EFFECT OF AEROBIC EXERCISE ON BRAIN-DERIVED NEUROTROPHIC FACTOR AND COGNITIVE FUNCTION IN OLDER ADULTS

Ade Mayra Hosiana[1], Nila Wahyuni[2]

[1] Biomedical Anti-Aging Medicine Magister Program Medical Faculty Universitas Udayana, 80234, Denpasar, Indonesia

[2] Physiology Department Medical Faculty Universitas Udayana, 80234, Denpasar, Indonesia
Email: ade.mayra@yahoo.com

ABSTRACT

Aging is a natural process experienced by all living things. In aging, there is a decrease in the functions of various organ systems in the human body, including a decrease in brain function. Decreased brain capacity is associated with various risks of diseases such as dementia, which can impair the quality of life. One of the proteins in the brain that related to brain plasticity, learning, memory abilities, and cognitive function is brain-derived neurotrophic factor (BDNF). Aerobic exercise is said to be able to increase serum BDNF levels and cognitive function in elderly individuals. The approach used for this study was a literature review. We look into and compare current literature on the effects of aerobic exercise on BDNF levels and cognitive function. The search method resulted up 540 articles. After eliminating duplicates and evaluating the abstracts, 496 full-text publications were then evaluated for eligibility. Following the evaluation of the entire article, 5 articles were added to the final review. It has been demonstrated that aerobic exercise raises BDNF levels in the elderly. Aerobic exercise also shown to improve several components of cognitive function. In conclusion, aerobic exercise is beneficial for the health of the brain, and it is recommended for older adult engaging moderate aerobic exercise, 150 minutes weekly.

Keywords: aerobic exercise; BDNF; cognitive function

INTRODUCTION

Aging is a persistent and progressive decline of intrinsic physiological function, leading to an increase in the incidence of illness and death.[1,2] The term "elderly" refers to people 60 years of age and older, who make up the fastest-growing demographic in worldwide.[3,4] The human body changes in many visible ways as we age, and body functions frequently deteriorate as people age.[4] The changes that occur with aging involve various organ systems. As the brain's ability to transfer messages and communicate declines with age, a variety of neurological illnesses are also linked to aging. The largest concern for elderly people is the loss of brain function, which includes personality loss in dementia (often Alzheimer's disease).[3] It is well established that certain cognitive abilities naturally decline with age, including speed of processing, many aspects of memory, speech, visual, spatial and executive function.[4,5]

In aging, the anatomy of the brain structure also changes. Namely, there is a significant shrinkage of brain volume, where the fastest shrinkage occurs in the nucleus accumben, followed by hippocampus, compared to the other cortex. This shrinkage increases the risk of cognitive decline in older people.[6] One of the factors thought to affect hippocampal volume is the serum level of brain-derived neurotrophic factor (BDNF).[7,8] BDNF is a group of small secreted proteins, which also comprises nerve growth factor, neurotrophin 3, and neurotrophin 4. Due to its strong effects on synapses and high levels of expression in the brain, BDNF stands out among all neurotrophins.[9] BDNF is a key molecule associated in plasticity alterations related to learning and memory abilities.[8] One study imply that age-related memory decline is connected with reduced BDNF function, along with inactivity and hippocampus shrinkage.[10] Several interventions, such as exercise or the administration of antidepressants, increase BDNF expression both normally and in pathological conditions.[8]

One of the common age-related changes is a decline in the effectiveness of cognitive functioning. However, many studies show that exercise can improve cognitive function. Additionally, recent study data indicates that the type of exercise training has an impact on executive function, with aerobic training appearing to have the biggest impact.[11] Exercise is thought to enhance cognitive function through the promotion of neurogenesis, angiogenesis, synaptic plasticity, decreased proinflammatory processes, and decreased cellular damage from oxidative stress, although the precise mechanism is unknown. Currently, research indicates that exercise training is most advantageous for executive function and memory, a broad term used to describe organizing and solving problems.[12] There are several ways to measure cognitive function, but The Mini-Mental State Examination (MMSE) is the most common, particularly in clinical practice.[13]

A person's level of wellbeing is enhanced by the beneficial biological and psychological benefits of exercise on the brain and cognitive performance.[14,15] Aerobic exercise, both in short and long-term, can significantly increase BDNF levels.[16,17] According to a study, adults who are sedentary can benefit from short-term aerobic exercise because it can promote neuroplasticity and lessen the biological and cognitive effects of aging.[18] Another study found that aerobic exercise, particularly when done for 30 minutes each time, for no more than 150 minutes each week, and no more than three times per week, improved cognitive function in Alzheimer's patients.[19,20] This literature aims to analyze the correlation between aerobic exercise, BDNF levels, and cognitive function in the elderly.

METHODS

Secondary information acquired from the internet, numerous journal searches, journal reviews, and publications was used to perform this literature study. Literature review guided by database searches in the following ones: Google Scholar, Pubmed, and Science Direct. The following key phrases were employed: "Aerobic Exercise, BDNF, Cognitive Function and Older Adult" and the period of time was from 2013 through 2023. The inclusion criteria include: 1) scientific articles written in English, 2) literature in the form of scientific articles published in journals 3) Articles published in 2013–2023; and 4) discussion of scientific articles on the effects of aerobic exercise on BDNF and cognitive function in older adults. Exclusion criteria include 1) scientific articles that cannot be accessed in full text and 2) articles in the form of (i) non-original studies, such as meta-analyses, conference papers, comments, or consensus documents; (ii) case reports or case series; (iii) studies assessing other conditions; and (iv) incomplete data. Scientific articles that did not meet the criteria were excluded and not used in this study.

RESULTS

The search strategy initially identified 540 articles. After removal of duplicates and abstract screening, 496 full-text articles were subsequently assessed for its eligibility. Finally, 5 articles (21-25) were included in the final review as shown in Table 1. This process resulted in selection of 5 studies evaluated the relationship between aerobic exercise on BDNF and cognitive function of older adults.

Table 1. Studies investigating the effects of aerobic exercise on BDNF level and cognitive function in elderly

Author and year of publication	Sample	Intervention	Result	Conclusion
Byun J and Kang E, 2016.[21]	24 women between the ages of 65 and 79 who are capable of carrying out routine daily activities and communication but have not engaged in	Participants were distributed into an exercise group (EG, n=13) and a control group (CG, n=11). The exercise program included senior brain health exercise (SBHE), which was performed four times per week for a total of 50 minutes at an intensity level	BDNF (ng/mL) Baseline • EG: 19.07±1.51 • CG: 18.99±1.69 After 12 weeks • EG: 20.14±1.31 • CG: 18.80±2.34 MMSE-K Baseline	Aerobic exercise has resulted in beneficial effect on cognitive function and BDNF.

	routine exercise in the previous six months.	of 9 to 14 on the rating of perceived effort (RPE) scale. The investigation lasted 12 weeks.	• EG: 26.23±1.64 • CG: 25.19±1.83 After 12 weeks • EG: 27.08±2.10 • CG: 25.09±2.12	
Kohanpour, et al., 2017.[22]	By using simple sampling, 40 older people with MMSE scores between 21 and 25 were purposefully chosen.	Participants were randomly assigned into 4 equal groups: aerobic exercise (A), lavender extract (L), aerobic-lavender (AL). and placebo (P). They each received their treatment for 12 weeks. For the first session, the aerobic activity consisted of an 8-minute run done at an intensity of 75-85% of one's maximum heart rate. After every two sessions, the running time was extended by one minute. As a result, at the conclusion of the 12-week training cycle, the running distance was 26 minutes. Two drops of lavender essence were given twice daily as part of the treatment.	BDNF (pg/mL) Baseline • A: 110.25±28.61 • L: 118.22±30.68 • AL: 108.82±32.88 • P: 110.75±26.07 After 12 weeks • A: 192.84±59.51 • L: 138.15±29.62 • AL: 179.81±62.69 • P: 111.09±24.19 MMSE Baseline • A: 22.70±1.63 • L: 22.80±1.75 • AL: 22.50±1.35 • P: 24.30±0.94 After 12 weeks • A: 24.40±1.42 • L: 24.30±1.05 • AL: 24.90±0.87 • P: 24.20±0.63	In older MCI patients, 12-week aerobic exercise significantly increased blood BDNF levels and cognitive function, either on its own or in combination with lavender essence.
Ennete, et al., 2020[23]	52 participants age 60 years or over were divided into three groups with randomization: continuous aerobic training (CAT) n = 14; interval aerobic training (IAT) n = 17; and Controls n = 21).	CAT and IAT included 30-min cycling workout twice per week for 9 weeks (for the total of 18 sessions) on an upright electronically braked cycle ergometer	BDNF (pg/mL) Baseline • CAT: 194.9 (95.1–315) • IAT: 353.8 (109–452.7) • CG: 254 (128.5–542.2) After 9 weeks • CAT: 282.7 (191–467.6) • IAT: 244.5 (180.6–380.7) • CG: 403.7 (205–516.9) MMSE Baseline • CAT: 18 (16–21) • IAT: 18 (17–19) • CG: 21 (17–23) After 9 weeks • CAT: 20 (18.3–21) • IAT: 17 (15–21) • CG: 19 (15–22)	Both types of aerobic exercise had no significant impact on plasma BDNF levels and cognitive abilities.
Liu, et al., 2020.[24]	Volunteers (N=80) who were older than 65 years with Mini-Mental State Examination	The participants were divided with randomization to conduct strength (S) or aerobic (A) training for 4 weeks in total.	BDNF (pg/mL) Baseline • S: 23458.35±5418.26 • A: 19253.6±7008.84 After 4 weeks • S: 25,413.81±7504.38	Both strength training and aerobic exercise improved cognitive funtion. Only

	scores ranging from 15 and 26 were involved in the study.		• A: 21,200.85±7406.38 MMSE Baseline • S: 22.7±4.28 • A: 23.87±4.65 After 4 weeks • S: 24.2±4.87 • A: 25.87±3.36	aerobic exercise increased BDNF level.
Kang, et al., 2020.[25]	The subjects were 20 elderly women between the ages of 68–80 years, assigned into an aquatic exercise group (n = 10) and a control group (n = 10), utilizing randomization.	The aquatic exercises were conducted for 60 minutes, three times weekly for the total of 16 weeks, and the intensity was gradually increased every 4 weeks (40–50% of heart rate reserve (HRR) for 4 weeks, 50–60% of HRR for 4 weeks, 60–65% of HRR for 4 weeks, and 65–70% of HRR for 4 weeks.	BDNF (ng/mL) Baseline • EG: 15.16 ±4.36 • CG: 15.71±3.05 • After 16 weeks • EG: 17.75±4.11 • CG: 15.51±3.02 MMSE-K Baseline • EG: 26.20±0.42 • CG: 26.10±0.32 After 16 weeks • EG: 26.80±0.92 • CG: 26.00±0.82	Performing aquatic exercise regularly can enhance the expression of BDNF, thus maintaining and improving cognitive function in elderly women

DISCUSSION

Regular exercise benefits in many possible ways to prevent age-related disease and promote longevity. Exercise significantly improved cardiorespiratory fitness and some cardiometabolic biomarker,[26] and it also has special advantages for the vascular and cellular systems that support a healthy brain. Exercise is involved in neuroprotection, synaptic plasticity, and neurogenesis.[27] Exercise is linked to better mental health,[28] a delay in dementia onset,[29,30] and better overall health and wellbeing.[31]

Aerobic is defined as "living, active, or occurring in the presence of oxygen." Therefore, oxygen is the crucial element in determining the difference between aerobic and anaerobic exercise. Aerobic exercise is a form of cardiovascular exercise, as the name suggests. The muscles receive constant energy from the oxygen when engaging in aerobic exercise. Then, large muscles acquire movements from retaining energy. When engaging in this type of workout, one should move continuously and repeatedly. The various forms of aerobic exercise consist of: running or jogging, walking, swimming, rowing, cycling, jumping ropes, step aerobics, etc.[32]

The aim of this review was to investigate studies that demonstrated how aerobic exercise affects BDNF levels and cognitive performance in older adults. Five studies were included in the present study. With regard to exercise protocol, one employed protocol of senior brain health program, one used running interventions, two used cycling, and one used aquatic exercise. The participants had a diversified condition with the inclusion criteria of healthy older adults and older adults with dementia, mild cognitive impairment (MCI), or Alzheimer disease. Two studies conducted to an elderly woman, meanwhile other studies conducted to both man and woman. Regarding the length of the longitudinal studies' intervention, 4–16 weeks range variation had been observed. Of these five studies, four researches showed beneficial effects of aerobic exercise in the BDNF levels and cognitive function.

In Byun J and Kang E study, a Senior Brain Health Exercise (SBHE) program was performed instead of the traditional aerobic exercise. SBHE performed to 24 healthy elderly women 4 times per week, of which training time was a total of 50 minutes each time with levels of effort ranging from nine to fourteen on the rating of perceived exertion (RPE) scale.[21] The BDNF level and MMSE-K score increased after the 12-week SBHE intervention. Similar results were obtained in a study conducted on healthy elderly woman by Kang et al.[22] Conducted a 16-week study, Kang et al. examine the effects of aquatic exercise on insulin-like growth factor-1 (IGF-1), BDNF, vascular endothelial growth factor (VEGF), and cognitive function in elderly women. Aquatic exercise including warm-up (10 minutes), aquatic exercise (40 minutes), and cool-down (10 minutes); three times/week. After the aquatic exercise regimen, BDNF levels, IGF-1 levels, and cognitive function all showed substantial improvements.

The effects of aerobic exercise in combination with the use of lavender essence on BDNF levels and cognitive function in elderly people with MCI are examined by Kohanpour et al.[19] For the first session, the aerobic activity included an 8-minute run at a 75%–85% HRR max intensity. After every two sessions, the running time was extended by one minute. According to the findings of this study, aerobic exercise for 12 weeks significantly increased serum BDNF levels and MMSE scores in older MCI patients, whether it was done alone or in conjunction with lavender essence. These findings are congruent with the study of Liu et al.[21] who found that aerobic exercise significantly increases BDNF level and cognitive function in dementia patient. In addition, Liu et al. study compared the BDNF level and cognitive function between aerobic exercise (cycling) and strength training for 4 weeks. The result is both groups showed increase of MMSE score, but BDNF level significantly increases only in aerobic group. This is consistent with the result of systematic review from Huang et al.[33] that involving 32 articles, which conclude that aerobic exercise, both short-term and long-term, can boost BDNF levels but strength training has no effect on peripheral BDNF. Other study conducted to elderly individuals also demonstrated that strength training does not influence BDNF level. The reason of this result might be due to a short-lived BDNF response, which might have been washed out when sampling.[34]

The induction of neurotrophins/growth factors, most notably BDNF, is a crucial biochemical mediator for the beneficial responses to exercise in the brain.[35] The majority of the brain regions studied—prefrontal cortex, perirhinal, striatum, and hippocampus—saw an increase in BDNF concentration following aerobic exercise. However, this response was modified by age.[36] BDNF encourages the survival, differentiation, migration, dendritic arborization, synaptogenesis, and plasticity of neuronal cells, among other aspects of brain development. BDNF also increases neutransmitter release, postsynaptic responses, membrane exitability, gene expression, increased dendritic growth and spine density, and altered spine morphology all of which may help to support modulation of synaptic transmission and connectivity.[35]

Exercise, especially aerobic or endurance exercise has been shown to promote BDNF expression and enhance cognitive performance. According to several studies, endurance exercise increases levels of FNDC5, a protein in the muscle that is activated during exercise and released as irisin. PGC-1 controls the expression of the FNDC5 gene in neurons, and PGC1a/ animals exhibit decreased FNDC5 expression in the brain. BDNF expression is elevated when FNDC5 is forcedly expressed in primary cortical neurons, whereas BDNF is decreased when FNDC5 is knocked down using RNAi.[37,38] Exercise may have a direct impact on the production of BDNF in the hippocampi, but it also has the potential to have an indirect effect through peripheral processes. Exercise may cause the liver to produce DBHB (D-b-hydroxybutyrate), which is subsequently circulated throughout the body and transferred to the hippocampus, where it modulates BDNF expression by inhibiting HDAC (histone deacetylases).[39]

Study conducted by Enette et al.[20] focused in seniors with Alzheimer Disease (AD). They comparing 3 groups consist of continuous aerobic training (CAT), interval aerobic training (IAT), and control group for 9 weeks. In contrast to the previously mentioned studies, this study demonstrated that BDNF level and cognitive state between the 3 groups are not significantly different. The results of this study are in contrast to previous similar studies conducted on AD, where aerobic exercise increased BDNF levels.[40] Ennete et al. study is the first study that compare the effect of two different types of aerobic exercise (CAT vs. IAT) on plasma BDNF levels in the specific group of seniors with mild to moderate AD. Furthermore, other additional variables, such as genetic diversity, metabolic abnormalities, or inflammatory processes, might affect an individual's basal BDNF synthesis and, consequently, the BDNF response to aerobic training.[41]

The advantages of aerobic exercise for older adults are well-known. After a three-month intervention period,[42] changes in hippocampal perfusion were favorably linked with increasing fitness levels, which also increased hippocampus volume.[43] Numerous studies have also demonstrated that aerobic exercise improving global cognitive ability and memory among older adults with MCI.[44] Both the short-term and long-term advantages of exercise on cognition may be attributed to improvements in synaptic activity, blood flow to the brain, brain irrigation, and neural plasticity.[45] Exercise stimulated neuroplasticity and mitochondrial function in the hippocampus, thereby attenuating cognitive dysfunction.[46] Several studies reported there is a strong association between aerobic fitness level and level of attention.[47,48] According to other studies, aerobic exercise may improve memory in older people, with higher intensity exercise possibly having the biggest benefits.[49] This could be as a result of high-intensity exercise routines induced greater increases in BDNF.[50] Apparently, the time period a person exercises also has an effect on BDNF levels. One meta-analysis offers solid proof that acute and ongoing (regular) exercise have an important influence on BDNF levels. A single exercise session raises BDNF levels, according to evidence from 14 research, with a moderate impact size. Additionally, compared to those who only complete acute exercise, regular exercise increases the degree of these benefits with higher BDNF responsivity, showing a moderate impact size.[51] From a systematic review, meta-analysis, and meta-regression on the various training load variables that affect the blood concentrations of neurotrophic factors, it is recommended engaging in aerobic exercise with moderate-high intensity (65% of VO2max), 2-3 times per week, for minimum 40 minutes of training session continuously in order to enhance BDNF concentration levels.[52] To be more practical, it is advised that older adults do 150 minutes of weekly moderate-intensity aerobic exercise.[53] If tolerated, vigorous intensity aerobic activity is suggested for greater and more intensive benefits.[54]

CONCLUSION

Despite the paucity of data, this literature review found that both healthy older adults and elderly people with various diseases have higher BDNF level and cognitive function after aerobic exercise. With these results, for the greatest benefits, it is advised that older persons complete 150 minutes of moderate-intensity aerobic activity each week. Given the importance of the topic, additional research is needed to identify the kinds, degrees of difficulty, and duration of physical activity that would be most effective in raising BDNF level and cognitive function in healthy aged people as well as in those with degenerative, neuropsychiatric, and metabolic illnesses.

CONFLICT OF INTEREST

No interest conflicts have been disclosed by the authors.

ACKNOWLEDGMENT

The authors appreciate the support and guidance of the Head and all staff of the Physiology Department Medical Faculty Universitas Udayana, Denpasar, Indonesia.

REFERENCES

1. Young F, Maguire S. 2022. Physiology of ageing. *Anaesthesia & Intensive Care Medicine*. Vol 23 (11):723–726
2. Preston J, Biddell B. 2021. The physiology of ageing and how these changes affect older people. *Medicine*. Vol 49(1):1–5.
3. Amarya S, Singh K, Sabharwal M. 2018. Ageing Process and Physiological Changes. *Gerontology. InTech*.
4. Chalise HN. 2019. Aging: Basic Concept. *Am J Biomed Sci Res*. Vol 1(1):8–10.
5. Harada CN, Natelson Love MC, Triebel KL. 2013. Normal cognitive aging. *Clin Geriatr Med.* Vol 29(4):737–752.
6. Sele S, Liem F, Mérillat S, Jäncke L. 2021. Age-related decline in the brain: a longitudinal study on inter-individual variability of cortical thickness, area, volume, and cognition. *Neuroimage*. Vol 240.
7. Brown BM, Bourgeat P, Peiffer JJ. 2014. Influence of BDNF Val66Met on the relationship between physical activity and brain volume. *Neurology.* Vol 83(15):1345–1352.
8. Miranda M, Morici JF, Zanoni MB, Bekinschtein P. 2019. Brain-Derived Neurotrophic Factor: A Key Molecule for Memory in the Healthy and the Pathological Brain. *Front Cell Neurosci.* Vol 13.
9. Leal G, Bramham CR, Duarte CB. 2017. BDNF and Hippocampal Synaptic Plasticity. *In: Vitamins and Hormones.* Academic Press Inc. p. 153–195.
10. Mizoguchi Y, Yao H, Imamura Y, Hashimoto M, Monji A. 2020. Lower brain-derived neurotrophic factor levels are associated with age-related memory impairment in community-dwelling older adults: the Sefuri study. *Sci Rep.* Vol 10(1).
11. Barha CK, Falck RS, Davis JC, Nagamatsu LS, Liu-Ambrose T. 2017. Sex differences in aerobic exercise efficacy to improve cognition: A systematic review and meta-analysis of studies in older rodents. *Front Neuroendocrinol.* Vol 46:86–105.

12. Northey JM, Cherbuin N, Pumpa KL, Smee DJ, Rattray B. 2018. Exercise interventions for cognitive function in adults older than 50: A systematic review with meta-Analysis. *Br J Sports Med*. Vol 52(3):154–160.
13. Riello M, Rusconi E, Treccani B. 2021. The Role of Brief Global Cognitive Tests and Neuropsychological Expertise in the Detection and Differential Diagnosis of Dementia. *Front Aging Neurosci.* Vol 13.
14. Mandolesi L, Polverino A, Montuori S. 2018. Effects of physical exercise on cognitive functioning and wellbeing: Biological and psychological benefits. *Front Psychol.*
15. Donnelly JE, Hillman CH, Castelli D. 2016. Physical activity, fitness, cognitive function, and academic achievement in children: A systematic review. *Med Sci Sports Exerc.* Vol 48(6):1197–1222.
16. Kyun Jeon Y, Ho Ha C. 2015. Expression of brain-derived neurotrophic factor, IGF-1 and cortisol elicited by regular aerobic exercise in adolescents. *J Phys Ther Sci.* Vol 27(3):737-41.
17. Briken S, Rosenkranz SC, Keminer O. 2016. Effects of exercise on Irisin, BDNF and IL-6 serum levels in patients with progressive multiple sclerosis. *J Neuroimmunol.* Vol 299:53–58.
18. Chapman SB, Aslan S, Spence JS. 2013. Shorter term aerobic exercise improves brain, cognition, and cardiovascular fitness in aging. *Front Aging Neurosci*. Vol 12;5:75.
19. Zhang S, Zhen K, Su Q, Chen Y, Lv Y, Yu L. 2022. The Effect of Aerobic Exercise on Cognitive Function in People with Alzheimer's Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Int J Environ Res Public Health*. Vol 19(23).
20. Jia RX, Liang JH, Xu Y, Wang YQ. 2019. Effects of physical activity and exercise on the cognitive function of patients with Alzheimer disease: A meta-analysis. *BMC Geriatr*. Vol 19(1).
21. Byun J-E, Kang E-B. 2016. The effects of senior brain health exercise program on basic physical fitness, cognitive function and BDNF of elderly women - a feasibility study. *J Exerc Nutrition Biochem*. Vol 20(2):8–18.
22. Kohanpour M-A, Peeri M, Azarbayjani M-A. 2017. The effects of aerobic exercise with lavender essence use on cognitive state and serum brain-derived neurotrophic factor levels in elderly with mild cognitive impairment. *Almqvist & Wiksell*.
23. Enette L, Vogel T, Merle S. 2020. Effect of 9 weeks continuous vs. interval aerobic training on plasma BDNF levels, aerobic fitness, cognitive capacity and quality of life among seniors with mild to moderate Alzheimer's disease: A randomized controlled trial. *European Review of Aging and Physical Activity*. Vol 17(1).
24. Liu IT, Lee WJ, Lin SY, Chang ST, Kao CL, Cheng YY. 2020. Therapeutic Effects of Exercise Training on Elderly Patients with Dementia: A Randomized Controlled Trial. *Arch Phys Med Rehabil*. Vol 101(5):762–769.
25. Kang D wang, Bressel E, Kim D yeon. 2020. Effects of aquatic exercise on insulin-like growth factor-1, brain-derived neurotrophic factor, vascular endothelial growth factor, and cognitive function in elderly women. *Exp Gerontol.* Vol 132.
26. Lin X, Zhang X, Guo J. 2015. Effects of exercise training on cardiorespiratory fitness and biomarkers of cardiometabolic health: A systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc*. Vol 4(7).
27. Vecchio LM, Meng Y, Xhima K, Lipsman N, Hamani C, Aubert I. 2018. The Neuroprotective Effects of Exercise: Maintaining a Healthy Brain Throughout Aging. *Brain Plasticity*. Vol 4(1):17–52.
28. Mikkelsen K, Stojanovska L, Polenakovic M, Bosevski M, Apostolopoulos V. 2017. Exercise and mental health. *Maturitas.* Vol 106:48–56.
29. George EK, Hemachandra Reddy P. 2019. Can Healthy Diets, Regular Exercise, and Better Lifestyle Delay the Progression of Dementia in Elderly Individuals? *Journal of Alzheimer's Disease*. Vol 72(s1):S37–S58.
30. Alty J, Farrow M, Lawler K. 2020. Exercise and dementia prevention. *Pract Neurol.* Vol 20(3):234–240.
31. Abd El-Kader SM, Al-Jiffri OH. 2016. Aerobic exercise improves quality of life, psychological well-being and systemic inflammation in subjects with alzheimer's disease. *Afr Health Sci.* Vol 16(4):1045–1055.
32. Aydin SB. 2022. A Critical Review on Anaerobic and Aerobic Exercise: Which One to Choose? The Difference, The Benefits and The Risks. *Perceptions Reprod Med*.
33. Huang T, Larsen KT, Ried-Larsen M, Møller NC, Andersen LB. 2014. The effects of physical activity and exercise on brain-derived neurotrophic factor in healthy humans: A review. *Scand J Med Sci Sports.* Vol 24(1):1–10.
34. Forti LN, Njemini R, Beyer I. 2014. Strength training reduces circulating interleukin-6 but not brain-derived neurotrophic factor in community-dwelling elderly individuals. *Age (Omaha).* Vol 36(5).
35. Park H, Poo MM. 2013. Neurotrophin regulation of neural circuit development and function. *Nat Rev Neurosci.* Vol 14(1):7–23.
36. Pietrelli A, Matković L, Vacotto M, Lopez-Costa JJ, Basso N, Brusco A. 2018. Aerobic exercise upregulates the BDNF-Serotonin systems and improves the cognitive function in rats. *Neurobiol Learn Mem*. Vol 155:528–542.

37. Wrann CD, White JP, Salogiannnis J. 2013. Exercise induces hippocampal BDNF through a PGC-1α/FNDC5 pathway. *Cell Metab*. Vol 18(5):649–659.
38. Xu B. 2013. BDNF (I)rising from Exercise. *Cell Metab*.Vol 18(5):612–614
39. Sleiman SF, Henry J, Al-Haddad R. 2016. Exercise promotes the expression of brain derived neurotrophic factor (BDNF) through the action of the ketone body b-hydroxybutyrate. *Elife*. Vol 2;5:e15092
40. Coelho FGDM, Vital TM, Stein AM. 2014. Acute aerobic exercise increases brain-derived neurotrophic factor levels in elderly with Alzheimer's disease. *Journal of Alzheimer's Disease*. Vol 39(2):401–408. https://doi.org/10.3233/JAD-131073
41. Balietti M, Giuli C, Conti F. 2018. Peripheral Blood Brain-Derived Neurotrophic Factor as a Biomarker of Alzheimer's Disease: Are There Methodological Biases? *Mol Neurobiol*. Vol 55(8):6661–6672.
42. Maass A, Düzel S, Goerke M. 2015 Vascular hippocampal plasticity after aerobic exercise in older adults. *Mol Psychiatry.* Vol 20(5):585–593.
43. Feter N, Penny JC, Freitas MP, Rombaldi AJ. 2018. Effect of physical exercise on hippocampal volume in adults: Systematic review and meta-analysis. *Sci Sports.* Vol 33(6):327–338.
44. Zheng G, Xia R, Zhou W, Tao J, Chen L. 2016. Aerobic exercise ameliorates cognitive function in older adults with mild cognitive impairment: A systematic review and meta-analysis of randomised controlled trials. *Br J Sports Med.* Vol 50(23):1443–1450.
45. Ferrer-Uris B, Ramos MA, Busquets A, Angulo-Barroso R. 2022. Can exercise shape your brain? A review of aerobic exercise effects on cognitive function and neuro-physiological underpinning mechanisms. *AIMS Neurosci*. Vol 9(2):150–174.
46. Park HS, Kim CJ, Kwak HB, No MH, Heo JW, Kim TW. 2018. Physical exercise prevents cognitive impairment by enhancing hippocampal neuroplasticity and mitochondrial function in doxorubicin-induced chemobrain. *Neuropharmacology*. Vol 133:451–461.
47. Tsai CL, Wang CH, Pan CY, Chen FC, Huang SY, Tseng YT. 2016. The effects of different exercise types on visuospatial attention in the elderly. *Psychol Sport Exerc*. Vol ;26:130–138.
48. Tsai CL, Chen FC, Pan CY, Wang CH, Huang TH, Chen TC. 2014. Impact of acute aerobic exercise and cardiorespiratory fitness on visuospatial attention performance and serum BDNF levels. *Psychoneuroendocrinology*. Vol 41:121–131.
49. Kovacevic A, Fenesi B, Paolucci E, Heisz JJ. 2020. The effects of aerobic exercise intensity on memory in older adults. *Appl Physiol Nutr Metab*. Vol 45(6):591-600.
50. Afzalpour ME, Chadorneshin HT, Foadoddini M, Eivari HA. 2015. Comparing interval and continuous exercise training regimens on neurotrophic factors in rat brain. *Physiol Behav*. Vol 147:78–83.
51. Szuhany, K. L., Bugatti, M., & Otto, M. W. 2015. A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor. *Journal of Psychiatric Research*. Vol 60, 56–64.
52. Feter N, Alt R, Dias MG, Rombaldi AJ. 2019. How do different physical exercise parameters modulate brain-derived neurotrophic factor in healthy and non-healthy adults? A systematic review, meta-analysis and meta-regression. *Sci Sports*. Vol 34(5):293–304.
53. Boulton ER, Horne M, Todd C. 2018. Multiple influences on participating in physical activity in older age: Developing a social ecological approach. *Health Expectations*. Vol 21(1):239–248.
54. Zaleski AL, Taylor BA, Panza GA. 2016. Coming of Age: Considerations in the Prescription of Exercise for Older Adults. *Methodist Debakey Cardiovasc J*. Vol12(2):98-104