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Effects of aquatic exercise on insulin-like growth factor-1, brain-derived neurotrophic factor, vascular endothelial growth factor, and cognitive function in elderly women

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ABSTRACT

The purpose of this study was to investigate the effects of a 16-week aquatic exercise program on brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF) levels, as well as cognitive function in elderly women. The subjects were 20 elderly women aged 68–80 years, randomly divided into an aquatic exercise group ($n = 10$) and a control group ($n = 10$). The aquatic exercises were performed for 60 min, three times per week for 16 weeks, and the intensity was progressively increased every 4 weeks (40–50% of heart rate reserve (HRR) for weeks 1–4, 50–60% of HRR for weeks 5–8, 60–65% of HRR for weeks 9–12, and 65–70% of HRR for weeks 13–16). The data were analyzed using two-way repeated measures analysis of variance, paired *t*-test, and independent *t*-test with an alpha level to indicate significance set at.05 for all tests. After the 16-week aquatic exercise program, the BDNF and IGF-1 levels ($p < .01$, respectively), and cognitive function ($p < .05$) of the aquatic exercise group showed significant changes. BDNF, IGF-1, and cognitive function levels ($p < .01$, respectively) were significantly different between the aquatic exercise group and control group. The results of this study suggest that regular aquatic exercise in elderly women during the early stages of aging can increase the expression of BDNF and IGF-1, thus maintaining and improving cognitive function.

1. Introduction

As a natural part of aging, humans experience biochemical, structural, and functional changes such as brain volume loss, synaptic degeneration, decreased blood flow, death of nerve cells, and changes in the structure and function of the hippocampus (Clouston et al., 2013). These changes degrade cognitive functions such as memory, perception, and linguistic abilities (Hogan, 2005), and lead to neurological diseases, such as dementia, Parkinson's disease, and cognitive dysfunction (Arancio and Chao, 2007; Duman et al., 2008).

Degradation of cognitive functions is accompanied by aging (Clouston et al., 2013; Hogan, 2005), but it has been recently demonstrated that brain plasticity also occurs in mature brains through the generation, regeneration, and recovery of neurons and vascularization (Schartt et al., 2006). As a consequence, the effects of brain plasticity on the activation and generation of cerebral nerve cell growth factors and cognitive function have been actively researched.

Neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF) improve brain plasticity and cognitive function (Heil et al., 2006; Paul et al., 2013; Ratey and Loehr, 2011; Skriver et al., 2014; Voss et al., 2013; Whiteman et al., 2014). Low levels of neurotrophic factors are highly correlated with brain neuropathy (Ejiri et al., 2005; Lommatzsch et al., 2005) and degradation of cognitive function (Ninan et al., 2010). Thus, the need to increase the levels of neurotrophic factors has been proposed.

BDNF is expressed in the hippocampus, cerebral cortex, and cerebellum (Sairanen et al., 2005), and 70–80% of plasma BDNF is derived from the brain (Rasmussen et al., 2009). BDNF plays an important role in the growth, differentiation, and plasticity of nerves (Bekinschtein et al., 2008; Kalinkovich and Livshits, 2015), and promotes learning, memory, and cognitive function. BDNF levels also decrease with aging (Driscoll et al., 2003; Leckie et al., 2014), and a higher level of BDNF plays a positive role in cognitive function (Komulainen et al., 2008).

IGF-1 is synthesized in various organs, including the liver and brain, and promotes cell proliferation and differentiation in the body (Yan

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Table 1
Changes in body composition after 16-week of aquatic exercise.

	Control group (n = 10)		Exercise group (n = 10)	
	Before	After	Before	After
Age (yr)	73.37 ± 4.19		73.83 ± 3.95	
Height (cm)	152.80 ± 4.66		153.97 ± 3.11	
Weight (kg)	54.05 ± 6.29	54.15 ± 6.43	57.73 ± 5.78	57.14 ± 6.09
SMM (kg/m^2)	19.07 ± 1.19	18.55 ± 1.38	20.32 ± 1.94	21.24 ± 2.43**
BFM (kg/m^2)	18.47 ± 4.72	18.57 ± 4.56	19.64 ± 3.42	18.16 ± 2.98***
%BF (%)	33.69 ± 5.28	33.86 ± 5.00	33.85 ± 3.24	31.66 ± 2.65***

Values are *M* ± *SD*.
SMM: skeletal muscle mass, BFM: body fat mass, %BF: percentage of body fat.
** $p < .01$.
*** $p < .001$.

et al., 2011). Circulating IGF-1 passes through the blood brain barrier (BBB) and improves the growth and differentiation of nerve cells and the synthesis and secretion of neurotransmitters (Sonntag et al., 2000). Furthermore, IGF-1 promotes brain development, including cognitive function, by controlling factors related to synaptic plasticity (Yan et al., 2011). In addition, IGF-1 reacts to various forms of exercise, thus increasing the expression of IGF-1 in the brain and peripheral nerves (Cassilhas et al., 2010). IGF-1 is an upstream mediator of signaling pathways that induces the expression of BDNF (Carro et al., 2000).

VEGF is synthesized by cells that stimulates the formation of blood vessels (angiogenesis) and vascularization (Jin et al., 2002; Cotman et al., 2007). VEGF passes through the BBB and flows into the central nervous system during long-term aerobic exercise (Jin et al., 2002; Cotman et al., 2007) where it induces the formation of new nerve tissues and vascular tissues (Cotman et al., 2007) and has positive effects on cognitive functions, such as learning, spatial cognition, and spatial memory (Plaschke et al., 2008). Low levels of serum VEGF have been associated with a high incidence of Alzheimer's disease (Mateo et al., 2007).

Therefore, performing an appropriate interventional therapy at a time when cognitive function is degrading naturally through aging has a positive effect on the nerve function of the brain and helps maintain and improve cognitive levels (Lista and Sorrentino, 2010).

Many studies have been conducted to identify methods of preventing the degradation of cognitive functions. In particular, regular and constant exercise has been reported to have a positive effect on the plasticity of the nervous system and protect brain cells (Zigmond and Smeyne, 2010), increase long-term memory (Bekinschtein et al., 2008), and maintain and improve cognitive functions (Bherer et al., 2013).

Recent studies have indicated that aquatic immersion and exercise may augment cognitive and processes when compared to equivalent land-based exercise. For instance, researchers have observed that healthy younger and older adults tended to make fewer 'cognitive' errors on memory recall tests while exercising or resting in chest-deep water compared to the same tasks on land (Bressel et al., 2018a; Bressel et al., 2018b; Schaefer et al., 2016). Additionally, aquatic exercise may promote stability more than exercise on due to factors such as buoyancy, resistance, pressure, and temperature (ACSM, 2010). Aquatic exercise often consists of repetitive walking, running, and jumping in water (AEA, 2010). The minimal influence of gravity due to buoyancy minimizes the weight load, puts less stress on joints, and reduces the risk of injury during exercise (Rahmann et al., 2008; Wang et al., 2007). Furthermore, aquatic exercise is often recommended for the older adults who may have arthritis, insufficient balance, or muscle strength (Katsura et al., 2010). The effect of aquatic exercise on IGF-1 and VEGF levels has not been tested previously. To our knowledge, this is the first study that examined the effects of aquatic exercise on IFG-1 and VEFG levels in elderly women, and we hypothesized that a 16-week aquatic exercise program would improve BDNF, IGF-1, and VEGF levels, as well as cognitive function, in elderly women. The results will provide scientific evidence for the positive effects of exercise therapy on brain health in elderly women.

2. Research method

2.1. Subjects

Twenty-six elderly women (age 68–80 years) who lived in G district in Busan and who had not been exercising regularly previously were recruited (sample of convenience) and divided by simple random sampling into a control group of 13 members and an aquatic exercise group of 13 members. All women were sedentary, did not regularly participate in physical activity (defined as < 20 min of exercise twice a week). The purpose of this study was fully explained, and informed consent was received before the experiment was initiated. Drop-outs due to personal circumstances and subjects with poor attendance were excluded. The measurements and test results were analyzed in 20 subjects, comprising 10 subjects in the control group and 10 subjects in the aquatic exercise group. Table 1 outlines the changes in body compositon after aquatic exercise program of the subjects.

2.2. Aquatic exercise program

The exercise program for this study was modified from a program proposed by the Korea Aquatic Exercise Association and consisted of 10 min of warm-up, 40 min of exercise, and a 10 min cool-down. It was performed three times weekly for 16 weeks in a swimming pool with a room temperature of 29–30 °C, humidity of 70–75%, water temperature of 28–29 °C, and water depth of 1.2 m. Exercise intensity was measured by rated perceived exertion and heart rate using the Borg scale and a cardiac monitor (Polar RS400sd, Bethpage, NY, USA). Exercise intensity was increased every 4 weeks as follows: 40–50% of heart rate reserve (HRR) for weeks 1–4, 50–60% of HRR for weeks 5–8, 60–65% of HRR for weeks 9–12, and 65–70% of HRR for weeks 13–16. Table 2 shows the details of the exercise program (ACSM, 2010).

2.3. Measurement items and analytical method

2.3.1. Blood collection and analysis

The subjects were asked to maintain an empty stomach from 8 pm the previous day, and blood was collected at 8–9 am (first time at rest before 16-week training period, second time at rest after 16-week training period). 10 ml of blood was collected by a clinical pathologist using a vacuum tube and a disposable syringe. The blood was collected in serum separating tubes, and the serum was separated by centrifugation (Combi-514R; Hanil, Seoul, Korea) at 3000 rpm for 10 min. The supernatant was moved to a 1.5 ml microtube and held at −80 °C until analysis. The blood analysis was entrusted to the N Medical

Table 2
Aquatic exercise program.

Warm-up (10 min)	Stretching, slow walking, and bounce
Main exercise (40 min)	1. Ankle inversion, eversion 2. Kick (soccer, Russian, back) 3. Jogging 4. Jumping jack 5. Cross country 6. Pendulum 7. Sidestep, step, & cross 8. Leg swing and curl 9. Leaping 10. Twist heel and toe 11. Fog jump, tuck jump 12. Scissors & jump 13. Jig 14. Aqua bar
Cool-down (10 min)	Stretching, slow walking, and bounce

Foundation and involved various analytical methods.

Blood BDNF levels were analyzed by enzyme linked immunosorbent assay (ELISA) using the Total BDNF Quantikine ELISA Kit (R&D Systems, Minneapolis, MN, USA) and Thermo Scientific Multiskan Go spectrophotometer (Thermo Scientific, Waltham, MA, USA). IGF-1 levels were analyzed by chemiluminescence immunoassay using the LIAISON IGF-1 Kit (DiaSorin, Saluggia, Italy) and the Liaison XL kit (Liaison XL, DiaSorin, Stillwater, MN, USA). VEGF levels were analyzed using the Human VEGF Quantikine ELISA Kit (R&D Systems) and a microplate reader (VERSA MAX, Molecular Devices, Sunnyvale, CA, USA).

2.3.2. Cognitive function

Cognitive function was tested in an interview using the Mini-Mental State Examination-Korean (MMSE-K) (Kwon and Park, 1989), which was modified from the MMSE (Folstein et al., 1975) for Korean elderly people. Inter-rater reliability was acceptable ($r = 0.999$) and Cronbach's α was 0.86 at the time of development of the MMSE-K. The test consists of six sections, recall (3 points), registration (3 points), attention and calculation (5 points), orientation to time (5 points), orientation to place (5 points), and language and visual composition (9 points), with a highest possible score of 30 points. The subject was classified as having definite dementia if the MMSE-K score was ≤19 points, suspected dementia if it was 20–23 points, and definitely healthy if the score was ≥24 points. Higher scores indicate a higher degree of cognitive function.

2.4. Data processing

Descriptive statistics were analyzed for the measurement items of each group using SPSS ver. 23.0 software (SPSS Inc., Chicago, IL, USA). Inter-group heterogeneity of the variables was tested using Levene's F-test. The intra-group average difference was tested using the independent *t*-test, and the inter-group and inter-time interaction test was performed using two-way repeated measures analysis of variance. A *p*-value < .05 was considered significant. A repeated test number (sample size) of 20 was derived from apriori sample size estimation using commercial software (G*Power, Version3.0.1, Universitat, Kiel, Germany) based on a repeated measures ANOVA F-statistic at $p < .05$, $\beta = 0.2$, and an effect size of 0.5.

3. Results

3.1. BDNF

The results for the intra-group and inter-group analyses of changes and interactions of BDNF are shown in Table 3. The BDNF levels in the exercise group increased significantly over time ($p < .05$). The inter-group comparison showed a significant difference in the change ($p < .05$), and a significant group × time interaction was found ($p < .05$).

3.2. IGF-1

The results for the intra-group and inter-group analyses of changes and IGF-1 interactions are shown in Table 4. The exercise group showed a significant increase in IGF-1 over time ($p < .01$). The inter-group comparison showed a significant difference in the change ($p < .05$), and a significant effect of the group × time interaction was found ($p < .05$).

3.3. VEGF

The results for intra-group and inter-group analyses of changes and interactions for VEGF are shown in Table 5. No significant differences were found in VEGF over time in either group and there was no group × time interaction.

3.4. Cognitive function

The results for intra-group and inter-group analyses of changes and interactions of cognitive function are shown in Table 6. The exercise group showed a significant increase in cognitive function over time ($p < .05$). The inter-group comparison showed a significant difference in the change ($p < .05$), and a significant group × time interaction was found ($p < .05$).

4. Discussion

Blood BDNF, IGF-1, and VEGF levels, as well as cognitive function, were analyzed to verify the effects of aquatic exercise on brain function indicators in elderly women. It may be observed from the results of this study that BDNF levels, IGF-1 levels, and cognitive function displayed significant gains after the aquatic exercise program. Additionally, BDNF, IGF-1, and cognitive function levels were greater in the aquatic exercise than control group. Reduced cognitive function with aging affects independence, social activities, and quality of life (Vaughan et al., 2012), whereas regular exercise increases the expression of neurotrophic factors and increases the values at rest (Berchtold et al., 2005). The results of the current study support this contention. The increase in neurotrophic factors improves learning and memory (Hillman et al., 2008) and prevents degradation of cognitive function (Griffin et al., 2011; Vaughan et al., 2012).

BDNF is the most prominent brain growth factor (Kozisek et al., 2008), which is widely distributed in the brain, muscle, and adipose tissues (Cassiman et al., 2011). Decreased blood BDNF levels in the elderly have been reported as a biomarker for impaired cognitive function and memory (Komulainen et al., 2008). Furthermore, BDNF secretion decreases with age (Bus et al., 2012), but regular exercise can delay the reduction and increase the secretion of BDNF (Duman et al., 2008).

Kim and Kim (2018) reported that the BDNF level in elderly women increases significantly after 16 weeks of aquatic aerobic exercise. Ruscheweyh et al. (2011) also showed that BDNF levels in elderly women increased significantly after 6 months of Nordic walking exercise.

Another study reported that moderate to high intensity exercise increases BDNF expression (Erickson et al., 2011; Ferris et al., 2007), and that a minimum exercise intensity must be satisfied to increase the BDNF level. The exercise program in the present study increased exercise intensity every 4 weeks, leading to increases in BDNF expression.

IGF-1 is involved in growth and metabolism, particularly in skeletal muscle hypertrophy, through protein assimilation (Phillips et al., 2014). IGF-1 penetrates the brain from the peripheral nerves through

Table 3
Changes in BDNF after 16-week of aquatic exercise.

Variable	Group	Pre	Post	Change	Paired-*t*	*F*	
BDNF (ng/mL)	CG (n = 10)	15.71 ± 3.05	15.51 ± 3.02	−0.20 ± 2.45	−0.252	Group	0.306
	EG (n = 10)	15.16 ± 4.36	17.75 ± 4.11	2.59 ± 2.92	2.801*	Time	3.938
	t-Value	0.324	−1.389	−2.308*		G × T	5.326*

Values are *M* ± *SD*.
* $p < .05$.

Table 4
Changes in IGF-1 after 16-week of aquatic exercise.

Variable	Group	Pre	Post	Change	Paired-*t*	*F*	
IGF-1 (ng/mL)	CG (n = 10)	43.95 ± 15.25	42.62 ± 11.47	−1.33 ± 7.30	−0.576	Group	0.302
	EG (n = 10)	42.42 ± 13.15	49.98 ± 8.82	7.56 ± 7.24	3.304**	Time	3.673
	t-Value	0.240	−1.608	−2.735*		G × T	7.479*

Values are *M* ± *SD*.
* $p < .05$.
** $p < .01$.

Table 5
Changes in VEGF after 16-week of aquatic exercise.

Variable	Group	Pre	Post	Change	Paired-*t*	*F*	
VEGF (pg/mL)	CG (n = 10)	194.3 ± 25.40	190.1 ± 28.74	−4.20 ± 14.27	−0.929	Group	0.027
	EG (n = 10)	189.9 ± 29.50	198.1 ± 20.26	8.18 ± 15.41	1.678	Time	0.359
	t-Value	0.352	−0.722	−1.862		G × T	3.468

Values are *M* ± *SD*.

the BBB (Sonntag et al., 2000) as IGF-1 levels increase both in the brain and peripheral nerves after exercise (Ploughman et al., 2005). Thus, IGF-1 is a major neurotrophic factor that contributes to the growth and survival of neurons in the brain and brain development, improving cognitive function (Foster et al., 2011; Yan et al., 2011).

A 12-week walking exercise program significantly increased the IGF-1 levels in elderly women (Kim et al., 2014), and a 24-week resistance exercise program significantly increased the IGF-1 levels in elderly men (Cassilhas et al., 2010). Gregory et al. (2013) reported that the IGF-1 level increases significantly in women in their 20s after 8 weeks of resistance exercise. The increased IGF-1 values of the current study for the 16-week aquatic exercise group are in agreement with these previous studies.

Tsai et al. (2014) compared IGF-1 levels according to single medium- and high-intensity resistance exercises in adult men and reported that IGF-1 levels increase after both medium- and high-intensity resistance exercises, but they increased significantly more after the high-intensity exercise condition. Therefore, exercise intensity, must be appropriate to lead to an increase IGF-1 levels. A previous study reported that higher exercise intensity leads to higher IGF-1 expression (Haydar et al., 2000; Tsai et al., 2014). Although IGF-1 increases with medium- and high-intensity physical activity and is mainly expressed in skeletal muscle. The aquatic exercise group and control group at baseline were similar in IGF-1 levels. However, after the aquatic exercise program, the aquatic exercise group had significantly higher IGF-1 levels than did the control group because exercise intensity was increased every 4 weeks for aquatic exercise group.

VEGF is a protein that is mainly expressed in the hippocampus and skeletal muscle to form surrounding vascular tissues (Jin et al., 2002). VEGF promotes the formation of nerve tissues and vascular tissues together with IGF-1 and plays a role in improving memory and cognitive function (Cotman et al., 2007; Voss et al., 2013). VEGF decreases in various parts of the brain during aging (Shetty et al., 2005); however, regular exercise can increase vascularization and reinforce learning and memory by enhancing VEGF production (Franzoni et al., 2005; Pati et al., 2009).

Table 6
Changes in cognitive function after 16-week of aquatic exercise.

Variable	Group	Pre	Post	Change	Paired-*t*	*F*	
Cognitive function (point)	CG (n = 10)	26.10 ± 0.32	26.00 ± 0.82	−0.10 ± 0.74	−0.429	Group	3.183
	EG (n = 10)	26.20 ± 0.42	26.80 ± 0.92	0.60 ± 0.70	2.714*	Time	2.419
	t-Value	−0.600	−2.058	−2.178*		G × T	4.742*

Values are *M* ± *SD*.
* $p < .05$.

A 12-week complex exercise program for obese middle-aged women significantly increased plasma VEGF levels (Lee et al., 2013). A high-intensity interval training for triathletes and cyclists increased their VEGF levels (Wahl et al., 2014). However, Steiner et al. (2005) did not find a significant difference in the VEGF level of middle-aged men, even though it increased after aerobic exercise. Jensen et al. (2004) reported that VEGF levels decreased as the training period increased from 2 to 4 and 7 weeks. Previous studies of VEGF have reported conflicting results. The blood VEGF levels in the present study did change significantly and could have been affected by the exercise period, content, intensity, or gymnastic changes.

First, VEGF decreases as the training period is increased (Jensen et al., 2004). Although the VEGF level increased in the early stages of an exercise program, it decreased after a certain period, as difficult motions became familiar after a period of time (Woodlee and Schallert, 2006). Similarly, sufficient vascularization occurs during the early and middle stages of the exercise program, and blood VEGF levels may not increase significantly thereafter. The reason being is that the same motions are repeated for 16 weeks, and the body adapted after some time.

Furthermore, VEGF expression increases due to hypoxia during high-intensity exercise (Wahl et al., 2014; Tang et al., 2010), but in this later study, hypoxia did not occur because the threshold level to stimulate VEGF expression was not reached. Therefore, to increase VEGF expression, exercise content and intensity need to be changed according to the length of the exercise program.

Furthermore, although VEGF is expressed in skeletal muscle through muscle contraction, blood VEGF is secreted by most organs of the body (Tang et al., 2010). Weight loss through exercise decreases blood VEGF levels (Cullberg et al., 2013). However, aquatic exercise in this study slightly increased the VEGF expression in fat cells by decreasing body fat mass (7.54%). The results of this study may be due to the fact that exercise stimulates VEGF protein production in skeletal muscle, which has been shown by other previous studies (Bloor, 2005).

Cognitive function is correlated with age, and a reduction in cognitive function appears as central nervous system function deteriorates (Hogan, 2005). Thus, degradation of cognitive function is a critical obstacle to independent daily living and social life because it prevents the performance of the activities of daily living (Vaughan et al., 2012). It has been reported that cognitive dysfunction is difficult to cope with and that multidisciplinary complex interventions are needed (Burgener et al., 2009). Among them, long-term regular exercise therapy is the most effective for preventing degradation of cognitive function (Vogel et al., 2009).

Colcombe and Kramer (2003) reported that aerobic exercise improves cognitive function of sedentary older adults, and a high exercise group (physical activity for > 3 h per week) was less cognitive decline than “no exercise” group (Lytle et al., 2004). It has been reported that the effect size was the highest at the exercise duration of 16 weeks or more, the exercise frequency at twice a week (Kim and Oh, 2018). Therefore, cognitive function was improved in this study due to aquatic exercise for 3 h and 16 weeks per week.

The MMSE-K scores increased significantly following a 12-week Korean dance intervention in elderly women (Hong et al., 2011). Furthermore, a 12-week aquatic aerobic exercise program significantly increased the MMSE-K score in elderly men and women with mild dementia (Yeon and Lee, 2017). In the present study, the MMSE-K scores increased significantly after aquatic exercise, as in a previous study, because regular exercise increased the expression of neurotrophic factors and cognitive function (Erickson et al., 2011; Ruscheweyh et al., 2011; Sonntag et al., 2005; Yan et al., 2011). Aquatic aerobic exercise improves the MMSE-K score by possibly increasing cerebral blood flow, expression of neurotrophic factors (Moraes et al., 2007), and neuroplasticity of the hippocampus (Ang et al., 2006), thus enhancing cognitive processes.

Cognitive function and physical strength decrease with age. However, the higher the level of physical activity, the better the cognitive function or the less the degradation of cognitive functions in old age (Lautenschlager and Almeida, 2006). Thus, cognitive function can be maintained and improved by increasing the expression of neurotrophic factors through regular exercise. The current study extends these results to aquatic based exercise.

The present study has several limitations. First, the mechanisms underlying the cognitive function improvements were not directly examined. Further research with this exercise program confirm the examination of potential mechanisms for this improvement. Second, a limitation of the current study is the relatively small sample size (n = 10 per each group). Therefore, the results of this study may be difficult to be generalized to other populations. Third, additional studies are needed to confirm the results of this study, compare the effects of the aquatic exercise on the variables of obese and nonobese or premenopausal and postmenopausal women by age or exercise type, and to develop effective aquatic exercise programs with different age groups.

5. Conclusion and suggestions

The results of this study suggest that regular aquatic exercise in elderly women during the early stages of aging can increase the expression of BDNF and IGF-1, thus maintaining and improving cognitive function.

Further research is needed to investigate the effects of the exercise period on neurotrophic factors to maintain and improve cognitive function in elderly women during the aging process and to reveal the effects of moderate and high-intensity exercise on neurotrophic factors in accordance with the exercise guidelines of the American College of Sports Medicine, which recommends combination of moderate and high intensity.

CRediT authorship contribution statement

Doo-wang Kang: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Visualization, Writing - original draft.**Eadric Bressel:** Conceptualization, Methodology, Visualization, Writing - original draft, Writing - review & editing.**Do-yeon Kim:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.

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