

# Effect of Multicomponent Exercise and Nutrition Support on the Cognitive Function of Older Adults: A Randomized Controlled Trial

This article was published in the following Dove Press journal:  
*Clinical Interventions in Aging*

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**Purpose:** This study compared the effects of a combination of soy peptide supplementation and exercise with those of exercise only, on the cognitive function of elderly adults.

**Patients and methods:** This randomized, non-blinded, controlled clinical trial included 67 participants aged 60 years or more with non-cognitive dysfunction who were divided into two groups according to the intervention method: an exercise group (Ex group, n = 36) and an exercise plus nutrition group (Ex+Nt group, n = 31). The Ex group completed a memory training activity for 15 mins and aerobic exercise for 45 mins once a week for 90 days. The Ex+Nt group completed the same training plus received soy peptide for 90 days. The Mini-Mental Status Examination score, trail-making test A/B score, skeletal muscle mass index, grip strength, gait speed, and geriatric depression scale were measured at baseline and post intervention. For comparison between the pretest and posttest measurements to determine the intervention effects, a two-way analysis of variance was performed. The significance level was set at < 5%.

**Results:** A two-way analysis of variance revealed significant time effects on trail-making test-A score, skeletal muscle index, grip strength, and gait speed in both groups. There were significant time x group interactions for greater increase in calculation score.

**Conclusion:** A combination of exercise and soy peptide supplementation was effective in improving a portion of cognitive function.

**Keywords:** dementia, Alzheimer's disease, Mini-Mental Status Examination, soy peptide

## Introduction

There has been a rapid increase in the prevalence of dementia owing to societal aging, and this poses a very serious problem.<sup>1</sup> According to the World Alzheimer's Association, the proportion of people with dementia is increasing at a rate of one person every 3 seconds. This value is likely to reach 74.7 million people worldwide in 2030, accompanied by increasing medical and nursing care expenses, at an estimated cost of 818 billion USD.<sup>2</sup> Risk factors for dementia include the presence of the apoE4 protein,<sup>3</sup> high blood pressure,<sup>4-6</sup> diabetes,<sup>7</sup> lipid abnormality,<sup>8</sup> depression,<sup>9</sup> inactivity,<sup>10</sup> low income,<sup>11,12</sup> and a decrease in the frequency of interpersonal exchanges.<sup>13</sup> Conversely, protective factors include the presence of higher education,<sup>14</sup> physical activity,<sup>15</sup> participation in cognitive activities,<sup>15</sup> antioxidant food intake,<sup>16,17</sup> moderate alcohol consumption,<sup>18</sup> and increased frequency of social participation and interpersonal exchanges.<sup>19</sup> Since effective drugs for this disease have not yet been developed, it is important to reduce the number of risk

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factors through lifestyle modifications to include as many protective factors as possible.

According to previous studies,<sup>20</sup> the risk of dementia is halved in people who exercise more than three times a week, compared to the risk in those without exercise habits. Amyloid  $\beta$  can start accumulating in the brain more than 20 years before the onset of Alzheimer-type dementia, and exercise is known to prevent this type of accumulation.<sup>21</sup> Previous studies have shown that the maintenance of strong motor function can help reduce future risk of dementia at older age.<sup>22</sup> One previous study has suggested that the promotion of brain derived neurotrophic factor (BDNF) expression due to exercising inhibits cognitive decline.<sup>23</sup>

In terms of nutrition, recent studies have demonstrated the properties of certain food components that might potentially prevent cognitive impairment and dementia.<sup>17</sup> Among them, we focused on soy peptide, which is obtained by hydrolyzing soy protein isolate (SPI) with food processing enzymes. Soy peptide is classified as a functional food with diverse physiological functions attributed in the form of bioactive peptides that are rapidly absorbed from the small intestine.<sup>24</sup> One study demonstrated that daily supplementation with soy peptide improved cognitive abilities, including sustained attention and short- and long-term memory in healthy middle-aged and elderly adults.<sup>25</sup> In addition, the oral administration of soy peptide for 6 months has been reported to suppress age-related cognitive decline and result in an upregulation of BDNF expression in senescence-accelerated mouse brains.<sup>26</sup>

However, to our knowledge, the effect of a combination of exercise and soy peptide intake on cognitive function has not yet been investigated. To this aim, we compared the effects of an exercise program including cognitive training in combination with soy peptide intake and those of the exercise program alone on the cognitive function of community-dwelling older individuals.

## Materials and Methods

### Trial Design and Participants

This non-blind randomized controlled trial (RCT) compared the effects of a multicomponent exercise program (multiple forms of exercise combined with songs and cognitive training) supplemented with soy protein on cognitive function in elderly adults with the effects of the exercise program alone. The Ethics Committee of the Osaka Kawasaki Rehabilitation University (Reference

No. OKRU29-A021) approved the trial protocol and the trial was registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN000030404). Written informed consent for study participation was obtained from all the participants in accordance with the tenets of the Declaration of Helsinki, and no stipend was provided.

Participants included community-dwelling elderly adults living in Osaka, Japan. People aged 60 years or older who could independently perform the activities of daily living were enrolled. Those with collagen disease, depression, a history of cardiovascular disease, medical contraindications to exercise, and Parkinson's disease were excluded. Using a computerized 1:1 randomization scheme, the eligible participants ( $n = 74$ ) were assigned to the exercise (Ex) ( $n = 37$ ) or the exercise plus nutrition (Ex +Nt) groups ( $n = 37$ ).

### Interventions

#### Multicomponent Exercise

Multicomponent exercise sessions were conducted at the Kaizuka City Welfare Center. Participants engaged in a 15-min memory training and 45-min aerobic exercise session once a week for 3 months. As part of the memory training, participants were required to listen to a novel story and repeat its contents, and perform the dual tasks of clapping their hands in multiples of three and five while stepping on the spot. The aerobic exercise session included self-stretching for 10 min, followed by an aerobic exercise regimen of 15 min. This was followed by conditioning for 10 min such that the heart rate normalized. The aerobic exercise regimen included gymnastics using songs featuring the locally popular character "Tsugasan." Gymnastics were practiced on yoga mats (60 cm  $\times$  173 cm). The regimen included lower-limb steps, rhythmic exercises of the upper limbs, and deft movement of the fingers. Finally, mindfulness exercises were performed in the recumbent position for 10 min. All exercises were taught by two physical therapists and several staff volunteers.

#### Nutrition

A commercial drink (Peptide Athleeta 4000, Fuji Oil Co., Osaka, Japan) was used for soy peptide supplementation. Table 1 shows the nutrition facts label of Peptide Athleeta 4000. The net weight of Peptide Athleeta 4000 that contains 4 g soy peptide was 190 g.

**Table I** Nutrition Facts Label of Peptide Athleeta 4000

Total calories (kcal)	48
Protein (g)	4.4
Fat (g)	0
Carbohydrate (g)	8.9
Sodium (mg)	112
Valine (mg)	184
Leucine (mg)	300
Isoleucine (mg)	177
Soy peptide (mg)	4000

## Cognitive Status Measures

The Japanese language version of the Mini-Mental State Examination (MMSE) is widely used for the evaluation of cognitive function and cognitive impairment screening.<sup>27</sup> The MMSE score ranges from 0 to 30, with lower scores representing weaker cognitive function.

The trail making test (TMT)—a well-known psychomotor test<sup>28</sup>—was used to evaluate attentiveness. In Part A of the TMT, participants are instructed to draw lines to connect 25 encircled numbers distributed on a page. Part B of TMT is completed by alternately linking the sequential numbers and letters on a page. This provides information on an individual's cognitive flexibility.<sup>29</sup>

## Assessment of Body Composition

Physiological parameters measured using bioelectrical impedance analysis (InBody270; InBody, Tokyo, Japan) with 20 and 1000 kHz frequencies were obtained from the participants' electronic medical records.<sup>30</sup> Participants were instructed to grasp the handles of the analyzer and stand on electrodes contacting the lower surface of their feet while they were wearing normal indoor clothing without socks or shoes. The surface of the hand electrode was placed in contact with each of the five fingers, while the participants' heels and forefoot were placed on the circular foot electrode. Measurements were recorded within 30 sec by the staff. Participants were required to fast and avoid vigorous exercise for at least one hour before the assessment. Body mass index (BMI) was calculated by dividing the body weight (kg) by height squared ( $m^2$ ). The appendicular skeletal muscle index (SMI) was derived from the appendicular muscle mass (kg) divided by height squared ( $m^2$ ).

## Muscle Strength

Handgrip strength is a well-known measure of muscle strength and is significantly associated with whole-body muscle strength.<sup>31</sup> The maximum voluntary isometric strength of the

handgrip was measured with the dominant hand while in a standing position, by means of a hand dynamometer Grip-D (Takei, Niigata, Japan). Other bodily movements were not permitted.

## Gait Speed

Participants were instructed to walk 6.4 m (divided into two 2.0-m zones at each end and a 2.4-m middle-zone) at a speed they found comfortable.<sup>32</sup> The time needed (in sec) to pass the 2.4-m middle zone was measured for the calculation of gait speed (m/s). Participants could use a cane or walker if they were unable to perform the gait test independently. An average of five gait tests was used for evaluation.

## Geriatric Depression Scale 15

The Japanese version of the Geriatric Depression Scale 15 (GDS-15)<sup>33</sup> is a self-report evaluation. The scale comprises 15 items: 10 items confirm depression if the answers are positive, while the remaining 5 items confirm depression if the answers are negative. Normal scores range from 0–4, depending on factors such as age, education, and complaints; a score of 5–8 indicates mild depression, 9–11 moderate depression, and 12–15 severe depression. In this study, GDS-15 was measured with permission from the copyright holder.

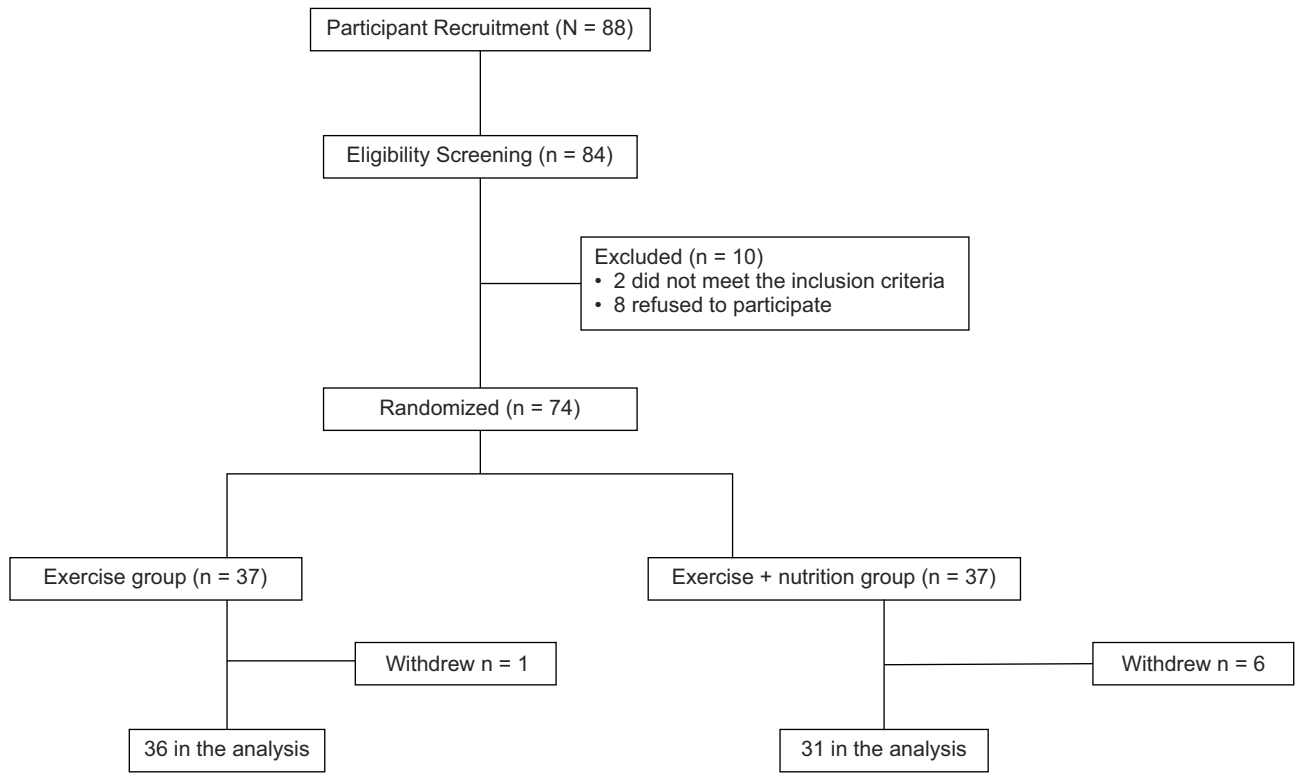
## Sample Size

To determine the sample size required for the detection of a significant interaction effect between intervention and time (pre/post), we performed a power calculation using the following parameters: a moderate effect size ( $f = 0.25$ ),  $\alpha$  error = 0.05,  $\beta$  error = 0.20. The required number of cases was 33 in each group. We estimated a 10% dropout rate, bringing the target number of participants to 37 per group.

## Statistical Analyses

Analysis of variance was used for within- and between-group comparisons of continuous variables and a chi-square test was used for between-group comparisons of categorical variables at baseline. In addition, the effect of each intervention on outcome measurements was analyzed using a mixed  $2 \times 2$  group (Ex, Ex+Nt group)  $\times$  time (pre, post) two-way analysis of variance (ANOVA).

In the sub-analysis, the sub-items of the MMSE—orientation time, orientation place, registration, attention and calculation, recall and language, and praxis—were analyzed separately in the Ex and Ex+Nt group using two-way ANOVA. All statistical analyses were performed



**Figure 1** A flowchart showing the distribution of participants the trial.

using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, New York).  $P < 0.05$  was considered to be statistically significant.

**Results**

Of the 74 individuals selected for the study, 67 (76.1%) completed the 3-month follow-up (Figure 1; Ex group: 36 [97.3%] and Ex + Nt group: 31 [83.8%]). The baseline characteristics of the participants were matched and found to be comparable (Table 2). The median relative adherence rate was 90% with nutritional supplementation. No health

problems, musculoskeletal complications, muscle pain, or fall incidents occurred during the study period.

Table 3 presents a comparison of the cognitive function and physical function test values before and after the intervention. The pre- and post-intervention group statistics and group-time interactions are shown in Table 3. Significant time-specific effects were observed for TMT-A, gait speed, grip strength, and SMI.

Table 4 presents the results of comparisons of MMSE total and subdivision changes in the Exercise and Exercise + Nutrition groups. There was a statistically significant interaction between time and group ( $p < 0.05$ ).

**Table 2** Baseline Characteristics of the Participants in the Two Groups

	Overall n=74			Exercise + Nutrition n=37			Exercise n=37			F-Value	P-Value
	Mean		SD	Mean		SD	Mean		SD		
Age	75.2	±	5.5	74.4	±	5.6	76.3	±	5.4	0.112	0.216
Height, cm	152.1	±	7.3	152.4	±	7.7	151.8	±	7.0	0.754	0.725
Weight, kg	53.8	±	9.4	53.1	±	9.2	54.5	±	9.5	0.513	0.514
BMI, kg/m <sup>2</sup>	23.2	±	3.1	22.8	±	2.9	23.6	±	3.2	0.360	0.273
Women, n %	61		82.4%	31		83.8%	30		81.1%		0.760

**Abbreviation:** BMI, body mass index.

**Table 3** Comparisons of Changes in Exercise and Exercise + Nutrition Groups

	Pre			Post			Two-Way ANOVA			
							Time Effect		Time × Group	
									Interaction	
	Mean		SD	Mean		SD	F-Value	P-Value	F-Value	P-Value
MMSE										
Exercise + Nutrition	28.3	±	1.8	28.8	±	1.4	0.93	0.339	1.66	0.20
Exercise	28.2	±	2.6	28.1	±	2.7				
TMT-A										
Exercise + Nutrition	98.4	±	26.4	88.1	±	22.9	15.65	<0.05*	0.04	0.85
Exercise	107.8	±	33.8	96.4	±	34.1				
TMT-B										
Exercise + Nutrition	142.2	±	74.3	146.6	±	47.3	0.10	0.75	0.86	0.36
Exercise	150.4	±	71.0	141.4	±	67.7				
Gait speed										
Exercise + Nutrition	1.24	±	0.2	1.32	±	0.2	32.84	<0.05*	2.37	0.13
Exercise	1.17	±	0.2	1.30	±	0.2				
Grip strength										
Exercise + Nutrition	21.7	±	5.7	24.0	±	5.0	56.28	<0.05*	0.27	0.61
Exercise	21.8	±	6.8	24.4	±	6.6				
SMI										
Exercise + Nutrition	5.76	±	0.8	5.87	±	0.9	8.90	<0.05*	0.00	0.9
Exercise	5.89	±	0.9	5.99	±	0.9				
GDS										
Exercise + Nutrition	3.52	±	2.4	3.16	±	2.7	0.11	0.74	0.59	0.44
Exercise	3.89	±	2.7	4.03	±	2.5				

Note: \*P < 0.05.

Abbreviations: MMSE, Mini-Mental State Examination; TMT, Trail Making Test; SMI, Skeletal mass index; GDS, Geriatric Depression Scale; SD, standard deviation.

## Discussion

There is no absolute method to prevent dementia. However, a healthy lifestyle that includes regular physical activity, cognitive activities, and a well-balanced diet reduces the risk of dementia.<sup>34</sup> Conventional exercise programs, such as those involving walking, have shown cognitive benefits in community-dwelling elderly people.<sup>35</sup> However, the beneficial effects of exercise cannot be experienced without continued participation.<sup>36</sup> In this study, therefore, we designed a multicomponent exercise program using songs featuring a locally popular character with cooperation from the local government to ensure a high rate of participation (final participation rate: 76.1%). Moreover, the program included a memory training session for the prevention of dementia. The 3-month multicomponent exercise intervention had beneficial effects on physiological function such as gait speed, grip strength, and on SMI in community-dwelling older adults.

In addition, 3-month multicomponent exercise intervention improved cognitive function as evidenced by the improved TMT-A, but not TMT-B. This result is consistent with those of a previous dance intervention study targeting mild cognitive impairment, in that the TMT-A score improved while the TMT-B score did not.<sup>37</sup> These results suggest a selective beneficial effect of exercise on cognitive function.

Soy peptide is generated by the enzymatic digestion of SPI. SPI has a Protein Digestibility Corrected Amino Acid Score of 1.0, the highest possible score.<sup>38</sup> This means that soy peptide derived from SPI has the ideal amino acid balance. Soy peptide ingestion can maintain and promote the synthesis and metabolism of noradrenaline in the brain.<sup>39</sup> Several studies have reported an alleviation of peripheral fatigue following its rapid absorption.<sup>24</sup> A recent clinical study also demonstrated the positive effects of soy peptide on brain function.<sup>40–42</sup> Furthermore, another study showed

**Table 4** Comparisons of MMSE Total and Subdivision Changes in Exercise and Exercise + Nutrition Groups

	Pre			Post			Two-Way ANOVA			
							Time Effect		Time × Group	
									Interaction	
	Mean		SD	Mean		SD	F-Value	P-Value	F-Value	P-Value
Orientation Time										
Exercise + Nutrition	4.81	±	0.5	4.9	±	0.3	0.07	0.79	2.23	0.14
Exercise	4.89	±	0.4	4.75	±	0.7				
Orientation Place										
Exercise + Nutrition	4.97	±	0.2	4.9	±	0.3	0.01	0.94	0.88	0.35
Exercise	4.78	±	0.5	4.83	±	0.6				
Registration										
Exercise + Nutrition	3	±	0	3	±	0	0.86	0.36	0.86	0.36
Exercise	2.92	±	0.5	3	±	0				
Calculation										
Exercise + Nutrition	3.84	±	1.4	4.42	±	1.2	3.29	0.06	<b>3.99</b>	<b>&lt;0.05*</b>
Exercise	4.11	±	1.4	4.14	±	1.6				
Recall										
Exercise + Nutrition	2.88	±	0.34	2.87	±	0.43	2.26	0.14	1.16	0.29
Exercise	2.75	±	0.6	2.61	±	0.8				
Language and Praxis										
Exercise + Nutrition	8.77	±	0.5	8.74	±	0.4	0.02	0.88	0.31	0.58
Exercise	8.7	±	0.7	8.75	±	0.55				
Total										
Exercise + Nutrition	28.26	±	1.8	28.84	±	1.44	0.93	0.34	1.66	0.20
Exercise	28.16	±	2.61	28.08	±	2.68				

Notes: \*P < 0.05. Bold indicates only one interaction.

that a soy peptide diet suppressed age-related cognitive decline via the upregulation of BDNF in a mouse model with accelerated senescence.<sup>26</sup> Therefore, we focused on soy peptide as the nutrition of choice combined with multi-component exercise.

The 3-month soy peptide supplemented with exercise intervention showed a significant effect on calculation function compared with exercise alone. Previous research indicates that exercise and soy peptide intake for 2 weeks in young people improved their computational ability.<sup>43</sup> In this study, the interaction of time and group for the computational ability was not observed, but the significant beneficial effect for the total score change combined with the recall ability was recognized in soy intake group. Previous research indicates that there is no relationship between typical soy isoflavone intake and the maintenance of cognitive function.<sup>44</sup> However, in this study, it is speculated that an increase in soy intake compared to typical use

concentrated on a three-month period had an effect on calculation improvement.

It has been demonstrated that physical exercise increases BDNF levels.<sup>45</sup> Thus, the synergistic effect of soy and exercise shown in our study might be due to increased BDNF levels that promote several aspects of brain function. In addition, we predicted a synergistic effect of soy and the multicomponent intervention on physical performance and skeletal muscle mass given that one previous report demonstrates that soy peptide intake after exercising enhances the levels of serum growth hormone involved in muscle synthesis.<sup>46</sup> However, those synergistic effects were not observed in this study.

The present study has some limitations. First, we did not record the dietary intake of liquids. There may have been changes in dietary intake owing to the consumption of the nutritional supplement. Second, the participants

were of Japanese nationality and, hence, caution must be exercised while generalizing the study's results to other ethnic groups. Finally, the persistence of the effects of exercise and nutrition remains unclear. Further studies are also needed to measure serum levels of soybean peptide-derived substances in patients to explain the physiological outcomes better. Future interventional trials using soy supplementation in different populations and over longer periods of time have been scheduled.

## Conclusions

In summary, this non-blinded controlled trial showed that participation in a three-month weekly program comprising multicomponent exercise both alone and with the addition of soy peptide supplementation effectively improved a portion of cognitive performance and physical function in elderly adults. A combination of exercise and nutrition may be effective in improving calculation function in such populations.

## Research Ethics and Informed Consent

The Ethics Committee of the Osaka Kawasaki Rehabilitation University (Reference No. OKRU29-A021) approved the trial protocol and the trial was registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN000030404). Written informed consent for study participation was obtained from all the participants in accordance with the tenets of the Declaration of Helsinki, and no stipend was provided.

## Data Sharing Statement

The datasets available from the corresponding author on reasonable request.

## Acknowledgment

The authors would like to thank Ms Kanako Kodama, Ms Masako Kawano, Ms Saeko Araki, Ms Kaori Hamamura, and senior volunteer staff for their contributions to data collection.

## Author Contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

## Funding

This work was supported by the Fuji Oil Co., Ltd. and Osaka gas Co., Ltd. The sponsors had no control over the interpretation, writing, or publication of this work.

## Disclosure

M Maebuchi and M Ibuki are employees of Fuji Oil Co. Ltd., which produces Peptide Athleeta 4000. The authors report no other conflicts of interest in this work.

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