J Nutr Health Aging. 2018;22(8):944-951

EFFECTS OF RESISTANCE EXERCISE TRAINING ON COGNITIVE FUNCTION AND PHYSICAL PERFORMANCE IN COGNITIVE FRAILTY: A RANDOMIZED CONTROLLED TRIAL

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Abstract: *Background:* Cognitive frailty is defined as the presence of both physical frailty and cognitive impairment (clinical dementia rating score = 0.5), in the absence of dementia. It is characterized by concurrent physical frailty and potentially reversible cognitive impairment. In this study, we sought to elucidate the effects of high-speed resistance exercise training on cognitive function and physical performance in older adults with cognitive frailty. *Methods:* We conducted a parallel-group, randomized controlled trial involving community-living older adults with cognitive frailty. The participants' mean age was 73.9 (± 4.3 SD) years, and 69.8% (n=30) were female. Two different 4-month interventions included high-speed resistance exercise training group (n=22) and a control group (balance and band stretching, n=23). Frailty score, cognitive function (memory, processing speed, cognitive flexibility, working memory, executive function), physical function (SPPB, TUG, gait speed), and muscle strength (grip strength, knee extension strength) were assessed at baseline, 8 weeks, and 16 weeks. *Results:* Statistical analysis showed that exercise improved performance significantly in the tests for cognitive function (processing speed and executive function, both $p < 0.05$), physical function (SPPB, TUG, gait speed, both $p < 0.05$), and muscle strength (grip strength, knee extension strength, both $p < 0.05$). However, no significant changes in frailty score were observed between intervention and either control group ($p < 0.05$). *Conclusion:* In conclusion, our findings indicate that high-speed resistance exercise training approaches are effective in improving cognitive function and physical performance in older adults with cognitive frailty. This study shows that it is feasible to identify older adults with cognitive frailty in the community and primary care setting for effective intervention to reduce their level of frailty and cognitive impairment.

Key words: Cognitive frailty, mild cognitive impairment, physical frailty, resistance training, randomized clinical trials.

Introduction

Frailty is an age-related, biological syndrome characterized by decreased biological reserves, due to dysregulation of several physiological systems. It increases the individual risk for stress-induced impairment, and is associated with poor outcomes (i.e., hospitalization, institutionalization, fall, functional disability, and disability) (1, 2). A widely used clinical research definition of the frailty syndrome in the Cardiovascular Health Study (CHS) frailty phenotype, consists of a combination of shrinking (unintentional weight loss), weakness (indicated by muscle strength), poor endurance and energy (per self-reported exhaustion), slowness (demonstrated by slow walking speed), and low physical activity (3). According to the current consensus, physical frailty is potentially reversible with appropriate intervention (4). Accordingly, early detection of at-risk older adults and the development of interventions focused on preventing loss in quality of life play an increasingly important role (5).

The relationship between physical frailty and cognitive impairment has become increasingly apparent with recent studies suggesting an interrelationship (5, 6). Physical and cognitive impairment frequently overlap in older adults, however, cognition is not included in the physical frailty phenotype (7). It has been consistently shown that physical frailty is associated with cognitive impairment and dementia (8). Although frailty and cognitive impairment have been shown to be related, both constructs have long been studied separately (5). To address this gap, the international consensus group comprised of investigators from the International Academy of Nutrition and Aging (IANA and the International Association of Gerontology and Geriatrics (IAGG recently convened in Toulouse, France to establish a definition of cognitive frailty in older adults (9). Additionally, the consensus group recommended formal assessments based on studies that supported findings correlating progressive physical frailty with cognitive impairment in older adults. The new construct called cognitive frailty, defined as the presence of both physical frailty and cognitive impairment (Clinical dementia rating score (CDR) = 0.5), in the absence of dementia, is characterized by concurrent physical frailty and potentially reversible cognitive impairment (9). The underlying rationale suggests that the cognitive impairment in these patients is primarily due to physical deterioration rather than neurodegenerative processes

Received February 8, 2018
Accepted for publication February 8, 2018

Published online August 7, 2018, http://dx.doi.org/10.1007/s12603-018-1090-9

(7).

Several meta-analyses and randomized controlled trials have reported that physical activity is associated with improvements in attention, processing speed, and executive function (10) as well as sensorimotor ability in older adults. Indeed, aerobic exercise may lead to an increase in brain volume (11) and enhance functional connectivity between parts of the frontal, posterior, and temporal cortices (12) in non-frail older adults. However, few studies have examined the effect of other types of exercises on cognitive function. For example, it has been observed that resistance training contributes positively and significantly to the improvement of brain functional plasticity, executive function and response inhibition (13, 14). However, currently no specific exercise interventions can be totally recommended for brain function and physical health promotion in older adults with cognitive frailty as the evidence base is small and of limited quality. Also, current evidence is limited, and studies are needed to determine the role of exercise parameters (e.g. volume, types, and intensity) in cognitive function (15).

Consequently, in this study, we sought to elucidate the effects of high-speed resistance exercise on cognitive function and physical performance in older adults with cognitive frailty. We hypothesized that low-intensity high-speed resistance exercise training may be effective in improving physical functions; muscle strength and cognitive function. We used a randomized control trial design to measure cognition and physical performance before and after, and high-speed resistance training intervention.

Methods

Study Sample

We selected 65 participants who were 65 years and older, lived in Seoul, Korea, and had no history of depression; chronic disease; degenerative neurologic disease; hospital admission in the past 12 months for any reason; not illiterate; had no stroke or other cardiopulmonary disease; or dementia. Additional inclusion criteria included the ability to walk 10 m without a walking aid, a CDR of 0.5, and pre-frail and frail older adults, as of August 2016. Thus, the remaining 65 subjects were eligible to participate in this study. Prefrail and frail older adults were identified based on five Cardiovascular Health Study (CHS) criteria defining physical frailty (9): unintentional weight loss, slowness, weakness, exhaustion, and low activity, which were scored 1 if present and 0 if absent. The total cumulative scores ranging from 0 to 5 were used to classify a participant as robust (score = 0), prefrail (score - 1 to 2), or frail (score = 3 to 5). Cognitive frailty was defined as the simultaneous presence of physical frailty, as described above, with cognitive impairment, defined as a CDR of 0.5, and absence of concurrent dementia (9). The participants were randomly assigned to one of the two groups: high-speed resistance exercise training group (n=32) and control group (balance and resistance band stretching, n=33). At the end of the 16-week study, 45 participants including 22 from the exercise group and 23 from the control group remained. The study protocol was approved by the Institutional Review Board of SNUBH (BRMH IRB No. 16-2016-26)

Measurements

Diagnosis of frailty phenotype

Frailty was measured according to the CHS criteria (3) involving five components operationally defined as:

1) Unintentional weight loss: body mass index (BMI: weight/height2) < 18.5 kg/m2 or self-reported unintentional weight loss of 4.5 kg in the last one year.

2) Slowness was assessed using 4-meter fast gait speed test. Participants were timed in seconds while walking 4 meters and an average of 2 measurements was obtained. A speed < 0.8 m/s indicated frailty-related slowness.

3) Weakness was defined as low grip strength in each individual corresponding to gender and body mass index (BMI). Grip strength was measured using a hand-to-hand dynamometer (Takei Scientific Instruments, Niigata, Japan). Each participant stood and gripped the hand-to-hand dynamometer handle. Upon verbal command, the handle was gripped as strongly as possible. It was repeated four times with a break in between. The average grip strength in kilograms was recorded.

4) Exhaustion included self-reported exhaustion, identified by two questions from the Center for Epidemiologic Studies Depression Scale (CES–D) scale. “How often have you ever felt that everything you had done was useless in the last week?” and “How often have you ever felt that everything you had to do was not in a mood to do during the last week?” Exhaustion was indicated by responses of “most of the time” and “often”

5) Low physical activity corresponded to responses to International Physical Activity Questionnaire (IPAQ) items concerning low, middle, and high levels of physical activity. Responses describing low physical activity were indicative of frailty.

Physical function and muscle strength

Short physical performance battery (SPPB) was used to assess gait speed, chair stand, and balance tests. It has been used as a predictive tool for possible disability and facilitated the monitoring of function in older people. Each test received a performance score, with scores ranging from 0 points (worst performance) to 12 points (best performance). The tests comprised the chair stand test (four points), balance test (four points), and 4-m gait speed test (four points) (16). The Timed Up and Go test (TUG) is a simple test used to assess a person’s mobility and requires both static and dynamic balance. TUG was defined as the time from the moment the buzzer sounded to the moment the subject sat back down on the chair, detected automatically using a piezo resistive pressure sensor located under the seat. The subject rises from the chair, walks 3 m in a linear path, performs a 180° turn, walks back to the chair, and sits down (17). In the gait speed test, the 4.44-m gait test was used. Three lines were drawn horizontally in the measuring area. The interval between the first and second lines was 1 m, and 4.44 m between the second and third lines, for a total of 5.44 m. Each participant stood on the first line and walked to third line immediately upon verbal command. The average duration of the two trials of walking speed test was recorded.

Lower limb concentric dynamic strength was measured using a HUMAC NORM isokinetic dynamometer (CSMi Solutions, Stoughton MA, USA). The knee extension peak torques of dominant lower limb were evaluated for the isokinetic contraction test. The subjects performed a maximal test of 3-time and 5-time repetitions. Each maximal strength test was conducted at an angular speed of 60°/s for isokinetic muscle strength and an angular speed of 180°/s for isokinetic muscle power measurement (18). The exercise was performed twice prior to testing in order to obtain optimal results by allowing the subjects to familiarize themselves with the test.

Assessment of cognitive function

To assess participants' cognitive function a sensitive and validated neuropsychological test battery was used. The Korean version of Mini-Mental State Examination (MMSE-K) (19), CDR scales, and the neuropsychological battery included the Korean version of the Consortium to Establish a Registry for Alzheimer's disease (CERAD-K), which were evaluated by a single rater for all participants. The MMSE is commonly utilized to screen for dementia. The test consists of 11 questions and tasks, in a total of five cognitive domains: orientation (10 points), memory (6 points), attention (5 points), language ability (7 points) and comprehensive/judgment (2 points). The highest score is 30 and a higher score indicates a higher level of cognitive function. The CERAD is a paper- and pencil-based memory test battery developed in Korea. Its reliability and validity have been verified and is widely used in clinical practice. These neuropsychological tests assess: an executive domain of the verbal fluency test (0 – 24 point), a language domain of the Modified Boston Naming Test (BNT) (0 – 15 points), a memory domain of the Word-List-Learning test (0 – 30 points) with delayed recall (0 – 10 points) and recognition (0- 10 points), and a visuospatial domain of the visual construction test (0 – 11 points). The total score of the CERAD was calculated by summing the six subtest scores (20). The CDR was calculated as the sum of all six items (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care) in the CDR scale. The composite rating consists of five levels: 0 (none), 0.5 (questionable), 1 (mild), 2 (moderate), and 3 (severe) (21).

The cognitive function was assessed using 4 cognitive tasks: 1) Rey 15-Item memory test, 2) Trail Making A&B Test, 3) Digit Span (both forward and backward) test, and 4) Frontal assessment battery (FAB)

* Memory: Recall and recognition were assessed using the Rey 15-Item memory test (22). The test involves memorization of 15 different items (letters, numbers, and simple geometric shapes) presented in five rows (three items/row). Each participant was shown a paper with 15 different items for 10 s. The paper was removed and the participant recorded in writing as many items as possible, based on recall. The recognition task scores used two parts.

* Processing speed and cognitive flexibility: Processing speed and cognitive flexibility were assessed using the Trail Making A&B Test (23). The trail making test consists of two parts. In Part A (TMT-A), the subject was tasked with listing numbers 1-25 in ascending order (23). In Part B (TMT-B), the subject drew numbers and letters in alternating order. The maximum amount of time to complete Part B was 300 s. TMT-B is more difficult than TMT-A because of the increased demand for motor speed and visual search (24).

* Working memory: The Digit Span test was used. Respondents were asked to recall numbers forward (range 3-9) and backward (range 2-8) (25).

* Executive functions: The patients underwent a global screening of executive functions using the Korean version of the FAB (26), which consisted of six subset test items including conceptualisation (abstract reasoning), item flexibility (verbal fluency), motor programming (organization, maintenance and execution of successive actions), sensitivity to interference (conflicting instructions), inhibitory control (inhibit inappropriate responses), and environmental autonomy (prehension behavior). The administration time of the FAB is about 10 min.

Based on these four cognitive tasks, five cognitive domain scores were created as a mean of factor analyses. A higher score in 3 domains and a lower score in 2 domains suggested better cognitive function.

Resistance exercise intervention

A high-speed resistance training program is defined as a contraction phase expected to be accomplished as quickly as possible, a 1-s pause, and an eccentric contraction exceeding 2 s (27). Independent exercise lasting 1h was conducted 3 times each week for 16 weeks. High-speed resistance exercise regimens were based on the use of elastic exercise bands, based on previous intervention (13). Each session included a 10-min warm-up, 40-min high-speed resistance training (seated row, one leg press, applied pec deck flus, seated leg raise, lateral raise, semi squats, wide squats, bridging), and 10 min of cooling down. The sessions were separated by a minimum of 48 h and were performed under the direct supervision of an exercise instructor to ensure safety and adherence with the exercise protocol. Exercise intensities were set by the color of the elastic exercise band. In the high-speed resistance training group, blue elastic bands (tension: low, 20 Nm) were used and the participants were instructed to perform exercise training at a perceived exertion rate of 12-13 ("Somewhat hard"). The high-speed resistance exercise consisted of 2-3 sets of 12-15

Table 1
General characteristics of subjects

	Total N=43	Intervention Group, N= 20	Control Group, N= 23	P-value
Demographics				
Age, mean (SD)	73.94 ± 4.27	73.82 ± 4.37	74.03 ± 4.27	.860
Female, n (%)	30 (69.8%)	14 (70.0%)	16 (69.6%)	.848
Education, y, mean (SD)	9.08 ± 4.13	8.09 ± 3.50	9.77 ± 4.44	.145
MMSE, mean (SD)	24.22 ± 2.31	24.23 ± 2.89	24.22 ± 1.86	.990
BMI (kg/m2)	24.57 ± 3.06	24.86 ± 2.73	24.38 ± 3.30	.569
BMD (g/m2)	1.11 ± 0.19	1.14 ± 0.18	1.10 ± 0.19	.468
Frailty criteria, n (%)				
Mean (SD) score, (range: 0-5)	1.49 ± 0.74	1.63 ± 0.90	1.37 ± 0.56	.237
Slow gait speed	15 (35%)	8 (40%)	7 (30%)	.531
Shrinking	4 (9%)	2 (10%)	2 (9%)	.702
Weakness	21 (49%)	11 (55%)	10 (43%)	.371
Exhaustion	9 (21%)	2 (10%)	7 (30%)	.519
Low activity level	11 (26%)	6 (30%)	5 (22%)	.443
CERAD, Total score	54.06 ± 19.42	59.50 ± 10.55	50.31 ± 23.10	.055
Verbal fluency (score)	14.26 ± 4.69	14.00 ± 4.69	14.44 ± 4.76	.740
Boston Naming Test (score)	10.07 ± 2.29	9.18 ± 2.42	10.69 ± 2.01	.016
Word-List-Learning test (score)	13.43 ± 3.32	13.32 ± 3.55	13.50 ± 3.20	.845
Delayed recall (score)	4.93 ± 1.65	4.91 ± 1.82	8.82 ± 1.05	.951
Recognition (score)	8.69 ± 1.43	8.82 ± 1.05	8.59 ± 1.64	.575
Visual construction test (score)	8.13 ± 1.76	9.27 ± 1.67	9.03 ± 1.84	.625

Abbreviations: BMI, body mass index; WHR, waist hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; Values are presented as mean±SD. ANOVA indicates two way repeated ANOVA measures between group and time; *p<0.05 compared pre with post training; **p<0.01 compared pre with post training, and ***p<0.001 compared pre with post training.

repetitions. Participants in the control group were asked to continue their routine daily activities and performed static and dynamic stretching (using elastic exercise band) twice weekly for 1 h, over 16 weeks. Our exercise program followed the guidelines for older adults recommended by the American College of Sports Medicine.

Statistical analyses

Statistical analyses were performed using SPSS 22.0 (IBM Corporation, Chicago, IL). Categorical variables were expressed as percentages and continuous variables with mean and SD. Intervention and control group older patients were compared using the x2 test (categorical variables) and Student's t-test (continuous variables). The training-related effects were assessed using a two-way ANOVA with repeated measures (group x time). Tukey's post hoc procedures were performed to locate the pairwise differences between the mean values. A p-value < .05 denoted statistical significance. The magnitudes of effect size were 0.20, 0.60, and 1.2 for small, moderate and large effects, respectively (28).

Results

We screened 65 potential participants. All the 66 were eligible and were randomized (33 to high-speed resistance exercise training and 33 to the control group). The participants' mean age was 73.9 (± 4.3 SD) years, and 69.8% (n=30) were female. Frailty symptoms included predominantly weakness (49%) and slowness (35%), low physical activities (26%), exhaustion (21%), and 9% shrinking. No significant differences ($p > 0.05$) were observed among the groups in descriptive ad dependent variables at baseline. (Table 1).

Table 2 summarizes the changes in cognitive function from baseline to follow-up at 8 and 16 weeks in the intervention and control groups. There was a significant decrease in processing speed over 16 weeks across intervention group, and significant group x time interaction ($p = 0.036$). At 8 and 16 weeks, intervention showed significant differences compared with control at the post hoc significance level of $p < 0.05$, $p < 0.01$, and 0.21 ES, respectively. Similarly, executive functions increased significantly over the 16 weeks across intervention

Table 2
Training effects (with 95% confidence limits) for the cognitive function variables between groups

	Baseline Mean ± SD	8 weeks Mean ± SD	16 weeks Mean ± SD	p-value	Effect size (Cohen's d)
Memory (score) :rey-15					
Intervention	8.55 ± 2.39	9.85 ± 3.22	10.00 ± 3.71	0.445	0.46#
Control	10.26 ± 2.85	10.96 ± 2.57	10.52 ± 2.79		0.09
Processing speed (sec) : TMT-A					
Intervention	54.15 ± 28.43	50.86 ± 27.07*	48.26 ± 27.33**	0.036	0.21#
Control	43.04 ± 11.95	43.07 ± 16.67	42.59 ± 15.92		0.03
Cognitive flexibility (sec) : TMT-B					
Intervention	163.37 ± 62.45	149.34 ± 46.81	140.82 ± 34.65	0.532	0.45#
Control	188.92 ± 81.38	176.55 ± 62.16	187.20 ± 70.14		0.02
Working memory (score) : Dig F/B					
Intervention	10.20 ± 1.54	10.15 ± 1.42	10.70 ± 1.34	0.448	0.35#
Control	10.09 ± 2.04	10.52 ± 2.11	10.39 ± 1.83		0.14
Frontal Assessment Battery (FAB), (score)					
Intervention	12.00 ± 2.45	12.65 ± 1.95	13.70 ± 2.11*	0.022	0.74##
Control	11.87 ± 2.12	12.43 ± 1.78	12.09 ± 2.00		0.11

Values are presented as mean ± SD. ANOVA indicates two way repeated ANOVA measures between group and time. TMT-A&B, Trail Making A&B Test; Dig F/B, Digit Span test forward and backward; *p<0.05 compared to baseline; **p<0.01 compared to baseline; # Small; ## Moderate; ### Large

group, and significant group x time interaction ($p = 0.022$). At 16 weeks, intervention showed significant differences compared with control at the post hoc significance level of $P < 0.05$, 0.74 ES. However, no significant changes (time x group interaction; $p > 0.05$) in memory, cognitive flexibility, or working memory were observed between intervention and either control group (Table 2).

The results of physical function domain of SPPB, TUG, and gait speed, and frailty score are shown in Table 3. In SPPB, the intervention group showed significant (group x time interaction; $p = 0.001$) increases over 16 weeks. At 8 and 16 weeks, intervention showed significant time effect at the post hoc level of $p < 0.05$, 0.81 ES, respectively. After 16 weeks of intervention, the TUG showed significant group x time interaction ($p = 0.000$). At 8 and 16 weeks, intervention showed significant impact of time at the post hoc significance level of $p < 0.01$, 0.65 ES, respectively. In terms of gait speed, the intervention group showed significant (group x time interaction; $p = 0.027$) increases over 16 weeks. At 8 and 16 weeks, intervention led to significant time effect at the post hoc level of $p < 0.01$, 0.94 ES, respectively. However, during the pre- to post-training period, no significant changes (time x group interaction; $p > 0.05$) in frailty score were observed between the intervention and control groups. (Table 3).

During the pre- to post-intervention period, relative to muscle strength, the intervention group showed a clinically significant (group x time interaction; $p < 0.05$) increase in grip strength ($p=0.020$, 0.30 ES), isokinetic 60°/sec peak torque ($p=0.004$, 0.19 ES), and isokinetic 180°/sec average power per rap ($p = 0.001$ 0.32 ES). Significant group x time interactions were noted for all measures ($p < 0.05$), with the intervention group resulting in significantly greater improvements in all strength parameters compared with the control group. At 8 and 16 weeks, intervention showed significant time effect at the post hoc level of $p < 0.05$ (table 4).

Discussion

The aim of the present study was to determine the effect of high-speed resistance exercise training on cognitive function and physical performance in older adults diagnosed with cognitive frailty. To our knowledge, this is the first intervention trial that evaluated the effects of resistance exercise intervention in reversing cognitive frailty. The study provided an opportunity to delineate the cognitive functions and frailty in a controlled trial of subjects with well-defined cognitive and physical performance. To achieve this objective, cognitive frailty was incorporated from the controlled trial study based on the following: 1) CDR of 0.5, and absence of concurrent dementia; 2) at least one CHS criterion of physical frailty (inclusion frailty and pre-frailty); and 3) 10-m walk without a walking aid.

High-speed resistance training significantly improved processing speed and executive function over the course of

Table 3
Training effects (with 95% confidence limits) for the physical function and frailty score variables between groups

	Basline Mean ± SD	8 weeks Mean ± SD	16 weeks Mean ± SD	p-value	Effect size (Cohen's d)
Frailty score					
Intervention	1.55 ± 0.89	0.70 ± 0.73	0.65 ± 0.93	0.683	0.99##
Control	1.48 ± 0.67	0.83 ± 0.72	0.70 ± 0.76		1.09##
SPPB (score)					
Intervention	9.25 ± 2.31	11.00 ± 1.45*	10.85 ± 1.60*	0.001	0.81##
Control	10.04 ± 1.46	10.35 ± 1.19	10.91 ± 1.20		0.65##
TUG (sec)					
Intervention	10.66 ± 2.41	8.82 ± 1.82**	9.26 ± 2.03**	<0.001	0.65##
Control	9.95 ± 1.51	9.61 ± 1.31	9.89 ± 1.59		0.04
Gait Speed (sec)					
Intervention	6.21 ± 1.04	5.44 ± 1.03**	5.34 ± 0.81**	0.027	0.93##
Control	6.04 ± 0.82	5.90 ± 0.72	5.58 ± 0.81		0.56#

Values are presented as mean ± SD. ANOVA indicates two way repeated ANOVA measures between group and time. SPPB, short physical performance battery; TUG, time up and go; *p<0.05 compared to baseline; **p<0.01 compared to baseline; # Small; ## Moderate; ### Large

Table 4
Training effects (with 95% confidence limits) for the muscle strength variables between groups

	Basline Mean ± SD	8 weeks Mean ± SD	16 weeks Mean ± SD	p-value	Effect size (Cohen's d)
Grip Strength (kg)					
Intervention	21.41 ± 6.58	25.02 ± 7.71*	23.60 ± 7.76*	0.020	0.30#
Control	21.81 ± 6.31	23.49 ± 5.62	23.78 ± 7.14		0.29#
Isokinetic 60°/sec peak torque / BW					
Intervention	65.05 ± 25.82	68.85 ± 37.12*	71.20 ± 36.68*	0.004	0.19
Control	70.77 ± 24.32	67.36 ± 22.45	64.23 ± 20.72		0.01
Isokinetic 180°/sec average power per rap (watt)					
Intervention	68.32 ± 40.60	79.77 ± 45.58*	82.09 ± 44.63*	0.001	0.32#
Control	72.77 ± 23.82	68.64 ± 22.69	66.59 ± 23.67		0.26#

Values are presented as mean ± SD. ANOVA indicates two way repeated ANOVA measures between group and time; *p<0.05 compared to baseline; **p<0.01 compared to baseline; # Small; ## Moderate; ### Large

16 weeks. Evidence strongly indicates that regular physical exercise leads to positive changes in human biology and psychology, and may prevent the loss of cognitive function (29). It has been previously reported that exercise improves mood, cognitive function, and quality of life in frail older adults (30). No significant differences were found in other tests following exercise intervention, thus corroborating the findings of several studies suggesting that combination training was more efficient in improving cognitive function in older adults than aerobic or resistance training alone (15). However, current evidence is limited, and research is needed on the role of exercise parameters (e.g. volume, types, and intensity) on specific cognitive functions. Indeed, it has been reported that the volume, intensity and variation of physical activities as well as the history of practice were positively associated with processing speed, memory, mental flexibility, executive function and overall cognitive function (31).

A significant improvement was found in SPPB, TUG, and gait speed following high-speed resistance exercise, compared with the control group after 16 weeks These results reinforce those reported in the LIFE study in which exercise intervention reduced the incidence of major mobility disability (1, 32).

Our results support a recent study showing an improvement in physical function after completion of high-speed resistance exercise and physical exercise intervention (13, 33). Previous studies have highlighted the importance of adherence to exercise programs to improve the scores in functional scales as well as in gait speed (1). Multicomponent training programs conducted over 5 months or longer (34) and performed 3 days per week for 30 to 45 min each session contribute to better outcomes.

The low-intensity high-speed resistance exercise training had no significant effect in reducing frailty score. Frailty is possibly reversible or modifiable by interventions. Previous studies investigating nonpharmacological interventions such as physical exercise showed promising effects on frailty status, functional, and cognitive outcomes (1, 6, 35). Exercise interventions should be provided for elderly subjects with physical frailty syndromes that are reversible to prevent a reduction in physical functions (6, 36). However, in a few studies, clinical trials failed to show convincing evidence of effectiveness (1, 37), whereas in others exercise partially improved functional outcomes in the frail population, such as sit-to stand performance, balance, agility, and ambulation, and the level of physical activity (35, 38). Furthermore, previous studies reported that the benefit of multi-domain interventions (nutritional supplementation, psychological treatment, social activities, and physical exercise; respectively) was not evident at 4-month follow-up and was apparent only at 12 months (given that there was no assessment at 6 months) (39). The lack of consistency among the studies is due to the differences in the definition of frailty, training protocols, intervention duration, characteristics of the control groups, and the main outcomes assessed. Thus, a definitive conclusion has yet to be established (35).

Our high-speed resistance exercise training program resulted in significant grip strength and knee extension peak torques in the isokinetic contraction test of dominant lower limb. Recent studies show a strong link between cognition and muscle strength (40). In addition, muscle strength is an important component of the physical phenotype. Furthermore, maximal strength is a useful predictor of all-cause mortality and old age disability. Maximal strength (especially handgrip strength) is relatively easy to complete and therefore, the variable can be used as a convenient prognostic tool in the elderly population. This study intervention used resistance exercise training, and the observed improvements in muscle strength (upper and lower body muscle strength) are consistent with those reported elsewhere.

Our study was limited by the small sample size and relatively shorter period of exercise intervention. Therefore, a randomized controlled trial with a larger sample size may provide a deeper insight into the effects of resistance exercise on cognitive function and physical performance. As a further step, the causes of frailty need to be identified to enable the implementation of evidence-based multidomain interventions depending on personalized needs. Evaluation of pharmacological therapy and use of protein and vitamin supplementation is also recommended. Multi-domain interventions might prove useful if focused on the physical exercise, nutritional, cognitive and psychological domains in order to improve the well-being and quality of life in the elderly (9). These strategies may be ineffective if focused on single components and, fail to capture the complexity of the phenomenon. Finally, the pathophysiological mechanisms of cognitive frailty are currently unknown. Therefore, ancillary neuroimaging or brain imaging studies of longitudinal exercise intervention may provide an opportunity to better understand the relation between cognitive frailty and cerebral atrophy, white matter hyperintensities, and amyloid deposits in the brain.

In conclusion, our findings indicate that high-speed resistance exercise training approaches are effective in improving cognitive function and physical performance in older adults with cognitive frailty. This study shows that identifying older adults with cognitive frailty in the community and primary care setting for targeted intervention effectively reduces their level of frailty and cognitive impairment.

Acknowledgement: This study was supported by the Institute of Health and Environment, Seoul National University and Fellowship for fundamental academic fields, Seoul National University.

Conflict of interest: On behalf of all the authors, the corresponding author states that there is no conflict of interest.

Ethical standard: The study protocol was approved by the Institutional Review Board of SNUBH. All participants signed written informed consent.

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