Original Article

JER

https://doi.org/10.12965/jer.1836108.054

Journal of Exercise Rehabilitation 2018;14(2):267-274

Effects of exercise training on stroke risk factors, homocysteine concentration, and cognitive function according the *APOE* genotype in stroke patients

Jun-Hee Lee[1], Sang-Min Hong[2], Yun-A Shin[3,*]

[1]Department of Physical Education, Centre for Sport Medicine, Kyung Hee University, Seoul, Korea
[2]Department of Physical Education, College of Education, Dongguk University, Seoul, Korea
[3]Department of Prescription & Rehabilitation of Exercise, College of Physical Exercise, and Department of Kinesiologic Medical Science, Graduate School Dankook University, Cheonan, Korea

The apolipoprotein E (*APOE*) gene has been suggested to be associated with stroke and dementia. However, the effects of exercise training on dementia according to the *APOE* genotype are not consistent to those reported by previous studies. Therefore, we examined the effects of exercise training on stroke risk factors including blood pressure, lipid profiles, homocysteine (Hcy) concentrations, and cognitive function according to the *APOE* genotype in stroke patients. We examined the stroke risk factors, Hcy, and cognitive function in 28 ischemic stroke patients before and after 6 months of exercise training. After exercise training, body weight, body mass index (BMI), and percent body fat decreased significantly in both APOE groups. According to the *APOE* genotype, the changes in BMI in the APOE ε4 group higher than those in APOE ε3 group significantly. Total cholesterol (TC), low-density lipoprotein (LDL)-C, triglyceride (TG), and Hcy decreased and high-density lipoprotein (HDL)-C increased significantly in the both groups. According to the *APOE* genotype, systolic blood pressure in the APOE ε4 group decreased, but in the APOE ε3 group increased after exercise training. TC, LDL-C, and TG in the APOE ε4 group decreased more extensively than those in the APOE ε3 group after exercise training. VO_{2max} (maximal oxygen consumption) and cognition increased significantly in both groups. Folate acid intake also increased significantly in both groups. The *APOE* genotype affects variations in the risk factors of stroke after exercise training. However, the Hcy and cognitive function did not differ based on the *APOE* genotype.

Keywords: *APOE* genotype, Homocysteine, Cognitive function, Exercise training, Stroke patients

INTRODUCTION

Stroke is one of the major causes of dysfunction and death worldwide (Barker and Mullooly, 1997), due to acute cerebrovascular disease that causes paralysis on one side of the body, accompanied by a sudden onset of consciousness due to cerebrovascular bleeding and infarction (Sarti et al., 2000). Factors such as race, age, sex, hypertension, smoking, diabetes, hyperlipidemia, obesity, and physical inactivity have traditionally been reported as risk factors for stroke and recent studies have shown that elevated levels of homocysteine (Hcy) in the blood are associated with the incidence of stroke (Pettigrew et al., 2008).

It is also reported that cognitive impairment, which increases with age, is caused by stroke. Epidemiological studies have shown that patients with stroke have a higher risk of developing dementia than the normal population (Leys et al., 2005; Savva and Stephan, 2010). Within 3 months after stroke, the cognitive function reduces by 23% to 55%, and it reduces by 11% to 31% within 1 year (Tham et al., 2002). Moreover, stroke increases the prevalence of dementia by 4 to 12 times (Leys et al., 2005). The mechanism behind development of dementia after the onset of stroke has not been clarified yet, but it is suggested that the level of Hcy in

*Corresponding author: Yun-A Shin https://orcid.org/0000-0002-8480-3454
Department of Prescription & Rehabilitation of Exercise, College of Physical Exercise, and Department of Kinesiologic Medical Science, Graduate School Dankook University, 119 Dandae-ro, Dongnam-gu, Cheonan 31116, Korea
Tel: +82-41-550-3831, Fax: +82-41-550-3831, E-mail: shinagel@dankook.ac.kr
Received: February 27, 2018 / Accepted: March 28, 2018

pISSN 2288-176X
eISSN 2288-1778

blood is related to the risk of stroke (Hogervorst et al., 2002).

Elevated serum Hcy levels induce inflammatory responses, affect the inflammatory function of endothelial cells at the gene expression stage (Roth et al., 2001), and increase oxidative stress (Konukoğlu et al., 2003). The highly reactive thiol group of Hcy is readily oxidized to the active form (Loscalzo, 1996), resulting in auto-oxidation and oxidative damage of Hcy, which has been reported to cause cognitive impairment, neurotoxicity (Obeid and Herrmann, 2006), and brain damage (Schafer et al., 2005).

Physical inactivity and low cardiorespiratory fitness are major risk factors for cardiovascular disease and indicate the prevalence of and mortality from all diseases (LaMonte et al., 2005). Regular exercise increases cardiorespiratory fitness, and decreases cardiovascular disease and cognitive function in elderly individuals (Kemoun et al., 2010). It has been suggested that the risk of recurrent stroke and prevalence of dementia may be lowered by exercise (Kramer and Erickson, 2007).

However, exercise training was reported to decrease or maintain Hcy concentrations (Gaume et al., 2005; Randeva et al., 2002) or even increase them after endurance training (Herrmann et al., 2003). Therefore, the effect of physical activity on Hcy concentration is still unclear.

These results can be explained by the effect of genetic factors and dietary intake on Hcy levels. The lack of coenzyme required for the metabolism of Hcy affects its elevation in the blood. If nutrient intake required for the metabolism of remethylated methionine is insufficient, i.e., in the presence of reduced levels of vitamin B_6, vitamin B_9 (folic acid), and vitamin B_{12} or when there is a lack of enzymatic activity required for Hcy metabolism, conversion to cysteine is not achieved, which induces an elevation in the concentration of Hcy in the blood (Brosnan and Brosnan, 2006).

In addition, the apolipoprotein E (*APOE*) gene has also been suggested to associate with stroke and dementia. APOE plays an important role in metabolism and cholesterol transport (Kuusi et al., 1989). The APOE E4 allele binds to low-density lipoprotein (LDL) receptors but is related to elevations in cholesterol (Mahley and Huang, 1999), which increases the risk of cardiovascular disease, stroke, and dementia (Hamzi et al., 2011). However, the effects of exercise training on dementia according to the APOE genotype are not consistent as reported in the literature. Allard et al. (2017) reported that individuals who lack the APOE E4 allele showed a significant increase in the related brain factors after 6 months of exercise training while individuals with APOE E4 did not. Another study reported that the risk of developing dementia was not significantly different between nonexercisers and exercisers after a 5-year follow-up in individuals with the APOE E4 allele while, the risk was higher in nonexercisers than exercisers among individuals who lack the APOE E4 allele.

Therefore, this study aimed to investigate the effects of combined aerobic and resistance exercise on the risk for stroke, including blood pressure, lipid profiles, Hcy concentrations, and cognitive function, according to the *APOE* genotype along with dietary intervention.

METERIALS AND METHODS

Subjects

The study participants were 68 ischemic stroke patients. Informed consent was obtained from all subjects before their participation. A questionnaire assessed the medical history of study subjects. Subjects were excluded based on the following criteria: (1) intake of drugs (folate, vitamin B_6, and B_{12} antagonists, etc.) that change plasma Hcy concentration, (2) excess of coffee (>4 cups) and alcohol (>2 cups) consumption, (3) comorbid diseases like coronary artery disease, (4) cigarette smoking, and (5) female sex, because plasma Hcy concentrations are affected by gender.

After explaining the purpose and procedure of the study to the participants, we collected blood samples, which were subjected to APOE genotype analysis. Of the 68 subjects, we identified 0 (0%) stroke patients with the ε2 genotype, 31 (45.58%) with the ε3 genotype (ε2/ε3 and ε3/ε3), and 37 (54.42%) with the ε4 genotype (ε3/ε4 and ε4/ε4) in this study. Results of this screening were used to classify subjects into the ε3 (n=13) or ε4 (n=15) genotype groups (Table 1).

Anthropometry measurements

Before and after the exercise training, anthropometric measurements were obtained for all subjects. Height and body weight were also recorded (Tanita, Seoul, Korea) and body mass index (BMI) was calculated from the ratio of weight (kg)/height (m^2).

Cognition measurements

To examine the cognitive function in participants, the Mini-Mental State Examination (MMSE) developed by Folstein et al. (1975) was used. To examine the cognition function of Korean elderly people, we used the simplified Korean version of MMSE (MMSE-K). MMSE-K is the most commonly used test method for cognitive function. It has 5 points of commands and orientation, 3 points of recall, 5 points of attention and calculation, 3 points of memory, 7 points of language, and 2 points of judgment

https://doi.org/10.12965/jer.1836108.054

and understanding. A higher score implies a higher cognitive function. A score below 20 implies cognitive impairment, from 21 to 23 implies cognitive impairment, and 24 or more implies normal status.

Ascertainment of diet intake

Diet intake was ascertained by interviewer-mediated 24-hr recall. Three-day diets were completed during the exercise training period, including 2 days on weekdays and 1 day on weekends. Food composition values for folate, vitamin B_6 and other macro-nutrients were obtained using Can pro professional 3.0 (The Korean Nutrition Society, Seoul, Korea) based on the Korean nutrient data base. Unfortunately, we could not examine vitamin B12intake, owing to limited data in Can pro professional 3.0. During the exercise-training period, nutrition education was provided to the stroke patients. However, nutritional intervention was not provided in order to verify the effect of exercise training.

Blood collection and assessment of biomarkers

Serum aliquots were stored at -80℃ until assayed. Total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were measured using an enzymatic colorimetric method and analyzed by the COBAS integra 800 (Roche Korea, Seoul, Korea). Plasma glucose levels were measured using a commercially available kit. Hcy was determined by FPLC, using a radiometric tyrosine assay.

Genotyping

Total blood DNA was extracted and purified from 200 μL of whole blood in anticoagulant tubes with ethylenediaminetetraacetic acid, using the Axygen DNA Blood Mini Kit according to manufacturer's instructions (Axygen Biosciences, Seoul, Korea). Genotyping of the APOE status was performed using the method described by Hagberg et al. (1999). APOE polymorphism was tested using the polymerase chain reaction amplification and restriction digestion with HinfI to distinguish the mutant and wild-type alleles.

Preliminary testing

Before the trials, each subject's maximal oxygen consumption (VO_{2max}) was measured to establish the exercise intensity. Subjects were familiarized with cycling and were informed of what was required of them with regard to the experiment. Next, they completed a cycling exercise test to determine each of their VO_{2max} adhering to the Ramp Protocol. Moreover, one repetition maximum (RM) for each subject according to the American College of Sports Medicine guidelines was measured for resistance training (Berger, 1965).

Exercise training

Exercise training was supervised by four experienced physical education instructors and was performed 5 days a week for six months. Each session consisted of 10 min of warming up, aerobic exercise by 45 min of cycling at 60% VO_2R for 3 days a week, resistance training at 60%–75% intensity of individual RM in the form of 3 sets with 12–15 repetitions (the chest, back, shoulder, triceps, biceps, abdomen, and lower-extremity muscle group) each for 2 days a week, and 5 min of cooling down.

Statistical analysis

All data are presented as means±standard deviation. Changes in risk factors before and after exercise training according to the genotype were analyzed using two-way analysis of variance with repeated measures, and within-group comparisons using a paired *t*-test for *post hoc* analysis. All statistical analyses were performed using IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA), and *P*-values of <0.05 were considered statistically significant.

RESULTS

The changes in body composition after exercise training according to *APOE* genotype

There were no significant differences in baseline values between the genotypes. After exercise training, body weight ($P<0.001$), BMI ($P<0.001$), percent body fat ($P<0.05$) decreased in the both APOE groups. According to the *APOE* genotype, changes in BMI showed a difference in the interaction between time and group ($P<0.05$). The change in BMI in the APOE ε4 group was significantly higher than that in the APO ε3 group ($P<0.01$) (Table 2).

Table 1. Characteristics of participants

Variable	Genotype		*t*	Sig.
	APOE ε3 (n=13)	*APOE* ε4 (n=15)		
Age (yr)	56.80±10.65	56.67±9.19	0.037	0.971
Region of attack, right:left	4:9	4:11	-0.728	0.473
Period of stroke (yr)	2.27±1.79	2.07±1.39	0.342	0.735

Values are presented as mean±standard deviation.

Table 2. Changes in body composition after exercise training according to the *APOE* genotype

Variable		Genotype		*F*		Sig.
		APOE ε3	*APOE* ε4			
Body weight (kg)	Pre	64.79±7.15	63.66±10.52	Time	56.134	0.000***
				Group	0.228	0.637
	Post	63.20±7.37	61.17±10.66	T×G	2.723	0.110
BMI (kg/m^2)	Pre	24.57±2.71	24.42±3.52	Time	16.535	0.000***
				Group	0.585	0.451
	Post	24.11±2.88	22.63±2.89	T×G	5.848	0.022*
Muscle mass (kg)	Pre	42.04±7.28	44.37±9.158	Time	0.866	0.360
				Group	0.425	0.520
	Post	41.98±8.28	43.54±8.30	T×G	0.627	0.435
Percent body fat (%)	Pre	29.18±7.416	24.44±6.45	Time	7.330	0.011*
				Group	3.680	0.065
	Post	28.00±9.49	22.46±6.22	T×G	0.474	0.497

Values are presented as mean±standard deviation.
BMI, body mass index.
*P<0.05. ***P<0.001.

Table 3. Changes in stroke risk factors after exercise training according to the *APOE* genotype

Variable		Genotype		*F*		Sig.
		APOE ε3	*APOE* ε4			
SBP (mmHg)	Pre	124.20±7.58	118.46±11.35	Time	0.344	0.562
				Group	0.223	0.641
	Post	119.13±9.87	121.33±15.55	T×G	4.473	0.043*
DBP (mmHg)	Pre	82.400±8.42	79.60±12.47	Time	0.056	0.814
				Group	0.001	0.972
	Post	80.13±8.11	82.73±7.44	T×G	2.185	0.151
Fasting glucose (mg/L)	Pre	112.13±30.11	110.00±23.81	Time	2.295	0.141
				Group	0.003	0.959
	Post	105.20±21.53	108.26±26.20	T×G	0.826	0.371
TC (mg/dL)	Pre	199.06±40.69	192.93±34.91	Time	8.434	0.007**
				Group	0.155	0.697
	Post	174.20±32.08	189.73±32.85	T×G	5.026	0.033*
LDL-C (mg/L)	Pre	325.86±40.31	302.20±54.47	Time	9.471	0.005**
				Group	0.447	0.509
	Post	294.26±36.36	297.20±48.53	T×G	5.003	0.033*
HDL-C (mg/L)	Pre	53.40±14.64	55.86±9.76	Time	5.552	0.026*
				Group	0.123	0.728
	Post	57.06±15.52	57.80±10.68	T×G	0.532	0.472
Triglycerides (mg/L)	Pre	146.60±72.45	139.73±94.12	Time	6.683	0.015*
				Group	0.176	0.678
	Post	109.86±59.10	139.93±82.34	T×G	6.831	0.014*
Homocysteine levels (μmol/L)	Pre	17.01±6.91	13.49±4.41	Time	5.936	0.021*
				Group	3.203	0.084
	Post	15.93±5.55	12.52±4.46	T×G	0.016	0.899

Values are presented as mean±standard deviation.
SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.
*P<0.05. **P<0.01.

Table 4. Changes in physical fitness and cognition after exercise training according to the *APOE* genotype

Variable		Genotype		*F*		Sig.
		APOE ε3	*APOE* ε4			
VO_{2max} (mL/kg/min)	Pre	22.59±11.61	29.73±10.17	Time	37.852	0.000***
				Group	1.664	0.208
	Post	32.50±11.88	35.47±11.37	T×G	2.682	0.113
Cognition (score)	Pre	25.13±2.92	25.00±4.45	Time	22.609	0.000***
				Group	0.003	0.955
	Post	27.33±2.71	27.60±3.52	T×G	0.157	0.695

Values are presented as mean±standard deviation.
***P<0.001.

Table 5. Changes in body composition after exercise training according to the *APOE* genotype

Variable		Genotype		*F*		Sig.
		APOE ε3	*APOE* ε4			
Vitamin $_6$ (mg)	Pre	1.90±0.55	1.60±0.43	Time	0.686	0.418
				Group	0.393	0.538
	Post	1.86±0.64	1.93±0.66	T×G	1.082	0.311
Vitamin $_{12}$ (mg)	Pre	188.42±55.53	215.86±62.82	Time	6.600	0.019
				Group	0.000	0.984
	Post	275.79±113.77	249.49±84.14	T×G	1.302	0.268

Values are presented as mean±standard deviation.

The changes in stroke risk factors after exercise training according to the *APOE* genotype

There were no significant differences in baseline values between the two genotypes. After exercise training, TC (P<0.01), LDL-C (P<0.01), TG (P<0.05), and plasma Hcy concentrations (P<0.05) decreased and HDL-C increased (P<0.05) in both groups significantly. According to the *APOE* genotype, systolic blood pressure (SBP), TC, LDL-C, and TG showed a difference in the interaction between time and group (P<0.05). SBP in the APOE ε4 group decreased, but in the APOE ε3 group increased after exercise training. TC, LDL-C, and TG in the APOE ε4 group decreased more extensively than those in the APOE ε3 group after exercise training (Table 3).

The changes in cardiorespiratory fitness and cognition after exercise training according to the *APOE* genotype

There were no significant differences in baseline values between the two genotypes. After exercise training, the VO_{2max} and cognition increased in both groups (P<0.001). However, there was no difference in these changes according to the *APOE* genotype (Table 4).

https://doi.org/10.12965/jer.1836108.054

The changes in vitamin 6 and folate acid intake during exercise training according to the *APOE* genotype

There were no significant differences in baseline values between the two genotypes. After exercise training, the folate acid intake increased significantly in both groups ($P < 0.05$) (Table 5). However, there was no difference in these changes according to the *APOE* genotype.

DISCUSSION

This study showed that lipid levels including TC, LDL-C, and TG decreased and HDL-C increased in both APOE groups after 6 months of exercise training. These results may be explained by the effects of exercise training including, induction favorable changes in blood lipid levels by up-regulation of lipoprotein lipase activity (Thompson et al., 1997), which regulates the release and transportation of free fatty acids from cyhlomicrons and very low-density lipoproteins to peripheral tissues and liver, consequently leading to a reduction in triglyceride levels (Wannamethee et al., 2000).

However, we found different changes in the lipid profiles of two groups including TC, LDL-C, and TG after exercise training. TC, LDL-C, and TG in the APOE ε4 group showed a higher reduction than those in the APOE ε3 group after exercise training.

APOE is a protein that regulates cholesterol, lipid metabolism, and cellular reparative processes in the circulating plasma and central nervous system (Mahley and Huang, 2012). The *APOE* gene has three isoforms, which account for the different affinities of APOE protein for lipoprotein particles and binding to LDL receptors (Fullerton et al., 2000). The APOE ε4 allele has been established to have an association with higher circulating cholesterol levels and the buildup of atherosclerotic plaque in peripheral arteries, which leads to an increased risk of cardiovascular disease up to 40% (Eichner et al., 2002). Individuals with the APOE ε4 allele have higher TC and LDL-C levels but lower HDL-C levels compared to those with the APOE ε3 allele (Hallman et al., 1991).

However, the effects of exercise training according to the *APOE* genotype are different. Bernstein et al. (2002) suggested that high-intensity physical activity with a high amount of energy expenditure may counteract the atherogenic effects of the APOE ε4 allele on lipid profiles. Individuals with the APOE ε4 allele who performed high-intensity physical activity with a lot of energy expenditure showed higher HDL-C and lower TG levels compared to individuals with the APOE ε3allele (Hagberg et al., 1999). Our results showing that long-term exercise training may induce favorable changes in stroke risk factors including lipid profiles by compensating for the APOE ε4 allele in stroke patients are similar to those published in a previous study.

Hyperhomocysteine also has been reported an independent risk factor for ischemic stroke in Asians, including young individuals (Tan et al., 2002). Also, mild elevations in Hcy concentrations occurred in 42% of patients with cerebrovascular disease, and Lehmann et al. (1999) reported that Hcy is an independent predictor of MMES and a risk factor for the development of dementia (Seshadri et al., 2002).

Despite the results of previous studies on the effects of exercise training on Hcy levels being inconsistent, we found that Hcy concentrations decreased with increasing cardiorespiratory fitness and intake of folate acid in both APOE groups after exercise training.

These results are consistent with those of previous studies, which suggested that Hcy concentrations show a negative correlation with cardiorespiratory fitness in men (Kurl et al., 2003; Mennen et al., 2002). However, the effects of increased intake of folate acid on the reduction of Hcy are not clear. Several previous studies have suggested that folate, vitamin B_6, and B_{12} are important enzymes for Hcy metabolism, and a negative correlation exists between folate intake and Hcy concentration. Despite a lot of studies showing these results, meta-analysis of the correlation between folate intake and Hcy levels showed that the evidence was not sufficient to establish the effects of folic acid supplementation on decreasing the Hcy concentration (Lee et al., 2010). The possible favorable effect of folic acid supplementation on Hcy levels is only applicable in early stages of vascular disease, but it is less effective in advanced disease. Our study participants included a chronic stroke patient. Therefore, our results suggest that the lower Hcy concentration after exercise training may be an effect of increase in cardiorespiratory fitness by long-term exercise training.

Prevention and treatment of poststroke dementia involves reducing the risk factors of stroke, and exercise trainings have been conducted for effectively slowing the cognitive decline and improving the risk factors of stroke (Kemoun et al., 2010). However, evidence showing that physical activity or exercise training can prevent or delay cognitive decline remains controversial. Moderate or vigorous physical activity decreases the incidence of cognitive impairment (Etgen et al., 2010) and exercise training even enhances cognitive function in older individuals (Luck et al., 2007). On the other hand, Slooter et al. (1997) could not demonstrate that exercise training prevented or delayed cognitive impairment.

This study showed that cognition increased after 6 months of exercise training but there was no difference between the different *APOE* genotypes. Individuals with the APOE ε4 allele have a higher risk of developing dementia and increased cognitive decline (Mortensen and Hogh, 2001; Smith, 2002), as the APOE ε4 allele is associated with multiple pathological impacts, including amyloid deposition and synaptogenesis, the increased accumulation and reduced clearance of amyloid β-peptide, which is a marker for extracellular neuritic plaques in the brain (Cedazo-Mínguez, 2007). However, exercise training could improve brain function in individuals with the APOE ε4 allele (Kivipelto et al., 2008); particularly, those who participated in higher energy expenditure exercise showed greater protection against dementia about 20 years later compared with individuals without the APOE ε4 allele. Another study even suggested that the effect of exercise training on reducing risk of cognitive decline was only observed in individuals with the APOE ε4 allele (Woodard et al., 2012).

However, in our study, there was no difference between the two *APOE* genotypes, despite the reduced risk of stroke, including lipid profiles and Hcy concentrations, and the increase in cardiorespiratory fitness. These inconsistencies in the effects of exercise training on cognition according to the *APOE* genotype may be because the neuropathology of vascular cognitive impairment is controversial, and also because cerebrovascular lesions are different in size (from small to large cortical infarcts), nature (vessel wall alteration, infarcts, or hemorrhages, etc.), and location (cortex, white matter, basal ganglia, and hippocampus). Various mechanisms that alter the blood flow and oxygen supply, cortical connectivity, or chronic inflammation in cerebrovascular lesions may have an impact on cognition impairment (Iadecola, 2013). Foster et al. (2014) suggested that poststroke dementia, subcortical ischemic dementia combined with Alzheimer disease and vascular dementia are related to cognitive dysfunction, which extends the pathological changes in cerebrovascular lesions and neuronal atrophy.

This study showed that 6 months of exercise training can result in positive changes in body composition, stroke risk factors including Hcy concentrations, and cognition in stroke patients. The changes in lipid levels showed a difference based on the *APOE* genotype. Lipid levels in the APOE ε4 group showed more favorable changes compared to the APOE ε3 group after exercise training. However, the changes in Hcy levels and cognition showed no difference according to the *APOE* genotype. Therefore, future studies should more carefully address the precise clinical phenotypes such as size, nature, and location of cerebrovascular lesions in the study participants and enroll a larger population for the analysis of *APOE* genotype.

CONFLICT OF INTEREST

No potenital conflict of interest relevant to this article was reported.

REFERENCES

Allard JS, Ntekim O, Johnson SP, Ngwa JS, Bond V, Pinder D, Gillum RF, Fungwe TV, Kwagyan J, Obisesan TO. APOEε4 impacts up-regulation of brain-derived neurotrophic factor after a six-month stretch and aerobic exercise intervention in mild cognitively impaired elderly African Americans: A pilot study. Exp Gerontol 2017;87(Pt A):129-136.

Barker WH, Mullooly JP. Stroke in a defined elderly population, 1967-1985. A less lethal and disabling but no less common disease. Stroke 1997; 28:284-290.

Berger RA. Application of research findings in progressive resistance exercise to physical therapy. J Assoc Phys Ment Rehabil 1965;19:200-203.

Bernstein MS, Costanza MC, James RW, Morris MA, Cambien F, Raoux S, Morabia A. Physical activity may modulate effects of ApoE genotype on lipid profile. Arterioscler Thromb Vasc Biol 2002;22:133-140.

Brosnan JT, Brosnan ME. The sulfur-containing amino acids: an overview. J Nutr 2006;136(6 Suppl):1636S-1640S.

Cedazo-Mínguez A. Apolipoprotein E and Alzheimer's disease: molecular mechanisms and therapeutic opportunities. J Cell Mol Med 2007; 11:1227-1238.

Eichner JE, Dunn ST, Perveen G, Thompson DM, Stewart KE, Stroehla BC. Apolipoprotein E polymorphism and cardiovascular disease: a HuGE review. Am J Epidemiol 2002;155:487-495.

Etgen T, Sander D, Huntgeburth U, Poppert H, Förstl H, Bickel H. Physical activity and incident cognitive impairment in elderly persons: the INVADE study. Arch Intern Med 2010;170:186-193.

Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-198.

Foster V, Oakley AE, Slade JY, Hall R, Polvikoski TM, Burke M, Thomas AJ, Khundakar A, Allan LM, Kalaria RN. Pyramidal neurons of the prefrontal cortex in post-stroke, vascular and other ageing-related dementias. Brain 2014;137(Pt 9):2509-2521.

Fullerton SM, Clark AG, Weiss KM, Nickerson DA, Taylor SL, Stengård JH, Salomaa V, Vartiainen E, Perola M, Boerwinkle E, Sing CF. Apolipoprotein E variation at the sequence haplotype level: implications for the origin and maintenance of a major human polymorphism. Am J

https://doi.org/10.12965/jer.1836108.054

Hum Genet 2000;67:881-900.

Gaume V, Mougin F, Figard H, Simon-Rigaud ML, N'Guyen UN, Callier J, Kantelip JP, Berthelot A. Physical training decreases total plasma homocysteine and cysteine in middle-aged subjects. Ann Nutr Metab 2005;49:125-131.

Hagberg JM, Ferrell RE, Katzel LI, Dengel DR, Sorkin JD, Goldberg AP. Apolipoprotein E genotype and exercise training-induced increases in plasma high-density lipoprotein (HDL)- and HDL2-cholesterol levels in overweight men. Metabolism 1999;48:943-945.

Hallman DM, Boerwinkle E, Saha N, Sandholzer C, Menzel HJ, Császár A, Utermann G. The apolipoprotein E polymorphism: a comparison of allele frequencies and effects in nine populations. Am J Hum Genet 1991;49:338-349.

Hamzi K, Tazzite A, Nadifi S. Large-scale meta-analysis of genetic studies in ischemic stroke: Five genes involving 152,797 individuals. Indian J Hum Genet 2011;17:212-217.

Herrmann M, Schorr H, Obeid R, Scharhag J, Urhausen A, Kindermann W, Herrmann W. Homocysteine increases during endurance exercise. Clin Chem Lab Med 2003;41:1518-1524.

Hogervorst E, Ribeiro HM, Molyneux A, Budge M, Smith AD. Plasma homocysteine levels, cerebrovascular risk factors, and cerebral white matter changes (leukoaraiosis) in patients with Alzheimer disease. Arch Neurol 2002;59:787-793.

Iadecola C. The pathobiology of vascular dementia. Neuron 2013;80:844-866.

Kemoun G, Thibaud M, Roumagne N, Carette P, Albinet C, Toussaint L, Paccalin M, Dugué B. Effects of a physical training programme on cognitive function and walking efficiency in elderly persons with dementia. Dement Geriatr Cogn Disord 2010;29:109-114.

Kivipelto M, Rovio S, Ngandu T, Kåreholt I, Eskelinen M, Winblad B, Hachinski V, Cedazo-Minguez A, Soininen H, Tuomilehto J, Nissinen A. Apolipoprotein E epsilon4 magnifies lifestyle risks for dementia: a population-based study. J Cell Mol Med 2008;12(6B):2762-2771.

Konukoğlu D, Serin O, Ercan M, Turhan MS. Plasma homocysteine levels in obese and non-obese subjects with or without hypertension; its relationship with oxidative stress and copper. Clin Biochem 2003;36:405-408.

Kramer AF, Erickson KI. Capitalizing on cortical plasticity: influence of physical activity on cognition and brain function. Trends Cogn Sci 2007;11:342-348.

Kurl S, Laukkanen JA, Rauramaa R, Lakka TA, Sivenius J, Salonen JT. Cardiorespiratory fitness and the risk for stroke in men. Arch Intern Med 2003;163:1682-1688.

Kuusi T, Nieminen MS, Ehnholm C, Yki-Järvinen H, Valle M, Nikkilä EA, Taskinen MR. Apoprotein E polymorphism and coronary artery disease. Increased prevalence of apolipoprotein E-4 in angiographically verified coronary patients. Arteriosclerosis 1989;9:237-241.

LaMonte MJ, Barlow CE, Jurca R, Kampert JB, Church TS, Blair SN. Cardiorespiratory fitness is inversely associated with the incidence of metabolic syndrome: a prospective study of men and women. Circulation 2005;112:505-512.

Lee M, Hong KS, Chang SC, Saver JL. Efficacy of homocysteine-lowering therapy with folic Acid in stroke prevention: a meta-analysis. Stroke 2010;41:1205-1212.

Lehmann M, Gottfries CG, Regland B. Identification of cognitive impairment in the elderly: homocysteine is an early marker. Dement Geriatr Cogn Disor 1999;10:12-20.

Leys D, Hénon H, Mackowiak-Cordoliani MA, Pasquier F. Poststroke dementia. Lancet Neurol 2005;4:752-759.

Loscalzo J. The oxidant stress of hyperhomocyst(e)inemia. J Clin Invest 1996;98:5-7.

Luck T, Riedel-Heller SG, Kaduszkiewicz H, Bickel H, Jessen F, Pentzek M, Wiese B, Koelsch H, van den Bussche H, Abholz HH, Moesch E, Gorfer S, Angermeyer MC, Maier W, Weyerer S; AgeCoDe group. Mild cognitive impairment in general practice: age-specific prevalence and correlate results from the German study on ageing, cognition and dementia in primary care patients (AgeCoDe). Dement Geriatr Cogn Disord 2007;24:307-316.

Mahley RW, Huang Y. Apolipoprotein E: from atherosclerosis to Alzheimer's disease and beyond. Curr Opin Lipidol 1999;10:207-217.

Mahley RW, Huang Y. Small-molecule structure correctors target abnormal protein structure and function: structure corrector rescue of apolipoprotein E4-associated neuropathology. J Med Chem 2012;55:8997-9008.

Mennen LI, de Courcy GP, Guilland JC, Ducros V, Bertrais S, Nicolas JP, Maurel M, Zarebska M, Favier A, Franchisseur C, Hercberg S, Galan P. Homocysteine, cardiovascular disease risk factors, and habitual diet in the French Supplementation with Antioxidant Vitamins and Minerals Study. Am J Clin Nutr 2002;76:1279-1289.

Mortensen EL, Høgh P. A gender difference in the association between APOE genotype and age-related cognitive decline. Neurology 2001;57:89-95.

Obeid R, Herrmann W. Mechanisms of homocysteine neurotoxicity in neurodegenerative diseases with special reference to dementia. FEBS Lett 2006;580:2994-3005.

Pettigrew LC, Bang H, Chambless LE, Howard VJ, Toole JF; Vitamin Intervention for Stroke Prevention Investigators. Assessment of pre- and post-methionine load homocysteine for prediction of recurrent stroke and coronary artery disease in the Vitamin Intervention for Stroke Prevention Trial. Atherosclerosis 2008;200:345-349.

Randeva HS, Lewandowski KC, Drzewoski J, Brooke-Wavell K, O'Callaghan C, Czupryniak L, Hillhouse EW, Prelevic GM. Exercise decreases plasma total homocysteine in overweight young women with polycystic ovary syndrome. J Clin Endocrinol Metab 2002;87:4496-4501.

Roth J, Goebeler M, Ludwig S, Wagner L, Kilian K, Sorg C, Harms E, Schulze-Osthoff K, Koch H. Homocysteine inhibits tumor necrosis factor-induced activation of endothelium via modulation of nuclear factor-kappa b activity. Biochim Biophys Acta 2001;1540:154-165.

Sarti C, Rastenyte D, Cepaitis Z, Tuomilehto J. International trends in mortality from stroke, 1968 to 1994. Stroke 2000;31:1588-1601.

Savva GM, Stephan BC. Epidemiological studies of the effect of stroke on incident dementia: a systematic review. Stroke 2010;4:e41-46.

Schafer JH, Glass TA, Bolla KI, Mintz M, Jedlicka AE, Schwartz BS. Homocysteine and cognitive function in a population-based study of older adults. J Am Geriatr Soc 2005;53:381-388.

Seshadri S, Beiser A, Selhub J, Jacques PF, Rosenberg IH, D'Agostino RB, Wilson PW, Wolf PA. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N Engl J Med 2002;346:476-483.

Slooter AJ, Tang MX, van Duijn CM, Stern Y, Ott A, Bell K, Breteler MM, Van Broeckhoven C, Tatemichi TK, Tycko B, Hofman A, Mayeux R. Apolipoprotein E epsilon4 and the risk of dementia with stroke. A population-based investigation. JAMA 1997;277:818-821.

Smith JD. Apolipoproteins and aging: emerging mechanisms. Ageing Res Rev 2002;1:345-365.

Tan NC, Venketasubramanian N, Saw SM, Tjia HT. Hyperhomocyst(e)inemia and risk of ischemic stroke among young Asian adults. Stroke 2002;33:1956-1962.

Tham W, Auchus AP, Thong M, Goh ML, Chang HM, Wong MC, Chen CP. Progression of cognitive impairment after stroke: one year results from a longitudinal study of Singaporean stroke patients. J Neurol Sci 2002;203-204:49-52.

Thompson PD, Yurgalevitch SM, Flynn MM, Zmuda JM, Spannaus-Martin D, Saritelli A, Bausserman L, Herbert PN. Effect of prolonged exercise training without weight loss on high-density lipoprotein metabolism in overweight men. Metabolism 1997;46:217-223.

Wannamethee SG, Shaper AG, Alberti KG. Physical activity, metabolic factors, and the incidence of coronary heart disease and type 2 diabetes. Arch Intern Med 2000;160:2108-2116.

Woodard JL, Sugarman MA, Nielson KA, Smith JC, Seidenberg M, Durgerian S, Butts A, Hantke N, Lancaster M, Matthews MA, Rao SM. Lifestyle and genetic contributions to cognitive decline and hippocampal structure and function in healthy aging. Curr Alzheimer Res 2012;9:436-446.

https://doi.org/10.12965/jer.1836108.054