescatello LS, editors. Philadelphia: Wolters Kluwer Health/ Lippincott Williams & Wilkins; 2010.
23. Borg G. Ratings of perceived exertion and heart rates during short-term cycle exercise and their use in a new cycling strength test. Int J Sports Med. 1982;3(3):153-8.
24. Persinger R, Foster C, Gibson M, Fater DC, Porcari JP. Consistency of the talk test for exercise prescription. Med Sci Sports Exerc. 2004;36(9):1632-6.
25. Yu F, Nelson NW, Savik K, Wyman JF, Dysken M, Bronas UG. Affecting cognition and quality of life via aerobic exercise in Alzheimer's disease. West J Nurs Res. 2013;35(1):24-38.
26. Singh SJ, Morgan MD, Hardman AE, Rowe C, Bardsley PA. Comparison of oxygen uptake during a conventional treadmill test and the shuttle walking test in chronic airflow limitation. Eur Respir J. 1994;7(11):2016-20.
27. Luxton N, Alison JA, Wu J, Mackey MG. Relationship between field walking tests and incremental cycle ergometry in COPD. Respirology. 2008;13(6):856-62.
28. Win T, Jackson A, Groves AM, Sharples LD, Charman SC, Laroche CM. Comparison of shuttle walk with measured peak oxygen consumption in patients with operable lung cancer. Thorax. 2006;61(1):57-60.
29. Singh SJ, Morgan MD, Scott S, Walters D, Hardman AE. Development of a shuttle walking test of disability in patients with chronic airways obstruction. Thorax. 1992c;47(12): 1019-24.
30. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry. 1984;141(11): 1356-64.
31. Yu F, Leon AS, Bliss D, Dysken M, Savik K, Wyman JF. Aerobic training for older men with Alzheimer's disease: individual examples of progression. Res Gerontol Nurs. 2011;4(4):243-50.
32. Aisen PS, Schafer KA, Grundman M, Pfeiffer E, Sano M, Davis KL, Farlow MR, Jin S, Thomas RG, Thal LJ. Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomized controlled trial. JAMA. 2003; 289(21):2819-26.
33. Schrag A, Schott JM, Alzheimer's Disease Neuroimaging Initiative. What is the clinically relevant change on the ADAS-Cog? J Neurol Neurosurg Psychiatry. 2012;83(2):171-3.
34. Doraiswamy PM, Kaiser L, Bieber F, Garman RL. The Alzheimer's Disease Assessment Scale: evaluation of psychometric properties and patterns of cognitive decline in multicenter clinical trials of mild to moderate Alzheimer's disease. Alzheimer Dis Assoc Disord. 2001;15(4):174-83.
35. Ku PW, Stevinson C, Chen LJ. Prospective associations between leisure-time physical activity and cognitive performance among older adults across an 11-year period. J Epidemiol. 2012;22(3):230-7.
36. Obisesan TO, Umar N, Paluvoi N, Gillum RF. Association of leisure-time physical activity with cognition by apolipoprotein-E genotype in persons aged 60 years and over: the National Health and Nutrition Examination Survey (NHANES-III). Clin Interv Aging. 2012;7:35-43.
37. Wendell CR, Gunstad J, Waldstein SR, Wright JG, Ferrucci L, Zonderman AB. Cardiorespiratory fitness and accelerated cognitive decline with aging. J Gerontol A Biol Sci Med Sci. 2014;69(4):455-62.
38. McDermott MM, Guralnik JM, Criqui MH, Liu K, Kibbe MR, Ferrucci L. Six-minute walk is a better outcome measure than treadmill walking tests in therapeutic trials of patients with peripheral artery disease. Circulation. 2014;130(1):61-8.
39. Houchen-Wolloff L, Boyce S, Singh S. The minimum clinically important improvement in the incremental shuttle walk test following cardiac rehabilitation. Eur J Prev Cardiol. 2015;22(8):972-8.
40. Singh SJ, Jones PW, Evans R, Morgan MD. Minimum clinically important improvement for the incremental shuttle walking test. Thorax. 2008;63(9):775-7.
41. American College of Sports Medicine Position Stand. Exercise and physical activity for older adults. Med Sci Sports Exerc. 1998;30(6):992-1008.
42. Fielding RA, Katula J, Miller ME, Abbott-Pillola K, Jordan A, Glynn NW, Goodpaster B, Walkup MP, King AC, Rejeski WJ. Activity adherence and physical function in older adults with functional limitations. Med Sci Sports Exerc. 2007;39(11): 1997-2004.
43. van Gool CH, Penninx BW, Kempen GI, Rejeski WJ, Miller GD, van Eijk JT, Pahor M, Messier SP. Effects of exercise adherence on physical function among overweight older adults with knee osteoarthritis. Arthritis Rheum. 2005; 53(1):24-32.
44. Bouchard C, Rankinen T. Individual differences in response to regular physical activity. Med Sci Sports Exerc. 2001;33(6 duppl):S446,51; discussion S452-3.
45. Bouchard C. Individual differences in the response to regular exercise. Int J Obes Relat Metab Disord. 1995;19(duppl 4):S5-8.
46. Kohrt WM, Malley MT, Coggan AR, Spina RJ, Ogawa T, Ehsani AA, Bourey RE, Martin 3rd WH, Holloszy JO. Effects of gender, age, and fitness level on response of VO2max to training in 60-71 yr olds. J Appl Physiol (1985). 1991;71(5): 2004-11.
47. Lees FD, Clarkr PG, Nigg CR, Newman P. Barriers to exercise behavior among older adults: a focus-group study. J Aging Phys Act. 2005;13(1):23-33.
48. Yu F, Bronas UG, Konety S, Nelson NW, Dysken M, Jack C Jr, Wyman JF, Vock D, Smith G. Effects of aerobic exercise on cognition and hippocampal volume in Alzheimer's disease: study protocol of a randomized controlled trial (The FIT-AD trial). Trials. 2014;15:394,6215-15-394.