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Master's Thesis of Science

**Effect of Aerobic Exercise and Its
Association with APOE e4 Allele in
Cognitive Function of Alzheimer's
Disease (AD) Patients**

알츠하이머병 환자의 APOE e4 유무에 따른
유산소 운동이 인지기능에 미치는 영향

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**Effect of Aerobic Exercise and Its
Association with APOE e4 Allele in
Cognitive Function of Alzheimer's Disease
(AD) Patients**

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A Thesis submitted in partial fulfillment of
the requirement for the degree of
MASTER OF SCIENCE

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Abstract

Background: Dementia including Alzheimer's Disease (AD) with other cognitive function of disorder is increasing in elderly people. The high risk factor of Alzheimer's Disease (AD) was genetics of APOE $\epsilon 4$. The prevention and treatment are still controversial and the medical industries are trying to develop medications and cognitive functions to dementia people. One of the ways to treat is an exercise that is a non-invasive treatment, in-expensive, lack of side effect, and it decreases the risk factors of dementia with preventing to reduce their cognitive functions. Also, there are lack of studies for exercise program for treatment to dementia.

Purpose: Aerobic exercise was more effective way to prevent decline early state of Alzheimer's Disease (AD). This study was figured out the effect of aerobic exercise according to APOE $\epsilon 4$ presences and how aerobic exercise affect neuropsychological test on between $\epsilon 4$ carriers and $\epsilon 4$ non-carriers group.

Results: The aerobic exercise capacity was significant difference both exercise $\epsilon 4$ carriers and $\epsilon 4$ non-carrier group compared into control group. This study showed exercise $\epsilon 4$ carriers and exercise $\epsilon 4$ non-carriers were improved ($p = 0.016$, $r = 0.66$) and between exercise $\epsilon 4$ carriers and control groups were significant improved ($p = 0.007$, $r = 0.72$). Only between exercise $\epsilon 4$ carriers group and exercise $\epsilon 4$ non-carriers group, both color reading reaction ($p = 0.035$, $r = 0.59$) and color reading time per item ($p = 0.031$, $r = 0.605$) in CWST were decreased. The COWAT in sematic wrong section was significant improved to decrease between exercise $\epsilon 4$ carriers and exercise $\epsilon 4$ non-carriers group ($p = 0.036$, $r = 0.627$). The DST in backward part also was significant improved scores in exercise $\epsilon 4$ carriers ($p = 0.039$, $r = 0.586$) and exercise $\epsilon 4$ non-carriers ($p = 0.011$, $r = 0.681$) than control group. The K-IADL scores was decreased between exercise $\epsilon 4$ non-carriers and control group ($p = 0.035$, $r = 0.594$) after 12 weeks.

Conclusion: There were improved between aerobic exercise and cognitive function in COWAT, CWST, DST, K-IADL after 12 weeks. The APOE $\epsilon 4$ carriers also had more effective in COWAT and CWST of cognitive function than exercise $\epsilon 4$ non-carriers after aerobic exercise. The DST was effective in the APOE $\epsilon 4$ carriers than control. But, the APOE $\epsilon 4$ non-carriers was only effective in K-IADL compared to control.

Keyword : Alzheimer's Disease, Aerobic Exercise, Aerobic Exercise Capacity, Blood Lactate, Cognitive Function

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Contents

I. Introduction	4
1) Significant of the Study	4
2) The purpose of Study	6
3) Research Hypothesis	7
4) Limitations.....	7
II. Literature Review	8
1) The definition of Alzheimer’s Disease (AD) and landmark	9
2) APOE genotype and its definition	9
3) The relationship between APOE allele in Alzheimer’s Disease (AD) and cognitive function.....	9
4) Timeline of Alzheimer’s Disease (AD) onset according to age: Lifespan with genetics of Alzheimer’s Disease (AD).....	11
5) Risk factors of Alzheimer’s Disease (AD).....	12
6) Treatment for Dementia and Alzheimer’s Disease (AD)	14
7) Interaction between physical exercise and APOE e4 allele	15
8) The effect of aerobic exercise and cognitive function within APOE genotype	16
a. The impact of aerobic exercise in APOE allele.....	16
b. Level of cardiovascular fitness and cognitive function in APOE e4 allele.....	19
9) The physiological mechanism between effect of aerobic exercise and cognitive function.....	22
III. Research Method	23
1) Participants	23
2) Sample size	24
3) Study Design	24
4) Exercise Program	25
a. Exercise Intensity	26
b. Exercise Time & Frequency.....	27
c. Exercise Type.....	27
5) Measurements.....	28
a. Neuropsychological Test.....	28
b. Submaximal Bike Ergometer Test with Maximal Oxygen Uptake (VO ₂ max).....	29
c. Senior Fitness Test (SFT).....	31
d. Cardiac Output & Rate-Pressure Product (RPP).....	32
e. Tinetti Performance Oriented Mobility Assessment (POMA) Test.....	34
6) Statistical Diagnosis & Analysis	34
IV. Results	36
1) Baseline of Characteristics	36
2) Difference Aerobic Capacity (VO ₂ max, Cardiac Output, Rate-Pressure Product) between 3 groups after 12 weeks	38
3) Difference Senior Fitness Test (SFT) between 3 groups after 12 weeks	39
4) Difference Tinetti POMA between 3 groups after 12 weeks	40
5) Difference CWST neuropsychological test between 3 groups after 12 weeks	41
6) Difference COWAT neuropsychological test between 3 groups after 12 weeks	42
7) Difference DSC neuropsychological test between 3 groups after 12 weeks	43
8) Difference TMT neuropsychological test between 3 groups after 12 weeks	43

9) Difference K-MMSE between 3 groups after 12 weeks	44
10) Difference DST between 3 groups after 12 weeks	44
11) Difference BADL between 3 groups after 12 weeks	45
12) Difference K-IADL between 3 groups after 12 weeks	45
V. Discussion	46
1) Aerobic Exercise Capacity & APOE e4 non- and e4 carriers.....	46
2) Neuropsychological test differences between APOE e4 non-carriers and e4 carriers after 12 weeks.....	46
V. Conclusion	47
Bibliography	48

I. Introduction

1) Significance of the Study

According to develop medical industries and health-well fares, an average of human life is expanded, and then a population of elderly people has been increasing. (Jung., 2009). In supporting current view, the Korean Longitudinal Study of Ageing (KLOSA) shows that the population of elderly people, who are less than 59 years old from 2006 and 2012, is 44.6 % on 2006 with the highest group and this population still are the highest in the group of 33.9 % in this study (2012). In this respect, this result explained Korean elderly group is fast growing up in this modern society. Moreover, the elderly people who are ranged over 65 years old were 73 million people (2.3% out of total Korean people) on 1960, the people were 545 million people (11%) on 2010, and this growing pattern of the people presents to increase a number of them will be 1,269 million (24.3%) at 2030 and 1,762 million (40.1%) at 2060 which will be the fast growing-up level of old aged group respectively (Statistic Korea, 2010).

Specially, a dementia including Alzheimer's Disease (AD) with other cognitive function of disorder is increasing in elderly people (Kim, 2010). For example, a report of Korean National Dementia Management presents the dementia mortality 9.18 % on 2012 and the number of dementia is increasing twice rates of dementia each two decades and the type of dementia has the highest percentages in Alzheimer's Disease (AD) with 71.3 %, vascular dementia of 16.9 %, and other dementia of 11.8% in Korea accordingly (본건복지부, 2012). In other words, the types and mortality of dementia have almost Alzheimer's Disease (AD) group. Also, when compared with other countries, the growing pattern of speed in Korean elderly people is the highest speed of 17 years, France of 11 years, the United States of 72 years and Japan 24 years respectively (이삼식 & 최효진, 2011).

A risk of dementia is a high level in cases of old age, woman and

lower level of education; and the risk of it with age on 65 to 69 years are more 2.15 times of risk than 70 to 74 years, age of 75 to 79 years are 3.76 times, 80 to 84 years are 5.7 times and over 85 years of age are 38.86 times (Korean Health Welfare., 2012). According to the risk factor of dementia, people who have this risk factors proceed Alzheimer's Disease (AD) of 12 % within one year and 80% out of this people become Alzheimer's Disease (AD) within eight years (Bozoki et al., 2001). Therefore, a current view of the risk factor of dementia shows Alzheimer's Disease (AD) are the most part in Korean Dementia and it is necessary to prevent and treat it.

Within the fast speeding of elderly people; however, the prevention and treatment are still controversial in the world, the medical industries are trying to develop medications and cognitive functions to dementia people (장용순, 2004). It shows a treatment of old age with dementia only is able to delay their disorders of cognitive functions with many intermittent medication therapy, cognitive rehabilitation, exercise and psychological social treatment (Burgener., 2009; 박윤진 외., 2013).

Especially, the exercise is a non-invasive treatment, in-expensive, lack of side effect and it decreases the risk factors of dementia with preventing to reduce their cognitive functions. Moreover, some studies agree a limitation of medical treatment in Alzheimer's Disease (AD) (Corder et al., 1993; Jennifer L. Etnier et al., 2007; Rabins et al., 1997; A. M. Saunders et al., 1993). According to past studies, the non-invasive treatment including the cognitive rehabilitation, motor psychological treatment, daily activities training and exercise improved a cognitive function (Huang, Lee, Liao, Wang, & Lai, 2012). Specially, an aerobic exercise had a positive effect both Alzheimer's Disease (AD) patients and normal old age people (Shaji, George, Prince, & Jacob, 2009; Yeager, Hyer, Hobbs, & Coyne, 2010).

There are many studies presented relationships between the exercise and the risk factor of dementia special in Alzheimer's Disease

(AD) patient. In addition, past studies explained that the biggest reasons of Alzheimer's Disease (AD) was a genetic problem of Apolipoprotein Epsilon (APOE) and this reason was an important risk factor of Alzheimer's Disease (AD) (Corder et al., 1993; Jennifer L. Etner et al., 2007; A. M. Saunders et al., 1993). According to ageing, the genotype of APOE e4 had a negative relationship in without dementia people (Corder et al., 1993; Jennifer L. Etner et al., 2007; A. M. Saunders et al., 1993). Furthermore, in a longitudinal study, elderly groups who were not dementia with presence of APOE-e4 decreased more their cognitive functions in passing a time than without APOE-e4 groups (Jennifer L. Etner et al., 2007; Feskens et al., 1994; Yaffe, Cauley, Sands, & Browner, 1997).

Current view of relationship between exercise and cognitive function in APOE e4 allele; however, there are still many controversial studies between the aerobic exercise and cognitive function according to presence of APOE e4 or not. First of all, it was the lack of evidence between maximal oxygen uptake and cognitive function detail. Secondly, past studies have only examined the relationship between maximal oxygen up-take within APOE genotype except for cognitive function change. All things considered, it is necessary to examine specific aerobic exercise capacity in APOE allele. In other words, it needs to figure out the relationship aerobic exercise capacity and cognitive function according to APOE genotype.

In addition, there are few past studies of the aerobic exercise affects Alzheimer's Disease (AD)'s cognitive function according to APOE e4 or not (Brown, Peiffer, & Martins, 2012). At this point, it is necessary of checking an aerobic exercise through APOE genotype for Korean Dementia people.

2) The purpose of the study

According to APOE e4 allele in Alzheimer's Disease (AD)

patients, it will be divided into two categorical group whether APOE e4 presence or not. As doing so, two groups will be measured their differences of body composition, senior fitness test (SFT), VO₂ max and cognitive function after 12 weeks of the aerobic exercise. In addition, the design of this study is patients-control study into two genotype groups. Therefore, this study is focused on 1) findings of cognitive differences into two groups and it will 2) verify the effective aerobic exercise is able to improve overall Alzheimer's Disease (AD) patients' qualities of lives; and, this study will be give basic medical documents of Alzheimer's Disease (AD) in the future.

3) Research Hypothesis

There are couples of hypothesis after following this sentence.

- a. An aerobic exercise will be significant differences VO₂ max, cardiac output (CO), rate pressure product (RPP) between APOE e4 carrier and e4 non-carrier.
- b. An aerobic exercise will be significant differences Cognitive Function (Neuropsychological Test) between APOE e4 carrier and e4 non-carrier.
- c. The e4 carriers will be more effective on cognitive function after 12 weeks aerobic exercise training.

4) Limitations

This study is limited in the following manners:

- a. The participants of e4 non-carriers, e4 carriers and control group were shown disproportion of gender, level of education, VO₂ max, and K-MMSE
- b. The participants could not control for daily intake and physical activity
- c. The sample size was small for evaluating the exercise

II. Literature Review

1) The definition of Alzheimer's Disease (AD) and landmark

The Alzheimer's Disease (AD) is one of type in a dementia and it is progressively decreased the cognitive function in the lifespan. After all, the disease is able to affect negative on their daily activities lives special in personal characteristic, lack of subjective behavior, routine behavior, abnormal judgment, abstract thinking disorder and solving problems (Barbara & Ruthana, 2011).

In the previous studies, it concluded that Alzheimer's Disease (AD) was called cortical degeneration disease including a neurotic plaques and neurofibrillary tangle (Cummings, 2004; Querfurth & Laferla, 2010). Another definition of Alzheimer's Disease (AD) was able to explain a sporadic disease because of ageing or caused by ageing (Hebert, Scherr, Bienias, Bennett, & Evans, 2003). Families who were sporadic diseases with Alzheimer's Disease (AD) had dementia in their families or Apolipoprotein E (APOE) allele, it had a high risk of Alzheimer's Disease (AD) (Corder et al., 1993; Gearing, 1995). Especially, people who had a homozygote of APOE e4 allele were 50 percentages of developing Alzheimer's Disease (AD) between mid 60 years and late 60 years and a heterozygote of APOE e4 increased symptoms of Alzheimer's Disease (AD) (50%) in mid and late of 70 years (Saunders et al., 1993).

The National Institute on Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer Diseases and Related Disorders Association (ADRDA) divide three types of Alzheimer's Disease (AD) such as "Probable", "Possible" and "Definite" in clinical fields (Mckhann, Drachman, Folstein, & Katzman, 1984). Moreover, a probable of Alzheimer's Disease (AD) is used Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) together and the DSM-IV's sensitivity is 81 percentages and 70 percentages of specificity to detect the Alzheimer's Disease (AD) currently (Berg et al., 1998; Knopman et al.,

2001; Mckhann et al., 2011).

2) APOE genotype and its definition

Human chromosome has 23 pairs from each parent and living 46 genes during lifetime. Also, people include two APOE genes including APOE e4 allele related to Alzheimer's Disease (AD) (William et al., 2004). APOE gene is located on chromosome 19 and it is divided into three sub-genotypes E2, E3 and E4 that combine to appear six genotypes (E2/E2, E2/E3, E2/E4, E3/E3, E3/E4, E4/E4) (Boulenouar et al., 2013; Laskowitz & Roses, 1998; Mahfouz et al., 2006). In the world, there are many prevalence rates of e3 (mean=78.3%, range=8.5-98%) and the next rate are e4 (mean=14.5%, range=0-49%) and e2 (mean=6.4%, range=0-37.5%) accordingly (Eisenberg, Kuzawa, & Hayes, 2010). In addition, three types of APOE such as E2, E3, E4 are made in different types in human body each genotypes of APOE allele affects neurological damage or regenerations in a ligand (Obisesan et al., 2012). Moreover, the APOE gene is important factor for late onset of Alzheimer's Disease (AD) and APOE protein is the major cholesterol carrier in brain, which can be involved in neuronal maintenance and repair (Bagyinszky, Youn, An, & Kim, 2014). The APOE is highly related to a Beta-amyloid and Tau in cerebrovascular blood (Prior, Wihl, & Urmoneit, 2000). APOE e4 alleles is strongly associated with an increased risk of developing atherosclerotic cardiovascular disease, a condition that itself is a risk for AD (Brown et al., 2012) and the APOE gene polymorphisms were associated with diseases of the respiratory system and cardiovascular disease (Yu et al., 2014). All things considered, there is important factor of APOE e4 allele and it is highly possible to develop types of dementia special in Alzheimer's Disease (AD).

3) The relationship between APOE genotype in Alzheimer's Disease (AD) and cognitive function

The APOE e4 allele located in the number 19 chromosome is highly associated with Alzheimer's Disease (AD) (Corbo & Scacchi, 1999). Also, there is a possibility of Alzheimer's Disease (AD) if either APOE e4 allele presence or not and both APOE e4 allele presence in its genotype (William et al., 2004). A previous study showed that the APOE e4 allele has positive relationship in Alzheimer's Disease (AD) and it decreases cognitive function with verbal memory skill and abstract thinking order (Schiepers et al., 2012). Moreover, there was 1.5 time higher decline of cognitive function for people who had the APOE e4 allele than without APOE e4 allele (Rajan, Wilson, Skarupski, Mendes de Leon, & Evans, 2014). Currently, a pathophysiological mechanism of Alzheimer's Disease (AD) is caused by Beta-amyloid accumulation and it increases a level of amyloid-42 to develop Alzheimer's Disease (AD) risk factors (William et al., 2004; Corbo & Scacchi, 1999).

Moreover, there is a significant study of the relationship between APOE e4 allele and Alzheimer's Disease (AD) in Korea (K. W. Kim et al., 1999). In this study, the frequency of the APOE e4 allele in the early onset Alzheimer's Disease (AD) (EOAD) and late onset Alzheimer's Disease (AD) (LOAD) group was significantly higher than in the control (healthy individuals) group (K. W. Kim et al., 1999). Additionally, the presence of the APOE e4 allele is negatively correlated with the cognitive abilities of aging, non-demented individuals (Caselli et al., 1999, 2004; Jennifer L. Etner et al., 2007; Feskens et al., 1994; Yaffe et al., 1997).

According to National Institute on Aging's Alzheimer's Disease (NIAD) Fact Sheet and Mayo Clinic's pages on Alzheimer's genetics, there were divided genotypes for six differences included e2/e2, e2/3, e2/e4, e3/e3, e3/e4 and e4/e4. To be specific, the risk factors of Alzheimer's Disease (AD) in e2/e2 and e2/e3 were 40% less likely and each e2/e4, e3/e4, and e4/e4 was 2.6, 3.2, 14.9 times of disease risk, respectively. The e3/e3 was the average risk factors of Alzheimer's Disease (AD). In other words, the most common variety of Alzheimer's

Disease (AD) usually begins after 65 years (Late-onset of Alzheimer's Disease (AD): LOAD). The most common gene associated with LOAD is called APOE. Therefore, when he or she had APOE-e4 gene, it is possible to increase dementia specific in developing Alzheimer's Disease (AD).

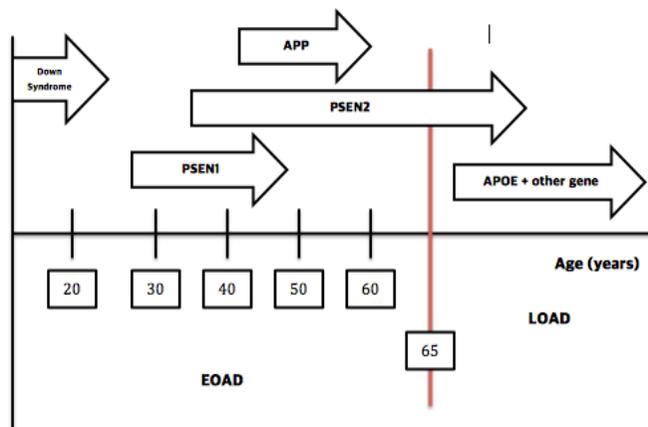
4) A timeline of Alzheimer's Disease (AD) onset according to age: Lifespan with genetics of Alzheimer's Disease (AD)

According to Bagyinszky et al., three genes are highly risk factors for early onset Alzheimer's Disease (AD) (EOAD). To be specific, mutations of amyloid precursor protein (APP), presenilin 1 (PSEN1) and presenilin 2 (PSEN2) might affect alternation of amyloid beta (Abeta) production (2014). The APP gene is located on chromosome 21 and might enhance Abeta accumulation (Bagyinszky et al., 2014). The PSEN1 and PSEN2 have similar structures. PSEN1 mutations might develop Alzheimer's Disease (AD) symptoms because of increasing the production of Abeta 42 and 40 (Campion et al., 1999). Also, the PSEN1 could be involved in sporadic Alzheimer's Disease (AD) and Late onset Alzheimer's Disease (AD) (LOAD) during 40s or early 50s (Bagyinszky et al., 2014).

It is clear from the *figure 1* that early stage of Alzheimer's Disease (AD) is not affected by APOE gene and it is definitely associated with APOE gene after 65 year-old people (Bagyinszky et al., 2014). In Korean people, one study estimated to count alleles and genotype frequencies of APOE and Alzheimer's Disease (AD) cases among 110 people of Alzheimer's Disease (AD). This study showed the genotype of e2/e3 with 7%, e2/e4 with 0.9, e3/e3 with 53.6%, e3.e4 with 32.7%, and e4/e4 with 5.5% respectively (K. W. Kim et al., 1999). This result explained e3/e3 genotype had high value of frequency and the lowest of frequency were e4/e4 genotype. However, when the age-and gender-adjusted Odd Ratio for this group, one or two copies of the APOE e4 allele was 3.2 (95% CI= 1.9-5.4) and the two copies of APOE e4 allele

(homozygous) people was 17.4 (95% CI= 2.0-147.3) (K. W. Kim et al., 1999). These OR indicated the number of APOE e4 allele was highly related to the risk of Alzheimer's Disease (AD). According to the distribution of the ages-at-onset by the status of APOE, one or two APOE e4 alleles in men was significant lower than that in the people with no APOE e4 allele in men ($p=0.03$ by Mann-Whitney U test). In addition, the frequencies of APOE e2 were significant related to the late onset of Alzheimer's Disease (AD) (K. W. Kim et al., 1999).

Figure 1: The age onset of Alzheimer's Disease (AD) depending on the different involvement of genes



(Bagyinszky et al., 2014)

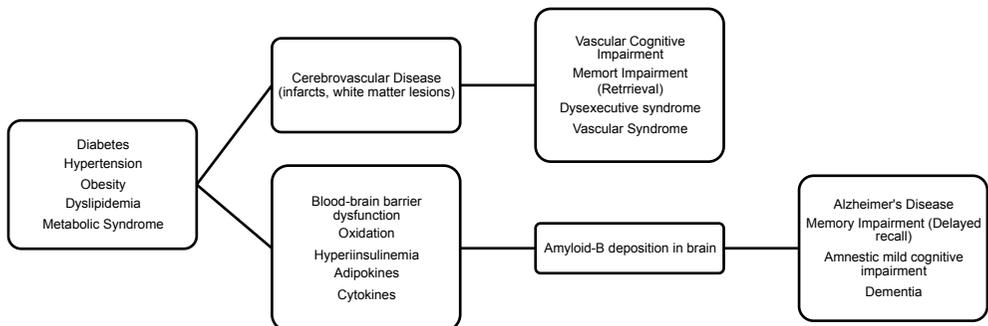
5) Risk factors of Alzheimer's Disease (AD)

There are many studies showing risk factors of Alzheimer's Disease (AD) and how to prevent cognitive decline. However, it is a controversial topic and many researchers have still been trying to find a solution of Alzheimer's Disease (AD) and the prevention of cognitive decline. In general, various risk factors have been found to be associated with dementia and Alzheimer's Disease (AD) (Reitz, Brayne, & Mayeux, 2011). Also, vascular risk factors including cardiovascular disease and stroke are associated with high risk for dementia. The vascular risk factors are related to vascular dementia for changing $A\beta$ deposition; but, Alzheimer's Disease (AD) are still unclear (Reitz et al., 2011).

Current risk factors are showed in Figure 3. This figure shows Cerebrovascular Disease, Blood Pressure, Type 2 Diabetes, Body Weight, Plasma Lipid Levels, Metabolic Syndrome, Smoking, Depressive Symptoms (Depression), Psychological stress, and Traumatic Brain Injury are associated with dementia and Alzheimer' Disease (Reitz et al., 2011). In this overall perspective, vascular risk factors should be considered to prevent and it is possible to prevent them through invasive treatment such as exercise or physical activity. This may all the more possible because physical exercise is positive relationship including cardiovascular risk factors and cerebrovascular disease.

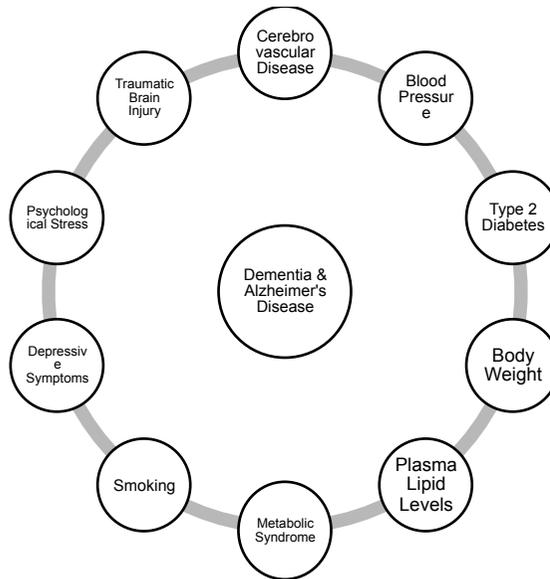
Protective factors of dementia and Alzheimer's Disease (AD) are diet, physical activity, and intellectual activity (Reitz et al., 2011). To be specific, the exercise in the protective factors suggested to reduce dementia risk factors by at least exercising swelling or breath hard over 2 times per week for 30 minutes (Ku et al., 2011). Also, the exercise program

Figure 2: Potential mechanisms linking vascular risk factors and cognitive impairment



(Reitz et al., 2011)

Figure 3: The vascular risk factor of Dementia and Alzheimer's Disease (AD)



(Reitz et al., 2011)

6) Treatment for Dementia and Alzheimer's Disease (AD)

From now on, many research institutes and related government in the world try to find a solution of Alzheimer's Disease (AD). There are many treatments for Dementia and Alzheimer's Disease (AD). And, the Korean medical society and government tried to discover an effective way of treatment to Dementia. Currently, the method of treatment for Dementia and Alzheimer's Disease (AD) only delayed or release their symptoms by severe invasive treatment including medication, cognitive rehabilitation, exercise therapy, psychological social therapy (박윤진, 조혜영, & 김명기, 2013). However, the medication treatment had limit effective way to treat for Dementia and Alzheimer's Disease (AD) (Corder et al., 1993; Jennifer L. Etner et al., 2007; a M. Saunders et al., 1993).

According to previous studies, the invasive treatment such as the cognitive rehabilitation, behavior therapy, I-ADL, exercise therapy improved Dementia and Alzheimer's Disease (AD)' cognitive function (Huang et al., 2012). For example, Dementia-mediated program in Korea

included a music therapy, laugh therapy, art therapy, and recall memorial therapy and their invasive treatments showed statistical significant results in MMSE-K ($t=-4.80$, $p<0.001$) and GDS-K ($t=2.33$, $p=0.022$) (Park & Jee, 2015). Also, I-ADL and NPI-K score were not significant results; but, I-ADL (pre: 56.67 (± 28.74) & post: 20.05 (± 28.80)) increased and NPI-K (pre: 20.55 (± 24.11) & Post: 16.82 (± 21.08)) decreased (Park & Jee, 2015).

7) Interaction between physical exercise and APOE e4 Allele

The exercise and physical activity interact with the APOE genotype to mediate the effects of the E4 allele on CAD (Raichlen & Alexander, 2014). According to previous studies within exercise and Alzheimer's Disease (AD), special in an aerobic exercise for Alzheimer's Disease (AD), it was a positive effect when comparing the cognitive function between Alzheimer's Disease (AD) and normal healthy-aged people (Shaji et al., 2009; Yeager et al., 2010).

In a cross-sectional study, E4 carriers showed a significant protective effect of high-intensity activity, with athletic E2, E3, and E4 carriers having similar blood lipid profiles and sedentary E4 carriers showing significantly high levels of lipid risk factors for CAD (Bernstein et al., 2002). Thus, physical activity seems to diminish CAD risks in APOE e4 allele carriers to E4 non-carriers levels, whereas sedentary lifestyle may exacerbate CAD risk factors among E4 carriers (Raichlen & Alexander, 2014).

Moreover, exercise appears to improve brain aging in individuals carrying the E4 allele (Raichlen & Alexander, 2014). Longitudinal studies suggest that physical inactivity leads to increased risk of developing dementia or AD in APOE E4 carriers (Kivipelto et al., 2008). Therefore, there is clear and growing support that engagement in physical exercise has a protective effect for APOE e4 carriers (Raichlen & Alexander, 2014).

As result of impact of physical exercise, there is growing evidence that physical activity, exercise, and aerobic fitness significantly reduce CAD risk and improve cognitive aging and biomarkers of Alzheimer's Disease (AD) pathology in APOE e4 carriers (Raichlen & Alexander, 2014).

It is clear that the physical exercise special in aerobic fitness will improve Alzheimer's Disease (AD) cognitive function and there will be possible to physiological mechanism change in Alzheimer's Disease (AD).

8) The effect of aerobic exercise and cognitive function according to APOE genotype

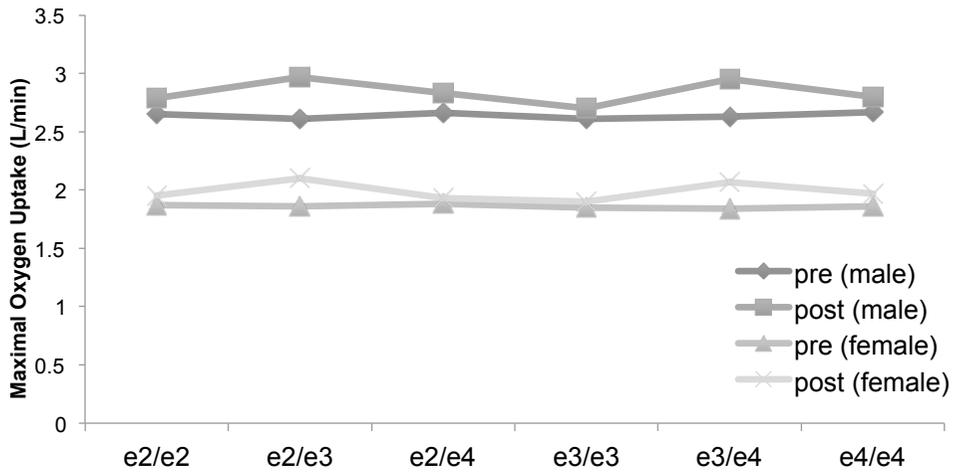
a. The impact of aerobic exercise in APOE e4 allele

A physical performance is a complex phenomena, it is affected both environment and genetic factor (Holdys, Gronek, Kryściak, & Stanisławski, 2013). Special in APOE e4 allele, it is highly risk factor for Alzheimer's Disease (AD) and people who did not have the allele reversed the cognitive dysfunction by ageing (Schiepers et al., 2012). According to Ageing, a homozygosity of APOE e4 allele had influences on increasing cognitive dysfunction; however, other factors affected individual cognitive susceptibility (Hyman et al., 1996). In results of previous study, the relationship between the other factors, included APOE e4 allele, aerobic fitness and cognitive function, explained that high level of aerobic fitness was more associated with high level of cognitive function than least level of aerobic fitness (J L Etnier et al., 1997). Moreover, the effect of aerobic fitness for people with APOE e4 allele had more greater positive in amyloid accumulation than people without APOE e4 allele (Brown et al., 2013; D Head et al., 2012; J. C. Smith, Nielson, Woodard, Seidenberg, & Rao, 2013; P. J. Smith, Potter, McLaren, & Blumenthal, 2013).

According to the APOE genotype, the e4 carriers had better impact of exercise than non-carriers significantly (P. J. Smith et al., 2013). This case is able to explain that an exercise engagement associates impact of APOE e4 allele on amyloid deposition by an attenuation of Pittsburgh compound B binding (Brown et al., 2012; Denise Head et al., 2012; J. C. Smith et al., 2013). In the fact of the exercise with neuroimaging markers, several studies appeared higher levels of aerobic fitness is associated with preserved brain health, as indicated by greater brain volume (Burns et al., 2008; P. J. Smith et al., 2013; Weinstein et al., 2012), lower white matter lesion volume (Burns et al., 2008), greater volume within the prefrontal cortex (Weinstein et al., 2012), caudate nucleus (Verstynen et al., 2012), and hippocampal formation (Brown et al., 2013; Kirk I. Erickson, Weinstein, & Lopez, 2012; Kirk I Erickson et al., 2011; Pereira et al., 2007), and greater blood flow velocity (Lucas et al., 2012; P. J. Smith et al., 2013).

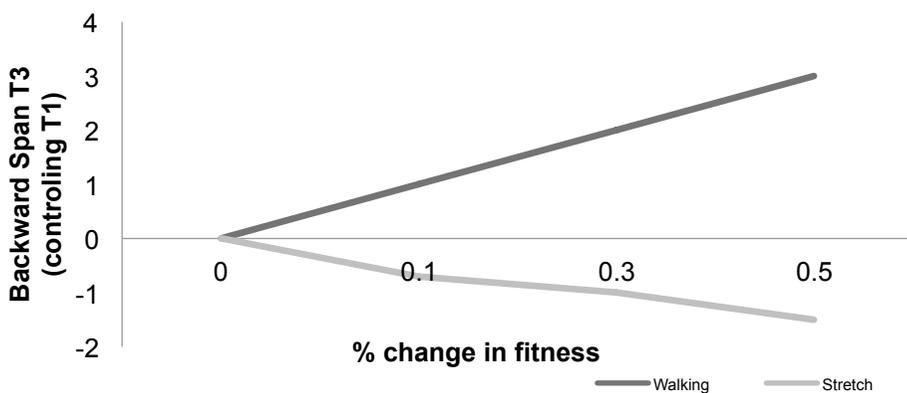
Genotype of APOE allele in young adult, total of 360 people young e2 adult (180 male and 180 female) were conducted VO₂ max measurement pre and post 6 months of supervised exercise training. In this case, VO₂ max after exercise training increased significantly higher in carriers of E2/E3 in male (OR=0.68, CI=0.04, 1.32; p=0.04) and female (OR=0.62, 95% CI=0.05, 1.18; p=0.03) and VO₂ max after exercise training significantly higher in carriers of E3/E4 in male (OR=0.60, 95% CI=0.09, 1.11; p=0.03) and female (OR=0.62, 95% CI=0.09, 1.15; p=0.02) (Yu et al., 2014). Moreover, no significant differences were found in carriers of E2/E2, E2/E4, E3/E3, E4/E4 in either male nor female (Yu et al., 2014). However, this study has limits to explain impact of aerobic exercise in APOE genotype because it only included to young adults' VO₂ max. Also, the influence of genotype had different activity in lifespan (Bagyinszky et al., 2014).

Figure 4: APOE genotype and Maximal Oxygen Uptake (L/min)



When compared aerobic exercise and other type of exercise, an increased aerobic fitness was associated with increased backward digit span in the walking group ($\text{pr}(31)=0.43$; $p=0.01$), but not in the stretching group ($\text{pr}(31)=-0.01$; $p=0.48$), independent of age, sex, and attendance (Voss et al., 2013).

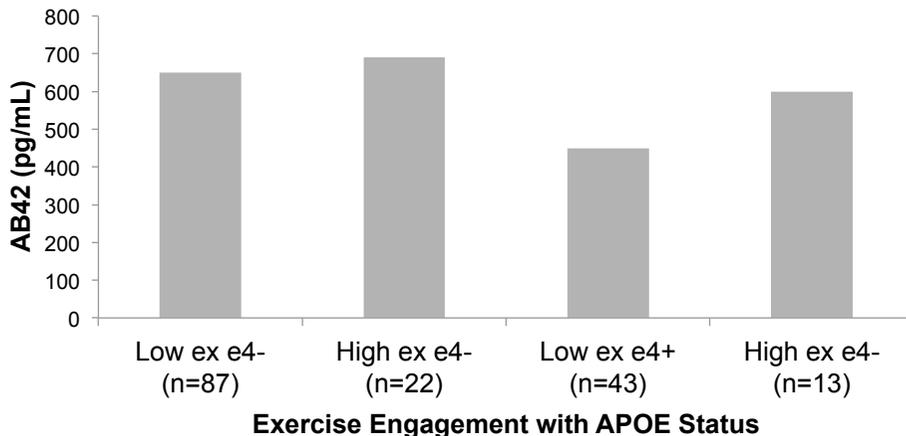
Figure 5: Correlated change in short-term memory and aerobic fitness



Moreover, the exercise engagement groups based on whether reported exercise levels were at or above 7.5 MET-hours/week (30 minutes of moderate exercise 5 days/week) recommended by the

American Heart Association (AHA) were particularly beneficial for cognitively normal e4+ individuals in reducing risk of brain amyloid deposition (Denise Head et al., 2012).

Figure 6: Association between APOE Status and Exercise Engagement for CSF AB42



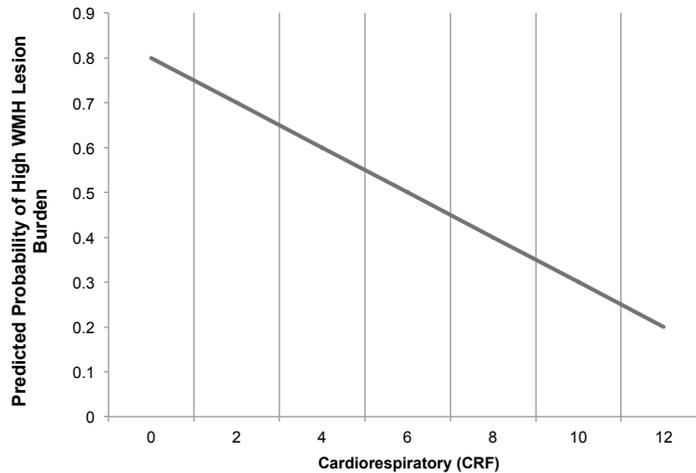
b. Level of Cardiorespiratory Fitness and Cognitive Function in APOE e4 allele

According to Etnier et al., an aerobic fitness is one variable that may influence the relationship between APOE e4 allele and cognition (2007). Associations between cardiorespiratory fitness and White Matter Hyperintensity (WMH) were an opposite relationship in people cognitive healthy middle-aged adults (M=58.58 years) (Boots et al., 2014). As you can see figure 7, when the CRF increased, the predicted probability of high WMH lesion burden were decreased (β (SE)=-0.33 (0.99), Wald $X^2=13.79$, OR=0.72, $p<0.001$) (Boots et al., 2014). This relationship explained the OR of 0.72 in CRF indicated to decrease 28% of white matter hyperintensity (WMH). In other words, higher cardiovascular levels are related to an attenuation of age-related losses in gray matter volume and a reduced risk for cognitive impairment (Weinstein et al., 2012).

The association between higher cardiorespiratory fitness and

cognitive function showed to improve psychological test performance. According to Weinstein et al., this study figured out the association between higher aerobic fitness levels and elevated executive function through 142 adults (M=66.6 years) (2012). The result indicated higher cardiorespiratory fitness values significantly predicted less Stroop percent interferences ($F(2, 139)=2.77$; $\beta=-0.202$; $p<0.05$) and better Spatial Working Memory (SPWM) 3-item accuracy ($F(2,136)=13.91$; $\beta=0.273$; $p<0.01$) when controlling age as a covariate factor (Weinstein et al., 2012).

Figure 7: Relationship between CRF and WMH Lesion Burden



Overall physical exercise was associated with reduced risk of dementia (Andel et al., 2008; P. J. Smith et al., 2013). Andel et al. study found that light exercise (low frequency) was associated with a 37% reduced risk of dementia, but more regular exercise reduced the risk of dementia by 60% (2008). Moreover, a cardiovascular fitness and cognitive function are highly correlated. For example, longitudinal study of the relationship between cardiovascular fitness and cognitive function showed that poor peak VO_2 has an association of more rapid cognitive decline after six years follow-up and the peak VO_2 demonstrated highly relation of global measures of cognitive function and attention/ executive function

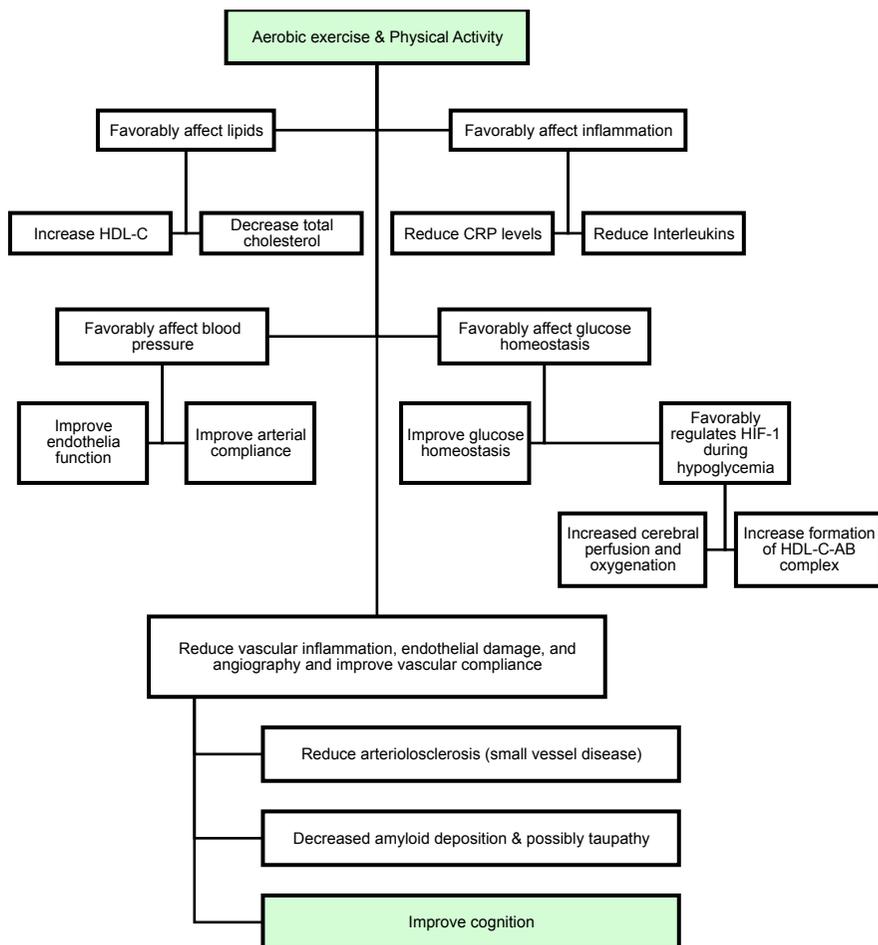
(Barnes, Yaffe, Satariano, & Tager, 2003).

There are several studies showed that a frequency and intensity of aerobic exercise for Alzheimer's Disease (AD). According to Fang Yu and et al., this review explained the older adults with Alzheimer's Disease (AD) had wide variations in the intensity, duration and frequency of aerobic exercise (2011). Although few evidences of the aerobic exercise was associated with improvements with their cognitive functions, it was not able to make a general exercise guideline for Alzheimer's Disease (AD) because of the wide variations about the exercise (Burns et al., 2008; Fang Yu, 2011).

9) The physiological mechanism between effect of aerobic exercise and cognitive function

In the previous studies, there were positive effects of aerobic training specially in Alzheimer's Disease (AD) with APOE e4 allele (Rovio et al., 2005; SCHUIT, M. FESKENS, LAUNER, & KROMHOUT, 2001; J. C. Smith et al., 2013). In general, the aerobic exercise-training and cognitive have clear views that aerobic exercise increases HDL-C and sub-fractions and decreases total cholesterol, C reactive protein, and interleukin-1, improve endothelial function and arterial compliance, and improve homeostasis and downregulates hypoxia (Obisesan et al., 2012).

Figure 8: physiological effect of aerobic exercise and cognitive function



(Obisesan et al., 2012)

III. Research Method

1) Participants

In this study, there will be included early stage of Alzheimer's Disease (AD) who were diagnosed from a special in dementia diagnosis of doctor and were followed over 6 months at S-hospital. In addition, the participants will be recruited people who will be able to do daily physical activity, normal Senior Fitness Test (SFT) score, and no depression. Following the below table 1, there is more specific inclusion criteria of the participants in this study.

Table 1: Inclusion Criteria of the Study

-
- Early Stage of Alzheimer's Disease (AD) who were diagnosed and followed up over 6 months from special diagnosis of dementia in a senior general hospital
 - Man and Female who are aged from 50 years old to 85 years old within over 6 years level of education
 - Who are in Amnesic type of clinical-based probable Alzheimer's Disease (AD) according to NIA-AA (National Institute on Aging-Alzheimer's Association workgroups, 2011) criteria
 - Rosen-Modified Hachinski Ischemia Score ≤ 3
 - Who are temporoparietal hypometabolism from FDG-PETT (grade >3 R/L Medial temporal atrophy less than 75 years old & grade > 5 R/L Medial Temporal atrophy over 75 years old in Comprehensive visual rating scale) from visual rating of temporal lobe atrophy in Brain MRI
 - Who are available for detecting APOE genotype from medical history chart
 - Who are available for doing daily physical activity and normal Senior Fitness Test (SFT) score
 - Who do not have symptoms of Cardiovascular Disease in 3 months
 - Who are uncontrolled Diabetes Mellitus, Hypertension, Hyperlipidemia
 - Who are available for understand or write an agreement of this study (or guardian)
-

2) Sample Size

In this study, the sample size will be based on the APOE allele genotype. Previous study showed that e3/e4 groups was significant different ($n = 29$, $p = 0.004$) in female and male (Yu et al., 2014). This study was used for statistical analysis for getting sample size through G-Power 3.10 version. More detailed, the sample size was calculated by ANOVA between factors and the effect size was 1.835 from the previous study. The groups was 4 including pre-exercise, post-exercise, pre-control, and post-control. The number of measurements were 4 such as senior fitness test (SFT), aerobic exercise capacity, tinetti POMA, and neuropsychological test. By using the G-Power program, it was measured F test using ANOVA between factors and the significant difference based on 0.05. As results, the critical F value was 4.06 and the total sample size 12 subjects needed. The actual power was 0.9997.

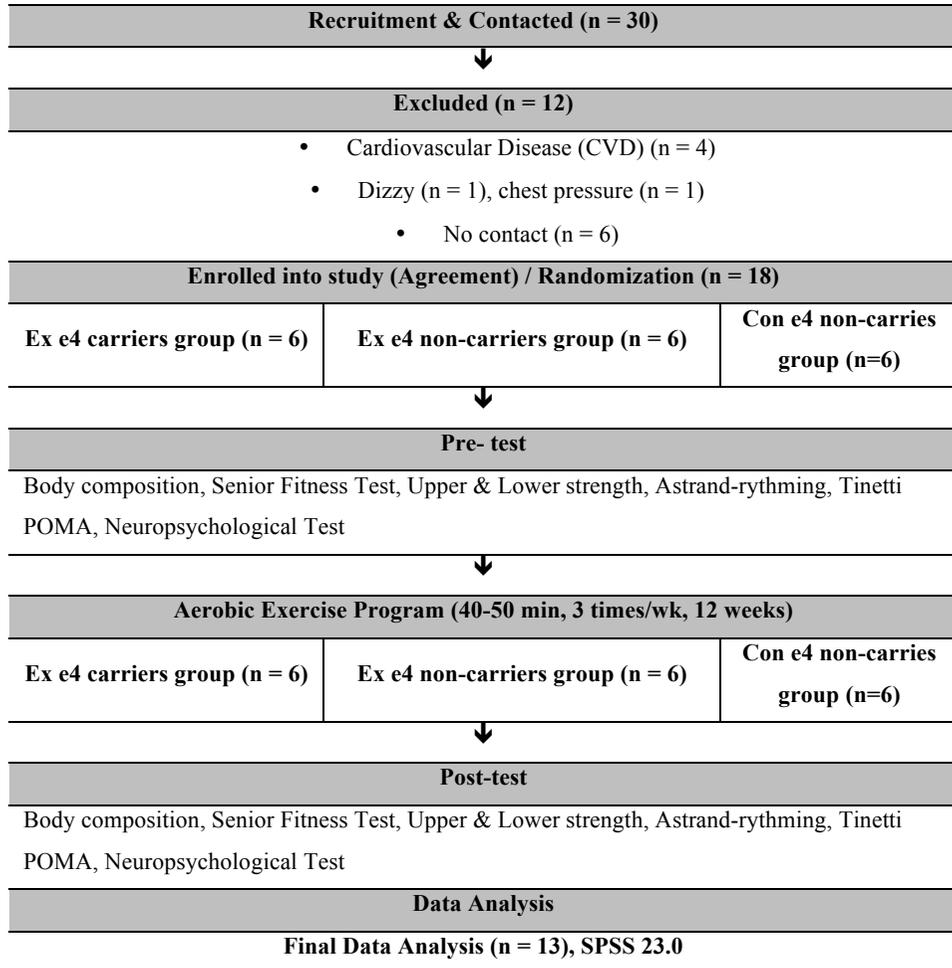
This study will recruit 12 subjects and it will be considered 30% drop rate. Therefore, the total sample size is 15 subjects.

3) Study Design

In this study, the subjects will be joined the 12 weeks of aerobic exercise program. Whole research procedure is below the line as showed table #. To be specific, the participants will be measured SFT, Tinetti POMA, VO2 max, neuropsychological test before starting the exercise program.

The randomized controlled study design will be performed for 12 weeks and detail procedures are shown in figure 8.

Figure 8: Study Design



4) Exercise Program

In recent, there are many previous studying showed positive relationship between aerobic and cognitive function. Also, an effect of resistance training or weight training is unclear as same as the aerobic training or exercise (Han, Han, Kim, Kim, & Im, 2012). The exercise program will be based on that the aerobic training has more positive improvement in cognitive function than resistance or complex exercise (Colcombe & Kramer, 2003; Han et al., 2012). According to the previous

results, it is following the below line shows the program included exercise intensity, time, and frequency, respectively. The exercise program will be followed by published “Exercise program for preventing dementia” from Seoul Dementia Center approved on 2009.

a. Exercise Intensity

As the previous study showed, the exercise intensity of purpose will be safe first and the second will be accuracy of measurement considering participants of age using Astrand-Rything test and Senior Fitness Test (SFT). These based on two tests of results will consider the aerobic program and intensity. Because muscular mass atrophy and reduction of absolute maximal oxygen consumption by ageing, the exercise intensity will be used Karvonen method. The safety of participant will be considered and the Karvonen method included a target heart rate (THR) calculation sets up based on participant’s exercise capacities. The THR is the below line after paragraphs.

$$\begin{aligned} & \textit{Target Heart Rate (THR)} \\ &= (\textit{Maximal Heart Rate} - \textit{Rest Heart Rate}) \\ & \times \textit{Target Intensity (\%)} + \textit{Rest Heart Rate} \end{aligned}$$

Previous research explained the aged people or old people should be considered their intensities by low intensity of 40-55% heart rate, moderate intensity of 55-70% heart rate, and high intensity of 70-85% heart rate and the exercise program will conduct progressive intensities considering their exercise capacities and heart rates (Han et al., 2012; C. Kim & Kim, 2009; C. Kim, 2011). One study showed there were no differences of cognitive decline rate between moderate intensity (35% reduction) and high intensity (38% reduction) and the effect of intensities were same both moderate and high intensities. According to the results, the intensity will be followed participants’ intensities.

b. Exercise Time & Frequency

The program will be continue over 20-30 minutes each sessions (Ahlskog, Geda, Graff-Radford, & Petersen, 2011). Also, the program will compose one by one personal customized exercise which are results from maximal oxygen uptake based on Astrand Rythming test. It will be safe and accuracy the test results.

c. Exercise Type

The aerobic exercise and cognitive function are positive relationship in previous studies (Brown et al., 2013; K I Erickson & Kramer, 2008; Denise Head et al., 2012), the Mild Cognitive Impairment (MCI) in dementia people showed better executive cognitive improvements on aerobic exercise group than resistance and stretching group (Scherder et al., 2005). Alzheimer's Disease (AD) people who joined walking, bike, aerobic ball training group improved overall cognitive function included focusing, memory, dialogue skills, executive function ability through 15 minutes to 60 minutes per day in 3 to 5 times per week during 12 weeks to 12 weeks (Diesfeldt & Diesfeldt-Groenendijk, 1977; Friedman & Tappen, 1991; Han et al., 2012; NT, KL, Flicker, & al, 2008; Palleschi et al., 1996). It is unclear of exercise in order to prevent cognitive decline or side effects, recently; however, many review articles recommended 1) exercise should do as soon as possible before occurring the dementia, 2) the aerobic exercise must be included for improving or preventing cognitive function, 3) overall exercises should be moderate intensity of HR 55-70%, 4) frequency of exercise is 20-30 minutes each sessions of 3 times per week, 5) exercise should be considered to prevent the falling with combined exercise included all of aerobic, resistance, and flexibility training (Han et al., 2012).

Therefore, this exercise program will be consisted of aerobic type of exercise including walking, running, rising steps, riding bicycle, arm cycling to use lower large muscle group.

Figure 9: Aerobic Program for Alzheimer’s Disease (AD)

Frequency	3 times per week
Intensity	Low intensity 40-55% of Heart Rate (HR) Moderate intensity 55-70% of Heart Rate (HR) High intensity 70-85% of Heart Rate (HR)
Type	Aerobic Type: Walking, Running, Rising Steps, Bike, Arm Cycling
Time	40-50 minutes each sessions

5) Measurements

a. Neuropsychological Test

There are 8 tests of neuropsychological measurements in this study. In many studies, the neuropsychological test offers the dementia rate and evaluates Alzheimer’s Disease (AD) essentially. This study follows a special neuropsychological agent and neurology of doctor’s suggestions to avoid error of special considerations. This study will be performed frontal and executive function test because previous study showed peak VO₂ demonstrated highly relation of global measures of cognitive function and attention & executive function (Barnes et al., 2003).

This test will follow (1) Digit Span Test (DST; Forward / Backward test) is measurements of attention and arousal levels and temporal focusing attention and attention ability as stimulating language tools. (2) Korean Version of Controlled Oral Word Association Test (K-COWAT) evaluates the frontal functional ability and fluent test of language. (3) Korean-Color Word Strop Test (K-CWST) is composed of “Word Reading” and “Color Reading”. This test must follow “Color Reading” after “Word Reading”. (4) Digit Symbol Coding (DSC) test connect the number from 1 to 9. (5) Korean-Trail Making Test-Elderly’s version (K-TMT-E) assesses information on executive functions, mental flexibility, speed of processing, visual search, and scanning. (6) Barthel-

Activities of Daily Living (B-IADL) evaluates daily physical function using 10 questions scores. (7) Short Version of the Geriatric Depression Scale (SGDS) test is short version of depression and evaluates personal depression. (8) Korean version of Mini-Mental State Examination (K-MMSE) is a neurocognitive test designed to screen cognitive impairment.

b. Submaximal Bike Ergometer Test with Maximal Oxygen Uptake (VO₂ max)

In this study, the maximal oxygen uptake will be measured by bike ergometer. The bike ergometer test is conducted the participants' safe and accuracy of measurements. It is a standard for evaluating for an aerobic capacity and appears for cardiovascular system function when subjects' abilities of physical activities. Maximal oxygen uptake is called physiological term for VO₂ max (ml/kg/min) and the VO₂ max is more often used to describe exercise capacity in apparently healthy individuals, in whom achievement of a maximal response is more likely (Balady et al., 2010). In the previous studies, the maximal oxygen uptake were different reactions depending on APOE genotype (Yu et al., 2014) and maximal oxygen uptake was related to APOE genotype so that this study will be figure out how to react maximal oxygen uptake reaction on APOE genotype.

The maximal and submaximal exercise testing are different concepts. The decision to use a maximal or submaximal exercise test depends largely on the reasons for the test, risk level of the client or patients, and availability of appropriate equipment and personnel (American College of Sports Medicine, 2014). In this study, submaximal exercise test will be conducted to determine the heart rate (HR) response to one or more submaximal work rates and use the results to predict VO₂ max (American College of Sports Medicine, 2014). This study will be designed as safety of subjects during exercise testing first because there will be many elderly people.

In addition, when considered the safety of subjects, mechanically cycle ergometers will be used in the exercise-testing mode. Advantages of this exercise mode include lower equipment expense, transportability, and greater ease in obtaining blood pressure (BP) and ECG (if appropriate) measurements (American College of Sports Medicine, 2014). Also, Cycle ergometers provide a non-weight-bearing test modality in which work rates are easily adjusted in small increments. In order to getting more accuracy of exercise test results, the cycle ergometer must be calibrated, and the subject must maintain the proper pedal rate because most tests require heart rate (HR) to be measured at specific work rates (Myers et al., 2009). Before exercise testing, this study will start cycle ergometer after subjects adapt to train before test. The procedures for submaximal testing of cardiorespiratory fitness will be followed by below the table.

The procedures for testing of this study

1. Obtain resting heart rate and blood pressure immediately prior to exercise in the exercise posture.
 2. The client should be familiarized with the cycle ergometer. If using a cycle ergometer, properly position the client on the ergometer (i.e., upright posture, ~ 25-degree bend in the knee at maximal leg extension, and hands in proper position on handlebars.
 3. The exercise test should begin with a 2-3 min warm-up to acquaint the client with the cycle ergometer and prepare him or her for the exercise intensity in the first stage of the test.
 4. A specific protocol should consist of 2-or 30min stages with appropriate increments in work rate.
 5. Heart rate should be monitored at least two times during each stage, near the end of the second and third minutes of each stage. If heart rate is > 110 bpm, steady state heart rate (i.e., two heart rate within 5 bpm) should be reached before the workload is increased.
 6. Blood pressure should be monitored in the last minute of each stage and repeated (verified) in the event of a hypotensive or hypertensive response.
 7. RPE (using Borg category) and additional rating scales should be monitored near the end of the last minutes of each stage.
 8. Client's appearance and symptoms should be monitored and recorded regularly.
 9. The submaximal test should be terminated when the subject reaches 70% heart rate reserve (85% of age-predicted HR max), fail to conform to the exercise test protocol, experiences adverse signs or symptoms, requests to stop, or experiences an emergency situation.
-

-
10. An appropriate cool-down and recovery period should be initiated.
 11. All physiologic observations (e.g., heart rate, blood pressure, signs and symptoms) should be continued for at least 5 min of recovery unless abnormal responses occur, which would warrant a longer posttest surveillance period. Continue low-level exercise until heart rate and blood pressure stabilize, but not necessarily until they reach pre-exercise levels.
-

(American College of Sports Medicine, 2014)

The exercise testing protocol of this study will be Astrand-rythming with cycle ergometer. The advantage of Astrand-rythming is to consider the subject's age and the correction factor for age. Older people do not reach maximal pulses as high as younger people, thus an age correction factor was considered. The age correction factors are too low causing underestimation when using the presented values. Also, the correction factor is applicable on both males and females. Therefore, the exercise protocol will be safe and it can be measured subjects' cardiovascular capacity with 6 minutes. The validity and reliability of Astrand-rythming test with using the correction age factors, the SEE of the predicted VO₂ max for the subjects was 0.42 L/min or 5.7 ml/kg/min ($r = .76$ and $.83$).

c. Senior Fitness Test (SFT)

Functional fitness performance is having the physiological capacity to perform normal everyday activities safely and independently without undue fatigue (Rikli & Jones, 2013). In addition, there are many possibilities of detecting senior fitness to improve their health-related factors using senior fitness test (SFT). By doing so, SFT measurements the underlying physical parameters associated with functional ability, and identifies whether an older adult may be at risk for loss of functional ability. The SFT meets scientific standards for validity and reliability (Rikli & Jones, 2013). Even though there are lack of studies a relationship between SFT and Alzheimer's Disease (AD), there is one possibility of using the SFT measurement with cognitive impairment. To be specific, the

SFT battery showed high to very high test-retest reliability and thus may be suitable for detecting changes in physical fitness and evaluating physical fitness in order people with cognitive impairment, both in research and for clinical purposes (Hesseberg, Bentzen, & Bergland, 2015).

In this study, subjects with Alzheimer's Disease (AD) will be measured by SFT in order to evaluating their physical fitness to identify relationship between cognitive function and aerobic capacity. Also, this study will be approached to see how much the exercise program will be affected in their physical functions on pre-/post time.

The SFT procedures will be followed and measured by 1) 30-second chair stand to assess lower body strength, needed for numerous tasks such as climbing stairs, walking and getting out of a chair, tub or car (reduces the chance of falling), 2) Arm-curl to assess upper body strength, needed for performing household and other activities involving lifting and carrying things, 3) 2-minute step test, alternative aerobic endurance test, for use when space limitations or weather prohibits taking the 6 minute walk test, 4) chair sit-and-reach to assess lower body flexibility, which is important for good posture, for normal gait patterns and for various mobility tasks, 5) Back Scratch to assess upper body (shoulder) flexibility, which is important in tasks such as combing one's hair, putting on overhead garments and reaching for seat belt, 6) 8-feet (244cm) up and go to assess agility or dynamic balance, which important in tasks that require quick maneuvering, such as getting off a bus in time or getting up to attend to something in the kitchen (Rikli, 2001).

d. Cardiac Output (CO) & Rate Pressure Product (RPP)

Cardiac output is an important hemodynamic index of blood flow from and to the heart (Hill, Sollers Iii, & Thayer, 2012). And compensatory changes in CO occurs in response to a change in tissue oxygen demand including the increase in CO typically seen during exercise (Hill et al., 2012).

In this study, CO will be measured by simple method because the method is simple way for measuring blood pressure of systolic and diastolic. When compared Modelfolw-derived CO and CO simple-method, one study showed the correlation between CO and CO simple-method was moderate ($r = 0.60$, $p < 0.001$). Also, this association was stronger in men ($r = 0.70$, $p < 0.001$) compared to women ($r = 0.54$, $p < 0.001$) (Hill et al., 2012).

The cardiac out (CO) will be measured with blood pressure and heart rate. And both blood pressure and heart rate will be obtained before exercise and 3 min after astrand-rythming test. The simple method of equation of cardiac out put is below the line.

$$\text{Cardiac Output}_{est} (L/min) = [2 \times \text{Pulse Pressure (SBP - DBP)}] \times \text{Heart Rate (beat/min)}$$

The rate-pressure product (RPP) or double product ($HR \times SBP/100$) has been used as an indirect measure of myocardial oxygen consumption (D. L. Smith & Fernhall, 2011) and the RPP has been shown to collate well with myocardial oxygen consumption under both static and dynamic exercise conditions (Nelson et al., 1974; D. L. Smith & Fernhall, 2011). As a result of the changes in systolic blood pressure (SBP) and heart rate (HR), the rate-pressure product (RPP) also increase with increasing workloads and reaches a plateau as maximal exercise is approached (D. L. Smith & Fernhall, 2011). In other words, RPP provides an index of cardiac work and myocardial oxygen consumption.

In this study, RPP will be measure from systolic pressure (SBP) and heart rate (HR), both systolic pressure (SBP) and heart rate (HR) will obtain before starting exercise and 3 min after astrand-rythming test. The RPP equation is the below the line.

$$\text{Rate-Pressure Product (RPP: torr/bpm)} = \text{Heart Rate (HR)} \times \text{Systolic Blood Pressure (SBP)}$$

e. Tinetti Performance Oriented Mobility Assessment (POMA) Test

The Tinetti Performance Oriented Mobility Assessment (POMA) is a physical task-oriented scale that measures the gait and balance activities of older persons and is widely available on the geriatrics assessments tools, or fall risk assessment (Lin et al., 2004; M E Tinetti, Williams, & Mayewski, 1986; Mary E Tinetti, 1986; Van Iersel, Benraad, & Olde Rikkert, 2007).

POMA is a quantitative tool and the validity of POMA is the concurrent validity 0.64-0.70 and predictive validity of sensitivity 61.5% and specificity 69.5%. In addition, the reliability of POMA is interrater reliability 0.75 to 0.90 reported; and, the test-retest reliability reported from 0.88 to 0.97 for different populations studied (Lin et al., 2004; M E Tinetti et al., 1986; Mary E Tinetti, 1986; Van Iersel et al., 2007).

The total time to administer of POMA is 15 to 20 minutes. The interpretation of POMA and scores are on a three point ordinal scale that ranges from 0 to 2. “2” indicates the highest level of independence, and “0” indicates the highest level of impairment. The two parts of scales include a total balance score of 16 and total gait score of 12, for a total possible score of 28. Scores of 25-28 indicate low fall risk, 19-24 medium fall risk, and less 19 is high fall risk (M E Tinetti et al., 1986; Mary E Tinetti, 1986).

6) Statistical Diagnosis

All data were presented as mean(M) \pm SD . Baseline characteristics between e4 carriers, e4 non-carriers and control group were compared by using one-way of ANOVA before starting program. The normality of the variables including neuropsychological test, aerobic exercise capacity, BMI, senior fitness test (SFT), upper strength, lower strength, and demographical variables (gender, age, level of education) was performed by Kolmogorov-Smirnov test.

The treatment effects within the neuropsychological test results

(K-MMSE, CWST, COWAT, DSC, TMT, DST, BADL, K-IADL) and aerobic exercise capacity (VO_2 max, Cardiac output, Rate-pressure product) were determined by non-parametric Friedman Test related to Two-way repeated ANOVA on the second factors. And then, if there is significant difference in time (12 weeks) between 3 groups, the independent sample s Kruskal-Wallis test (K-W test). An adjusted p value of less than 0.05 was taken to indicate a significant difference. All analyses procedures were performed in SPSS version 23.0 software (SPSS Inc.).

IV. Results

1) Baseline of Characteristics

Subjects in this study were 18 people with early stage of Alzheimer's Disease (AD). 6 subjects were exercise group with e4 carriers group, 6 subjects were exercise group with e4 non-carriers group, and the control group with e4 non-carriers group (n=6) were divided. As you can see Table 1, it describes overall subjects characteristics. Using ANOVA with compare mean between groups, there were no significant differences between 3 groups before starting program before starting exercise program.

Table 1: Baseline between 3 groups

	Ex e4 carrier group (n=6, M±SD)	Exercise e4 non-carrier group (n=6, M±SD)	Control e4 carriers group (n=6, M±SD)	<i>F</i>	<i>P</i>
Gender	1.33 ± 0.51	1.17 ± 0.41	2.0 ± 0	0.682	0.521
Age (years)	75.67 ± 7.21	71.67 ± 5.61	74.5 ± 5.08	0.697	0.513
BMI (kg/m²)	22.6 ± 1.59	22.95 ± 1.9	23.35 ± 1.36	0.336	0.720
Education Level	3.0 ± 1.09	3.0 ± 1.09	2.83 ± 0.98	0.050	0.952
VO₂max (ml/min)	1397±329	1264.8±205	1210±289	0.118	0.889
Lower Str (kg)	47 ± 1.41	46.05 ± 2.45	48.06 ± 2.12	1.463	0.263
Upper Str (kg)	25.68 ± 1.29	25.1 ± 1.32	25.7 ± 1.57	0.356	0.706
SFT (%)	48.48 ± 13.6	44.79 ± 4.63	52.04 ± 3.6	0.619	0.558
Tinetti	18.01 ± 2.12	20.25 ± 2.75	18.25 ± 1.71	0.629	0.547
SGDS	2.7 ± 1.9	3.5 ± 3.27	3.5 ± 2.16	0.221	0.804
K-MMSE	17.17 ± 1.17	17.83 ± 0.98	17.5 ± 0.84	0.659	0.532

ANOVA: group compare mean

*Level of Education: 1=elementary, 2=Middle, 3=High, 4=College/University

*Gender: 1=male, 2=female

Table 2: Normality of APOE e4 carriers and e4 non-carriers with exercise

	Group	Kolmogorov-Smirnov		
		Value	df	P
Gender	Ex e4 carriers group	0.407	6	0.002*
	Ex e4 non-carriers group	0.492	6	0.000*
	Con e4 non-carriers group	0.319	6	0.56
Age (year)	Ex e4 carriers group	0.260	6	0.200
	Ex e4 non-carriers group	0.835	6	0.200
	Con e4 non-carriers group	0.294	6	0.114
Level of Education	Ex e4 carriers group	0.333	6	0.036*
	Ex e4 non-carriers group	0.333	6	0.036*
	Con e4 non-carriers group	0.401	6	0.003
BMI (kg/m2)	Ex e4 carriers group	0.228	6	0.200
	Ex e4 non-carriers group	0.211	6	0.200
	Con e4 non-carriers group	0.232	6	0.200
Lower Strength	Ex e4 carriers group	0.167	6	0.200
	Ex e4 non-carriers group	0.168	6	0.200
	Con e4 non-carriers group	0.170	6	0.200
Upper Strength	Ex e4 carriers group	0.246	6	0.200
	Ex e4 non-carriers group	0.175	6	0.200
	Con e4 non-carriers group	0.192	6	0.200
SFT	Ex e4 carriers group	0.773	6	0.053
	Ex e4 non-carriers group	0.763	6	0.051
	Con e4 non-carriers group	0.804	6	0.109
VO2max (ml/kg/min)	Ex e4 carriers group	0.332	6	0.037*
	Ex e4 non-carriers group	0.330	6	0.040*
	Con e4 non-carriers group	0.265	6	0.200
SGDS	Ex e4 carriers group	0.262	6	0.200
	Ex e4 non-carriers group	0.227	6	0.200
	Con e4 non-carriers group	0.258	6	0.200
K-MMSE	Ex e4 carriers group	0.223	6	0.200
	Ex e4 non-carriers group	0.302	6	0.094
	Con e4 non-carriers group	0.398	6	0.004*

Kolmogorov-Smirnov Test (S-W test)

Level of Education: 1=elementary, 2=Middle, 3=High, 4=College/University

Gender: 1=male, 2=female

2) Differences Aerobic Exercise Capacity (VO₂ max, Cardiac Output, Rate Pressure Product) between 3 groups after 12 weeks

There are a significant change in VO₂ max $\chi^2(2) = 10.33$, $p = 0.006$ over times (12 weeks). To be specific, there is significant difference in midterm ($\chi^2 = 7.941$, $p = 0.019$) and post-term ($\chi^2=11.453$, $p = 0.003$). For midterm, there is only significant difference between ex e4 group and con e4 carriers group (K-W = 7.941, $z = 2.786$, $p = 0.016$, $r = 0.66$). For post-term, there are significant differences between ex e4 group and ex e4 non-carriers group (K-W = 8.583 $z = 2.786$, $p = 0.016$, $r = 0.66$) or control e4 carriers group (K-W = 9.417, $z = 3.057$, $p = 0.007$, $r = 0.72$).

There are no significant differences in cardiac output ($\chi^2(2) = 0.00$, $p = 1.00$) and rate pressure product ($\chi^2(2) = 0.607$, $p = 0.607$) over times (12 weeks).

Table 3: Aerobic exercise capacity differences between 3 groups after 12 weeks

Type	Ex e4 non-carriers (n=6)			Control e4 carriers group (n=6)			Ex e4 carriers group (n=6)			Friedman test	
	Pre (M±SD)	Mid (M±SD)	Post (M±SD)	Pre (M±SD)	Mid (M±SD)	Post (M±SD)	Pre (M±SD)	Mid (M±SD)	Post (M±SD)	χ^2	p
VO ₂ max	1264.	1317.4	1035.9	1210.2	1221.9	1026.3	1397	1638.3	1819.1	10.3	0.00
	8±205	±146	±22	±289	±133	±1.66	±329	±314^a	±218^{a,b}	3	6
CO	11679.	13519.7	15359.7	10775.9±	10667.	10558.	12878.	11494.4±	10110.2±	0.00	1.00
	7±230	±2209.8	±2317.3	1761.9	3±1427	8±1873	5±210	1068.4	333.8		
RPP	17402.	19385.5	19521.5	15496.2±	15593.	15744.	18201.	15399.8±	13300.8±	1.00	0.60
	3±255	±1233.3	±581.5	3036.7	3±4147	4±5255	2±288	2832.2	2801.8		

Friedman non-parametric test related to Two-way Repeated ANOVA on the second factors

Kruskal-Wallis Test in 3 groups * $p < 0.05$, ** $p < 0.001$

Significant diff K-W analysis = a: ex e4 carriers & cont e4 carriers, b: ex e4 carriers & ex e4 non-carriers, c: ex e4 non-carriers & cont e4 carriers

3) Differences Senior Fitness Test (SFT) between 3 groups after 12 weeks

There are no significant differences between Sit up ($\chi^2(2) = 0.623$, $p = 0.732$), Dumbbell ($\chi^2(2) = 1.057$, $p = 0.59$), Back hand ($\chi^2(2) = 0.04$, $p = 0.98$), 2 min walking ($\chi^2(2) = 0.79$, $p = 0.471$), Sit & reach ($\chi^2(2) = 0.353$, $p = 0.838$), 244 cm ($\chi^2(2) = 0.592$, $p = 0.744$) for 12 weeks in 3 groups. Also, the upper ($\chi^2(2) = 3.121$, $p = 0.21$) and lower strength ($\chi^2(2) = 3.633$, $p = 0.163$) are not significant different for 12 weeks in the 3 groups.

Table 4: Differences SFT scores in APOE e4 non-carriers and e4 carriers after 12 weeks

Type	Ex e4 non-carrier (n=6)			Con e4 carrier (n=6)			Ex e4 carrier (n=6)			Friedman Test	
	Pre (M±SD)	Mid (M±SD)	Post (M±SD)	Pre (M±SD)	Mid (M±SD)	Post (M±SD)	Pre (M±SD)	Mid (M±SD)	Post (M±SD)	χ^2	p
Sit up	16.8±2.0	17.2±1.5	17.0±2.0	14.7±1.4	13.8±1.8	13.0±2.9	15.8±2.6	16.2±1.3	19.0±2.0	0.62 3	0.73 2
Dumbbell	24.2±3.1	24.0±3.2	24.3±3.3	22.7±0.8	22.0±0.6	21.0±0.8	24.2±3.1	24.0±3.2	24.3±3.3	1.05 7	0.59 0
Back Hand	- 18.5±3.9	- 19.2±4.7	- 19.7±6.6	- 18.0±2.6	- 18.2±2.9	- 19.3±1.8	- 24.5±11.8	- 22.7±12.1	- 22.0±11.5	0.04 8	0.98 1
2 Min	89.2±3.5	92.2±4.2	89.8±9.6	97.0±7.8	93.7±4.2	90.5±3.5	91.7±4.6	97.5±7.4	109.8±1.9	0.79 0	0.47 1
Sit Reach	- 12.0±7.6	- 12.2±8.2	- 12.5±9.2	-4.8±8.1	-5.8±7.7	-6.0±7.6	- 12.0±8.8	- 10.3±8.2	-8.3±8.3	0.35 3	0.83 8
244 cm	5.4±0.44	5.6±0.94	5.6±0.71	5.8±1.2	6.0±1.2	6.3±1.3	5.6±0.94	5.4±0.9	5.1±1.04	0.59 2	0.74 4
Upper Strength	25.1±1.3	25.13±1.2	25.7±0.8	25.7±1.6	25.7±1.6	26.2±1.6	25.7±1.3	25.8±1.4	25.8±1.2	3.12 1	0.21 0
Lower Strength	46.1±2.5	48.6±1.0	48.7±1.0 2	48.1±2.1	47.2±1.6	46.2±1.8	47.0±1.4	46.0±2.9	48.6±0.5	3.63 3	0.16 3

Friedman non-parametric test related to Two-way Repeated ANOVA on the second factors

Kruskal-Wallis Test in 3 groups * $p < 0.05$, ** $p < 0.001$

Significant diff K-W analysis = a: ex e4 carriers & cont ex e4 carriers, b: ex e4 carriers & ex e4 non-carriers, c: ex e4 non-carriers & cont e4 carriers

4) Differences Tinetti POMA between 3 groups after 12 weeks

There are only significant changed tinetti balance ($\chi^2(2) = 8.14, p = 0.017$) for 12 weeks in 3 groups. But, within each groups, there are not significant differences in pre (K-W = 0.420, $p = 0.811$), mid (K-W = 0.905, $p = 0.636$) and post times (K-W = 5.884, $p = 0.053$).

Table 5: Differences tinetti POMA between 3 groups after 12 weeks

Type	Ex e4 non-carriers (n=6)			Control e4 carriers group (n=6)			Ex e4 carriers group (n=6)			Friedman test	
	Pre (M±SD)	Mid (M±SD)	Post (M±SD)	Pre (M±SD)	Mid (M±SD)	Post (M±SD)	Pre (M±SD)	Mid (M±SD)	Post (M±SD)	χ^2	p
Gait	11.0±1.8	10.3±2.6	10.8±2.9	10.2±2.0	9.3±0.5 2	9.8±2.8	10.0±1.4	10.0±0.9	11.2±1.3	4.69	0.09 6
Balance	8.0±1.8	7.8±0.93	8.7±0.82	8.2±0.76	8.2±0.7 6	8.0±0.6	7.5±1.6	8.2±1.3	9.5±1.2 ^{a,b}	8.14	0.017 *
Score	19.0±3.0	19.1±3.3	19.3±3.8	18.3±1.4	17.8±1.4	17.5±1.5	17.5±1.8	19.7±1.8	21.8±1.5	0.88 5	0.64 2

Friedman non-parametric test related to Two-way Repeated ANOVA on the second factors

Kruskal-Wallis Test in 3 groups * $p < 0.05$, ** $p < 0.001$

Significant diff K-W analysis = a: ex e4 carriers & cont ex e4 carriers, b: ex e4 carriers & ex e4 non-carriers, c: ex e4 non-carriers & cont e4 carriers

5) Differences CWST neuropsychological test between 3 groups after 12 weeks

There are significant differences in color reading reaction time ($\chi^2(2) = 14.96, p = 0.001$) and color reading time per item ($\chi^2(2) = 14.97, p = 0.001$) for 12 weeks. In color reading reaction time, it was significant changed between ex e4 carriers group and ex e4 non-carriers group for mid term (K-W = -6.083, $Z = -2.519, p = 0.035, r = 0.59$) and post term (K-W = -7.167, $Z = -2.565, p = 0.031, r = 0.60$).

In the color reading time per item, it was significant changed between ex e4 carriers group and ex e4 non-carriers group for mid term (K-W = -6.083, $Z = -2.519, p = 0.035, r = 0.594$) and post term (K-W = -7.167, $Z = -2.565, p = 0.031, r = 0.605$).

Table 6: Differences CWST between 3 groups after 12 weeks

Type	Ex e4 non-carrier (n=6)			Cont e4 carriers (n=6)			Ex e4 carriers (n=6)			Friedman Test	
	Pre (M±SD)	Mid (M±SD)	Post (M±SD)	Pre (M±SD)	Mid (M±SD)	Post (M±SD)	Pre (M±SD)	Mid (M±SD)	Post (M±SD)	χ^2	<i>p</i>
WR Correct Item	84.3±2.7	83.8±2.6	83.8±2.9	89.3±3.7	88.5±4.5	87.3±5.6	87.5±2.2	87.2±1.9	88.5±2.3	4.651	0.098
WR Wrong Item	27.7±2.7	27.8±2.9	28.2±2.9	22.7±3.8	23.7±4.7	24.7±5.6	24.5±2.3	23.8±2.3	23.5±2.3	0.974	0.61
WR Reaction Time	115.8±3.4	115.9±3.7	116.0±4.7	113.3±7.6	115.1±5.9	116.8±4.9	111.8±7.7	110.2±6.7	108.3±6.2	0.553	0.758
WR Correct Response Rate	0.75±0.02	0.75±0.02	0.74±0.03	0.79±0.03	0.78±0.04	0.78±0.05	0.78±0.02	0.78±0.01	0.79±0.02	0.182	0.913
WR Time per Item	1.03±0.03	1.04±0.03	1.04±0.04	1.01±0.07	1.03±0.05	1.03±0.04	0.99±0.06	0.98±0.06	0.96±0.05	0.667	0.717
CR Correct Item	33.2±13.7	32.3±13.4	32.7±13.9	52.±5.5	51±5.9	50.5±5.6	41.3±20.3	43.1±21	44.8±21.8	1.90	0.387
CR Wrong Item	78.8±13.7	78.7±14	79.3±13.9	60.0±5.5	60.5±5.7	61.5±5.6	70.7±20.3	69±20.9	67.2±21.8	1.41	0.494
CR Reaction Time	120.0±0	120.0±0	120.0±0	120.0±0	119.8±0.41	119.2±0.75	120±0	119.2±0.75 ^b	118.0±1.9 ^b	14.96	0.001*
CR Correct Response Rate	0.2961±0.122	0.294±0.123	0.291±0.124	0.46±0.05	0.45±0.05	0.45±0.05	0.37±0.18	0.38±0.19	0.4±0.19	1.059	0.589
CR Time per Item	1.07±0	1.07±0	1.07±0	1.07±0	1.069±0.004	1.064±0.01	1.07±0	1.06±0.006 ^b	1.05±0.02 ^b	14.97	0.001*

Friedman non-parametric test related to Two-way Repeated ANOVA on the second factors

Kruskal-Wallis Test in 3 groups * $p < 0.05, **p < 0.001$

Significant diff K-W analysis = a: ex e4 carriers & cont ex e4 carriers, b: ex e4 carriers & ex e4 non-carriers, c: ex e4 non-carriers & cont e4 carriers

6) Differences COWAT neuropsychological test between 3 groups after 12 weeks

There are significant differences between Semantic Wrong ($\chi^2(2) = 8.974, p = 0.011$) and Phonemic (\sqsubset) ($\chi^2(2) = 7.538, p = 0.023$) for 12 weeks in 3 groups. Within 3 groups, there is only significant difference in semantic wrong section between ex e4 carriers and ex e4 non-carriers group (K-W = 11.773, Z = 2.662, p = 0.036, r = 0.627).

Table 7: Differences COWAT between 3 groups after 12 weeks

Type	Ex e4 non-carrier group (n=6)			Cont e4 carriers group (n=6)			Ex e4 carriers group (n=6)			Friedman Test	
	Pre (M±SD)	Mid (M±SD)	Post (M±SD)	Pre (M±SD)	Mid (M±SD)	Post (M±SD)	Pre (M±SD)	Mid (M±SD)	Post (M±SD)	χ^2	p
Sematic Correct	22.0±5. 2	22.1±5. 1	22.1±5. 3	21.7±1. 6	21.1±1. 9	20.5±2. 3	19.7±6. 9	20.5±7. 1	21.3±7.5	3.846	0.146
Sematic Wrong	20.3±4. 6	19.8±4. 7	19.8±4. 7	19.0±1. 3	18.8±1. 7	18.8±2. 2	20.0±4. 1	19.5±3. 4	17.9±3.7^b 3	11.77	0.003
Phonemic \sqsupset	20.3±3. 9	19.8±3. 5	20.1±3. 3	15.0±7. 3	15.3±6. 9	15.7±6. 6	20.1±2. 2	20.3±2. 1	20.3±1.5	2.364	0.307
Phonemic \sqsubset	15.0±7. 3	15.3±6. 9	15.7±6. 6	18.1±1. 9	18.0±2. 3	18.0±2. 3	20.7±4. 9	21.5±3. 7	22.3±2.9	7.538	0.023
Phonemi c \wedge	20.2±2. 2	20.3±2. 1	20.3±1. 5	21.0±2. 3	20.7±1. 8	20.5±1. 5	19.7±1. 6	20.7±1. 2	22.0±1.3	1.44	0.486

Friedman non-parametric test related to Two-way Repeated ANOVA on the second factors

Kruskal-Wallis Test in 3 groups *p < 0.05, **p < 0.001

Significant diff K-W analysis = a: ex e4 carriers & cont e4 carriers, b: ex e4 carriers & ex e4 non-carriers, c: ex e4 non-carriers & cont e4 carriers

7) Differences DSC neuropsychological test between 3 groups after 12 weeks

There are no significant differences in correct response ($\chi^2(2) = 1.574, p = 0.455$).

Table 8: Differences DSC between 3 groups after 12 weeks

Type	Ex e4 non-carrier group (n=6)			Cont e4 carriers group (n=6)			Ex e4 carriers group (n=6)			Friedman Test	
	Pre (M±SD) ()	Mid (M±SD) ()	Post (M±SD) ()	Pre (M±SD) ()	Mid (M±SD) ()	Post (M±SD) ()	Pre (M±SD) ()	Mid (M±SD) ()	Post (M±SD) ()	χ^2	p
Correct Response	12.2±7.6	12.0±7.7	12.0±8.0	18.2±11.5	16.8±9.9	17.2±10.4	19.7±4.6	20.0±4.3	20.5±3.8	1.574	0.455

Friedman non-parametric test related to Two-way Repeated ANOVA on the second factors

Kruskal-Wallis Test in 3 groups *p < 0.05, **p < 0.001

Significant diff K-W analysis = a: ex e4 carriers & cont e4 carriers, b: ex e4 carriers & ex e4 non-carriers, c: ex e4 non-carriers & cont e4 carriers

8) Differences TMT neuropsychological test between 3 groups after 12 weeks

There are no significant differences in TMT-a ($\chi^2(2) = 0.257, p = 0.879$) and TMT-b ($\chi^2(2) = 0.400, p = 0.819$) section between 3 groups over 12 weeks.

Table 9: Differences TMT between 3 groups after 12 weeks

Type	Ex e4 non-carrier group (n=6)			Cont e4 carriers group (n=6)			Ex e4 carriers group (n=6)			Friedman Test	
	Pre (M±SD)	Mid (M±SD)	Post (M±SD)	Pre (M±SD)	Mid (M±SD)	Post (M±SD)	Pre (M±SD)	Mid (M±SD)	Post (M±SD)	χ^2	p
a	82.7±29.2	83.2±31.3	84.2±33.5	57.2±29.9	59.5±32.7	61.8±35.9	64.3±34.1	61.8±34.1	59.2±33.6	0.257	0.879
b	245.2±85.2	245.0±85.3	245.2±84.9	173.2±103.2	175.3±101.4	177.0±100.2	185.0±126.4	181.5±123.2	180.8±123.2	0.400	0.819

Friedman non-parametric test related to Two-way Repeated ANOVA on the second factors

Kruskal-Wallis Test in 3 groups *p < 0.05, **p < 0.001

Significant diff K-W analysis = a: ex e4 carriers & cont e4 carriers, b: ex e4 carriers & ex e4 non-carriers, c: ex e4 non-carriers & cont e4 carriers

9) Differences K-MMSE neuropsychological test between 3 groups after 12 weeks

There are no significant differences in K-MMSE ($\chi^2(2) = 3.511$, $p = 0.879$) section between 3 groups over 12 weeks.

Table 10: Differences K-MMSE between 3 groups after 12 weeks

Type	Ex e4 non-carrier group (n=6)			Cont e4 carriers group (n=6)			Ex e4 carriers group (n=6)			Friedman Test	
	Pre (M±SD)	Mid (M±SD)	Post (M±SD)	Pre (M±SD)	Mid (M±SD)	Post (M±SD)	Pre (M±SD)	Mid (M±SD)	Post (M±SD)	χ^2	p
MMS	17.8±0.9	18.2±0.7	18.5±0.8	17.5±0.8	17.0±0.8	16.7±0.8	17.2±1.2	17.8±0.7	19.2±0.7	3.51	0.17
E	9	5	4	4	9	2	2	5	5	1	3

Friedman non-parametric test related to Two-way Repeated ANOVA on the second factors

Kruskal-Wallis Test in 3 groups * $p < 0.05$, ** $p < 0.001$

Significant diff K-W analysis = a: ex e4 carriers & cont e4 carriers, b: ex e4 carriers & ex e4 non-carriers, c: ex e4 non-carriers & cont e4 carriers

10) Differences DST neuropsychological test between 3 groups after 12 weeks

There are significant differences in backward ($\chi^2(2) = 7.737$, $p = 0.021$) and no significant difference in forward ($\chi^2(2) = 0.235$, $p = 0.899$) between 3 groups over 12 weeks. Within the 3 groups, it is significant changed in ex e4 non-carriers and control group for midterm (K-W = 7.7, $Z = 2.805$, $p = 0.015$, $r = 0.661$). Also, it is significant changed between ex e4 carriers (K-W = 7.167, $Z = 2.487$, $p = 0.039$, $r = 0.586$) or ex e4 non-carriers (K-W = 8.33, $Z = 2.892$, $p = 0.011$, $r = 0.681$) and control group.

Table 11: Differences DST between 3 groups after 12 weeks

Type	Ex e4 non-carrier group (n=6)			Cont e4 carriers group (n=6)			Ex e4 carriers group (n=6)			Friedman Test	
	Pre (M±SD)	Mid (M±SD)	Post (M±SD)	Pre (M±SD)	Mid (M±SD)	Post (M±SD)	Pre (M±SD)	Mid (M±SD)	Post (M±SD)	χ^2	p
Backward	3.2±0.41	2.83±0.41	2.67±0.52	2.67±0.52	2.0±0.0	1.33±0.52	2.33±0.82	2.7±0.52 ^c	2.5±0.55 ^c	7.73	0.021
Forward	4.17±1.2	4.17±0.75	4.17±1.17	3.83±1.47	3.3±1.21	3.33±1.37	4.0±0.63	4.3±0.52	4.4±0.55	0.23	0.899

Friedman non-parametric test related to Two-way Repeated ANOVA on the second factors

Kruskal-Wallis Test in 3 groups * $p < 0.05$, ** $p < 0.001$

Significant diff K-W analysis = a: ex e4 carriers & cont e4 carriers, b: ex e4 carriers & ex e4 non-carriers, c: ex e4 non-carriers & cont e4 carriers

11) Differences BADL neuropsychological test between 3 groups after 12 weeks

There are no significant differences between 3 groups over 12 weeks ($\chi^2(2) = 0.194$, $p = 0.194$).

Table 12: Differences BDAL between 3 groups after 12 weeks

Type	Ex e4 non-carrier group (n=6)			Cont e4 carriers group (n=6)			Ex e4 carriers group (n=6)			Friedman Test	
	Pre (M±SD)	Mid (M±SD)	Post (M±SD)	Pre (M±SD)	Mid (M±SD)	Post (M±SD)	Pre (M±SD)	Mid (M±SD)	Post (M±SD)	χ^2	p
BDA	16.7±1.	16.7±1.	16.8±1.	17.0±3.	16.2±3.	15.5±3.	17.2±3.	17.7±3.	18.0±2.	0.19	0.90
L	5	5	5	3	4	1	8	4	4	4	8

Friedman non-parametric test related to Two-way Repeated ANOVA on the second factors
Kruskal-Wallis Test in 3 groups * $p < 0.05$, ** $p < 0.001$
Significant diff K-W analysis = a: ex e4 carriers & cont ex e4 carriers, b: ex e4 carriers & ex e4 non-carriers, c: ex e4 non-carriers & cont e4 carriers

12) Differences K-IADL neuropsychological test between 3 groups after 12 weeks

There are significant changed between 3 groups over 12 weeks ($\chi^2(2) = 7.366$, $p = 0.025$). Within 3 groups, it was significant changed KIADL between ex e4 non-carriers group and control (K-W = 6.667, $Z = 2.520$, $p = 0.035$, $r = 0.594$) after 12 weeks.

Table 13: Differences K-IADL between 3 groups after 12 weeks

Type	Ex e4 non-carrier group (n=6)			Cont e4 carriers group (n=6)			Ex e4 carriers group (n=6)			Friedman Test	
	Pre (M±SD)	Mid (M±SD)	Post (M±SD)	Pre (M±SD)	Mid (M±SD)	Post (M±SD)	Pre (M±SD)	Mid (M±SD)	Post (M±SD)	χ^2	p
KIAD	1.5±0.6	1.2±0.4	1.0±0.6	0.92±0.3	0.83±0.4	0.83±0.4	1.45±0.5	1.33±0.5	1.17±0.75	16.1	0.00*
L	4	1	3	8	1	0	2	2	c	8	*

Friedman non-parametric test related to Two-way Repeated ANOVA on the second factors
Kruskal-Wallis Test in 3 groups * $p < 0.05$, ** $p < 0.001$
Significant diff K-W analysis = a: ex e4 carriers & cont ex e4 carriers, b: ex e4 carriers & ex e4 non-carriers, c: ex e4 non-carriers & cont e4 carriers

V. Discussion

1) Aerobic Exercise Capacity & APOE e4 non-carriers and e4 carriers

The aerobic exercise capacity was significant difference both exercise e4 carriers and e4 non-carrier group compared into control group. This study showed exercise e4 carriers and exercise e4 non-carriers were improved ($p = 0.016$, $r = 0.66$) and between exercise e4 carriers and control groups were significant improved ($p = 0.007$, $r = 0.72$). It can support that previous study explained e4 carries group were more beneficial for aerobic exercise (P. J. Smith et al., 2013). Also, the aerobic exercise was effective special in APOE e4 carriers than APOE e4 non-carriers.

2) Neuropsychological test differences between APOE e4 non-carriers and e4 carriers after 12 weeks

Only between exercise e4 carriers group and exercise e4 non-carriers group, both color reading reaction ($p = 0.035$, $r = 0.59$) and color reading time per item ($p = 0.031$, $r = 0.605$) in CWST were decreased. The COWAT in sematic wrong section was significant improved to decrease between exercise e4 carriers and exercise e4 non-carriers group ($p = 0.036$, $r = 0.627$). The DST in backward part also was significant improved scores in exercise e4 carriers ($p = 0.039$, $r = 0.586$) and exercise e4 non-carriers ($p = 0.011$, $r = 0.681$) than control group. The K-IADL scores was decreased between exercise e4 non-carriers and control group ($p = 0.035$, $r = 0.594$) after 12 weeks. Therefore, there is clear and growing support that engagement in physical exercise has a protective effect of cognitive dysfunction special in COWAT sematic wrong section, CWST color reading reaction time and CWST color reading time per item for APOE e4 carriers (Raichlen & Alexander, 2014). Also, DST in backward score

with both exercise groups were improved than control and the exercise e4 non-carriers group ($r = 0.681$) was more effective than exercise e4 carriers group ($r = 0.586$). K-IADL was not supported the previous study, but exercise e4 non-carriers group was improved than control group. In other words, the exercise can be improved the K-IADL score than without exercise.

VI. Conclusion

There were improved between aerobic exercise and cognitive function in COWAT, CWST, DST, K-IADL after 12 weeks. The APOE e4 carriers also had more effective in COWAT and CWST of cognitive function than exercise e4 non-carriers after aerobic exercise. The DST was effective in the APOE e4 carriers than control. But, the APOE e4 non-carriers was only effective in K-IADL compared to control.

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국 문 초 록

알츠하이머병 환자의 APOE e4 유무에 따른 유산소 운동이 인지기능에 미치는 영향

본 연구의 목적은 치매 중 알츠하이머 병 환자들을 대상으로 유산소성 운동이 몸의 움직임과 관련 수행능력의 인지기능을 평가함으로써, 유산소성 운동이 알츠하이머 병 환자의 인지기능에 미치는 영향을 파악하는 것이다. 또한 알츠하이머 병에서 유전자적 위험 요인인 APOE e4 carrier 와 non-carrier로 구분하여 사전 연구에서 밝혀진 운동에 대한 효과가 e4 carrier를 가진 사람들에게 긍정적인 효과가 더 큰것으로 나타난것 처럼, 본 연구에서는 유전자적 위험요인을 구분하여 유산소 운동 능력의 효과를 통해 검증 하고자 한다. 그리고 실험적 연구 디자인으로 운동에 대한 효과를 알츠하이머병 환자들 대상으로 한 연구가 부족 하여 이에 대한 본 연구를 진행할 것이다.

본연구는 치매를 진단하는 전문 상급 병원에서 알츠하이머 병으로 진단 받은 30명의 피험자를 선별하여 무작위 배정을 하였고, 연구에 불참여 및 연락 두절 (12명)을 제외한 총 18명을 대상으로, 운동그룹 중 e4 보유인자(n = 6), 운동그룹 중 e4 미보유인자(n = 6), 대조군 중 e4 보유인자(n = 6)로 총 3 그룹으로 나뉘어 진행하였다. 본 운동 프로그램은 유산소성 운동 종류로 주 2회 이상 실시 및 강도는 심박수를 기초한 저강도 (40-55%), 중강도 (56%-70%), 고강도 (71%-85%)로 12 주간 진행 하였다.

12 주간의 유산소성 운동을 실시한 결과, 운동 그룹 중 e4 보유인자와 미보유 인자에서 COWAT 과 CWST 에서 유의한 차이를 보였으며, DST 검사는 e4 보유인자만이 운동에 대한 효과가 나타났다. 또한 K-IADL은 e4 미보유인자에서만 운동에 대한 교과가 나타났다. 따라서 본 연구는 12주간의 유산소성 운동이 알츠하이머 병 환자의 인지기능에 미치는 영향을 통해 유산소성 운동 중재의 효과를 확인 할 수 있었다. 더 나아가 본 연구의 결과를 기반으로 운동이 원인을 모른 치매 환자들에게 적용할 수 있는 운동 프로그램을 개발하여 건강을 증진하는데 긍정적인 영향을 미칠 것으로 기대한다.

주요어: 유산소성 운동, 인지능력, 알츠하이머 병, 신경심리 검사

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