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# Association between exercise habits and subcortical gray matter volumes in healthy elderly people: A population-based study in Japan

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ABSTRACT

*Background and aims:* The relationship between exercise and subcortical gray matter volume is not well understood in the elderly population, although reports indicate that exercise may prevent cortical gray matter atrophy. To elucidate this association in the elderly, we measured subcortical gray matter volume and correlated this with volumes to exercise habits in a community-based cohort study in Japan.
*Methods:* Subjects without mild cognitive impairment or dementia ($n = 280$, 35% male, mean age 73.1 ± 5.9 years) were evaluated using the Mini-Mental State Examination (MMSE), an exercise habit questionnaire, and brain magnetic resonance imaging. Subcortical gray matter volume was compared between groups based on the presence/absence of exercise habits. The MMSE was re-administered 3 years after the baseline examination.
*Results:* Ninety-one subjects (32.5%) reported exercise habits (exercise group), and 189 subjects (67.5%) reported no exercise habits (non-exercise group). Volumetric analysis revealed that the volumes in the exercise group were greater in the left hippocampus ($p = 0.042$) and bilateral nucleus accumbens (left, $p = 0.047$; right, $p = 0.007$) compared to those of the non-exercise group. Among the 195 subjects who received a follow-up MMSE examination, the normalized intra-cranial volumes of the left nucleus accumbens ($p = 0.004$) and right amygdala ($p = 0.014$)showed significant association with a decline in the follow-up MMSE score.
*Conclusion:* Subjects with exercise habits show larger subcortical gray matter volumes than subjects without exercise habits in community-dwelling elderly subjects in Japan. Specifically, the volume of the nucleus accumbens correlates with both exercise habits and cognitive preservation.

## 1. Introduction

Exercise and/or physical fitness may be protective against the development of dementia. A number of studies that examined the effects of exercise in elderly people with or without dementia have been summarized by meta-analyses [1–5]. These meta-analyses showed that aerobic exercise training is associated with modest improvements in cognitive function such as attention, processing speed, executive function and memory. Based on studies using animal models and human subjects, several hypotheses have been proposed to describe the mechanisms behind the beneficial effects of exercise on cognition; these include a reduction in oxidative stress [6], an increase in growth factor levels (e.g., brain-derived neurotrophic factor, insulin-like growth factor, and vascular endothelial growth factor) [7–10], and reduced levels of amyloid-β (Aβ), a key pathogenic factor in Alzheimer's disease (AD) [11].

In regard to brain volume, several studies of elderly subjects revealed that exercise intervention for 6 to 12 months increased gray matter volumes in the hippocampus and the prefrontal and anterior cingulate cortices [7,8,12]. However, few studies have examined the relationship between subcortical gray matter volume and exercise habits. In this study, we examined the association between exercise habits and

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subcortical gray matter volume in healthy elderly subjects in a population-based cohort study in Japan.

## 2. Methods

### 2.1. Subjects

The subjects included in this study were a sub-population of those from the Ama-cho study, a population-based cohort study of individuals aged 65 years or older in Japan. A detailed account of the Ama-cho study has been described previously [13]. The subject inclusion criteria for the present study were as follows: (1) no indications of dementia, or mild cognitive impairment (MCI) at baseline; (2) underwent brain magnetic resonance imaging (MRI); (3) answered questionnaires that included information on exercise habits; (4) received a neuropsychological examination by a neurologist or clinical psychologist. The exclusion criteria for the study subjects were as follows: (1) a Clinical Dementia Rating (CDR) score of 0.5 or more or (2) a medical history of head trauma, brain tumor, stroke, neurological disease, or psychiatric illness.

The study was approved by the Committee for Medical Research Ethics at Tottori University, and followed the principles outlined in the Declaration of Helsinki. All participants provided written informed consent to participate in the study.

### 2.2. Demographics and medical history

Information on education level, medical history of hypertension, hyperlipidemia, diabetes mellitus, alcohol consumption and/or smoking, and exercise habits were obtained from a self-administered questionnaire and a review of electronic databases in the healthcare system. Blood pressure (BP) was assessed during medical examinations by neurologists [14]. High-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and 1,5-anhydroglucitol (1,5-AG) were measured for this investigation [15].

### 2.3. Assessment of cognitive function, motor function, and mood

Cognitive function was assessed using the Mini-Mental State Examination (MMSE) [16], and the CDR [17]. Motor function was assessed using an abbreviated (10-item) version of the motor portion of the Unified Parkinson's Disease Rating Scale (modified UPDRS) [14]. Depressed mood was assessed using the Japanese version of the Geriatric Depression Scale (GDS) with 15 questions [18,19].

A diagnosis of dementia or MCI was determined by neurologists [19] according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition revised (DSM-IV) [20] and the International Working Group on MCI criteria, respectively [21].

### 2.4. Definition of exercise habits

We used the definition of exercise habits published by the Minister of Health, Labor and Welfare in Japan (http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/kenkou/kenkenkounip21.html). The exercise habits criteria were as follows: (1) >30 min; (2) more than twice a week; (3) maintained for >1 year.

### 2.5. Brain MRI

Brain MRI was performed between March and May 2010 using a 1.5 Tesla scanner (Gyroscan Intera; Philips Electronics Japan, Tokyo, Japan) with a multi-channel head coil system. A sagittal volumetric magnetization-prepared rapid gradient echo sequence was used to acquire a three-dimensional T1-weighted image with the following parameters: repetition time/echo time/inversion time (TR/TE/TI), 8.5/4/1000 ms; flip angle, 8°; 240 mm field of view; 192 × 192 acquisition; 256 × 256 reconstruction matrix; and a 1.2 mm slice thickness. Axial proton-density (TR/TE, 3000/12 ms) and T2-weighted (TR/TE, 3000/96 ms) images were also acquired for diagnostic purposes. This scanning protocol followed the MRI methods used in the Alzheimer's Disease Neuroimaging Initiative (ADNI) [22].

### 2.6. Survey procedure

The baseline study was conducted from 2008 to 2010 and the follow-up study was conducted from 2011 to 2013. During the baseline study, we collected personal and demographic information, and administered the MMSE, the GDS, and brain MRI. The MMSE was re-evaluated during the follow-up study.

### 2.7. Subcortical segmentation using the FMRIB's Integrated Registration and Segmentation Tool (FIRST)

Fourteen subcortical gray matter regions (bilateral nucleus accumbens, amygdala, caudate nucleus, hippocampus, pallidum, putamen and thalamus) were automatically segmented using the FMRIB's Integrated Registration and Segmentation Tool (FIRST) [23], and their volumes were calculated using the functions of the FMRIB Software Library (FSL) package [24] (Fig. 1). For each subject, the subcortical gray matter volumes were divided by the intra-cranial volume (ICV) for normalization to the individual's head size. The ICV was calculated by summing the segmented gray/white matter and cerebrospinal fluid (CSF) volume output using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/) implemented in the SPM8 software package (http://fil.ion.ucl.ac.uk/spm), running under a MATLAB environment (version 8.0; MathWorks, Natick, MA, USA).

### 2.8. Statistical analyses

Differences in demographic and clinical variables, MMSE scores, and GDS scores between the groups were analyzed using Student's *t*-tests or a chi-square test. A paired Student's *t*-test was used to analyze differences between the baseline and follow-up MMSE scores for each group. Multiple regression analyses, including age, sex and education level as covariates, were used to examine the effects of exercise habits on the ICV-normalized subcortical gray matter volumes, and to evaluate the relationship between changes in MMSE score (ΔMMSE) and subcortical gray matter volumes. The ΔMMSE value was obtained by subtracting the baseline MMSE score from the follow-up MMSE score. Also, medical history or demographics variables that showed a tendency toward significance ($p < 0.05$) in the univariate analysis were entered as explanatory variables in the logistic regression model. The Statistical Package for the Social Sciences (SPSS) program version 20.0 (release 20; Tokyo, Japan) was used for all data analyses.

## 3. Results

### 3.1. Study flow chart

Fig. 2 shows a flow chart of the number of subject involved in this study. The total number of residents (aged 65 years or older) in the town was 924, which represented 38.0% of the total population at baseline. Twenty-four subjects were deceased or had moved outside of the town at the start of the investigation. Therefore, 900 individuals were considered eligible for the study. Among the 900 subjects, 689 (76.6%) underwent brain MRI, and 390 subjects (43.3%) were judged to be cognitively healthy without a diagnosis of dementia or MCI. One hundred and ten subjects were subsequently excluded from the analysis based on the inclusion/exclusion criteria, a lack of answers pertaining to exercise habits, or poor quality MR images. Thus, 280 subjects (31.1% of the eligible residents and 71.8% of the 390 cognitively healthy subjects) were selected for this study. The 110 subjects excluded from the study

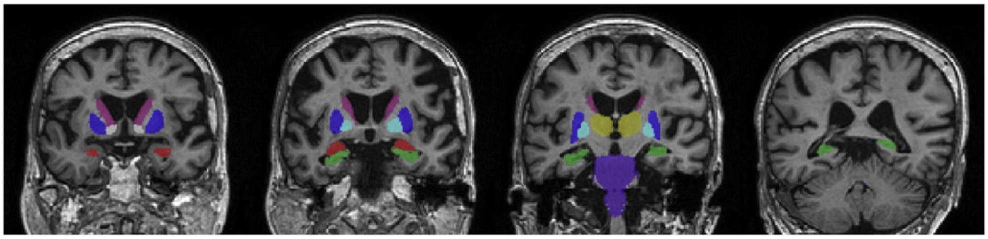

**Fig. 1.** The FMRIB's Integrated Registration and Segmentation Tool (FIRST) segmentations of the subcortical gray matter. Each region is shown as indicated in the brain reconstruction; bilateral hippocampus (green), nucleus accumbens (white), thalamus (yellow), caudate nucleus (pink), putamen (blue), globus pallidus (light blue), and amygdala (red). The brain stem including cerebral aqueduct (violet) was not included in the analysis.

had a greater proportion of males and were older than the 280 subjects selected for the study. Education levels were similar between the included and excluded subjects. At the follow-up study conducted 3 years after the baseline study, 195 of the 280 subjects were re-administered the MMSE.

### *3.2. Exercise habits and subcortical gray matter volume*

Ninety-one subjects (32.5%) had exercise habits (exercise group), and 189 subjects (67.5%) did not (non-exercise group). The exercise group was characterized by a higher proportion of males, younger age,

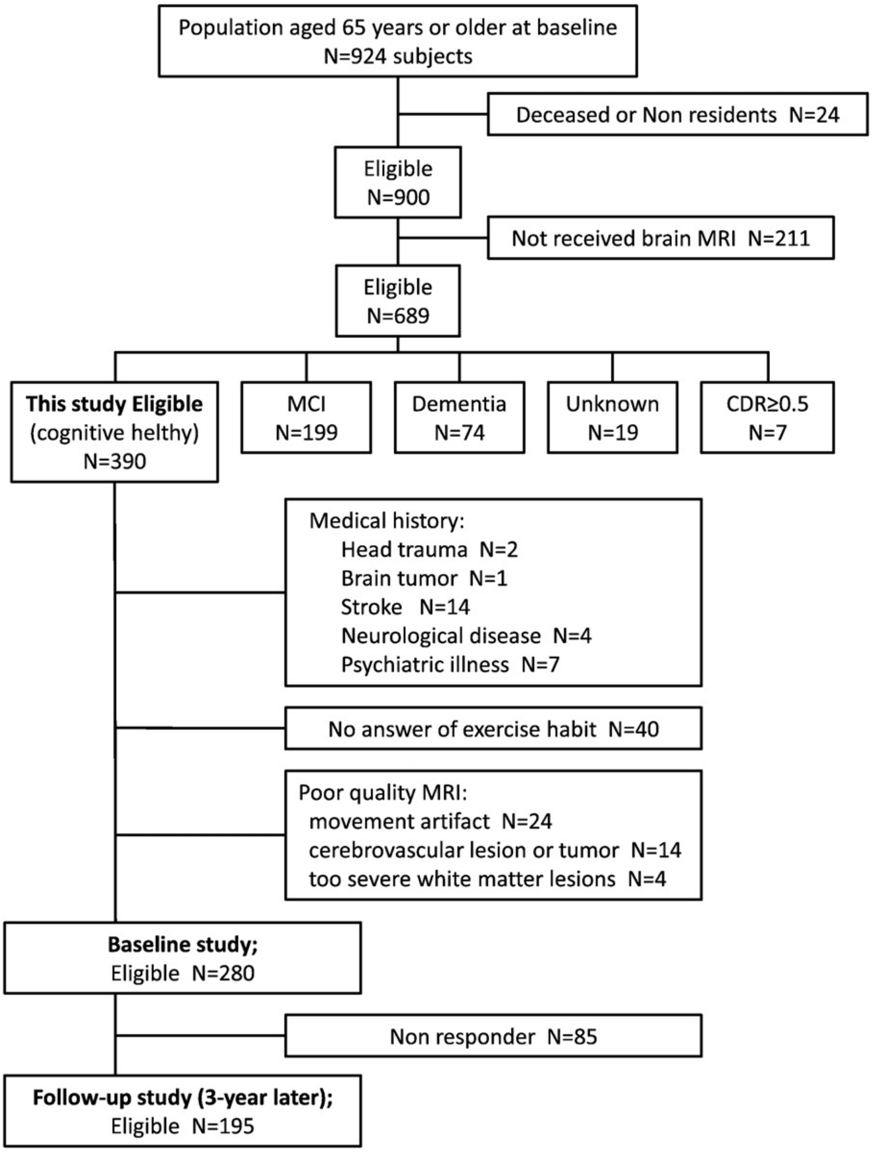

**Fig. 2.** Flow chart of the study.

**Table 1**
Characteristics of the subjects.

| | Non-exercise group (N=189) | Exercise group (N=91) | p value |
|---|---|---|---|
| Sex (male) | 30.7 | 44.0 | 0.033 |
| Age, y | 73.5 (6.1) | 72.1 (5.4) | 0.047 |
| Education, y | 10.1 (1.9) | 10.5 (2.3) | 0.126 |
| Baseline MMSE score | 28.3 (1.3) ┐ # | 28.2 (1.4) ┐ | 0.446 |
| Follow-up MMSE score* | 27.7 (2.7) ┘ | 28.4 (1.4) ┘ | 0.014 |
| modified UPDRS score | 1.4 (0.6) | 0.9 (0.3) | 0.062 |
| GDS score | 2.8 (2.6) | 1.8 (2.3) | 0.002 |
| Alcohol consumption | 32.6 | 43.2 | 0.103 |
| Smoking | 23.1 | 33.0 | 0.103 |
| Hypertension | 67.4 | 52.7 | 0.024 |
| Hyperlipidemia | 30.5 | 23.1 | 0.255 |
| Diabate melitus | 12.3 | 17.6 | 0.270 |
| sBP, mm Hg | 140.2 (17.5) | 143.8 (14.3) | 0.110 |
| dBP, mm Hg | 78.1 (9.9) | 79.6 (8.7) | 0.268 |
| HDL-C, mg/dl | 57.4 (12.7) | 57.1 (14.3) | 0.859 |
| LDL-C, mg/dl | 149.8 (102.8) | 175.3 (135.7) | 0.117 |
| TG, mg/dl | 101.8 (29.2) | 99.8 (30.2) | 0.591 |
| 1,5AG, μg/ml, male | 21.3 (10.2) | 21.2 (9.8) | 0.966 |
| female | 21.2 (8.3) | 20.7 (8.9) | 0.772 |

Value are % or mean (SD). Abbreviations: y; years, MMSE; Mini-Mental State Examination, mUPDRS; motor portion of the Unified Parkinson's Disease Rating Scale, GDS; Geriatric Depression Scale, sBP; systolic blood pressure, dBP; diastolic blood pressure, HDL-C; high-density lipoprotein cholesterol, LDL-C; low-density lipoprotein cholesterol, TG; triglycerides, 1,5AG; 1,5-anhydroglucitol. *Non-exercise group; N=127, Exercise group; N=68. #$p<0.005$ by a paired Student's t-test.

lower GDS score, and lower proportion of hypertension (Table 1). The baseline MMSE scores and modified UPDRS scores were similar between the two groups. Fig. 3 shows the ICV-normalized subcortical gray matter volumes of each brain region for each group. Multiple regression analysis, adjusted for age, sex and education level showed that exercise habits were significantly associated with larger volumes in the ICV-normalized left hippocampus ($p = 0.036$) and bilateral nucleus accumbens (left, $p = 0.047$; right, $p = 0.006$; Table 2). Furthermore, the inclusion of hypertension as a covariate factor did not affect, the outcome of the results ($p = 0.031$, $p = 0.042$, and $p = 0.007$, respectively).

### *3.3. Cognitive decline and subcortical gray matter volume*

The follow-up MMSE score was higher in the exercise group compared to the non-exercise group. Paired Student's *t*-tests showed that the follow-up MMSE score had declined from the baseline score in the non-exercise group ($p = 0.004$), while in the exercise group the MMSE score was unchanged ($p = 0.798$). Multiple regression analyses, adjusted for age and sex, revealed that cognitive decline represented by ΔMMSE was associated with smaller ICV-normalized volumes in the left nucleus accumbens ($p = 0.004$) and right amygdala ($p = 0.014$; Table 3).

## 4. Discussion

The main findings of this study are summarized below. (1) Although there was no difference in the baseline MMSE score between the exercise group and the non-exercise group, the follow-up MMSE score only showed a decline in the non-exercise group. (2) At baseline, the ICV-normalized volumes of the left hippocampus and bilateral nucleus accumbens were significantly larger in the exercise group compared to the non-exercise group. (3) Both the left nucleus accumbens and the right amygdala were shown to be associated with cognitive decline.

Similar to previous reports [1–4], our study suggests that exercise has a positive impact on cognitive function in elderly subjects. Given that we did not obtain detailed information, such as the subjects' level of physical fitness, type, frequency, or intensity of the exercise performed, our findings regarding the effects of exercise habits on cognition may seem limited. However, the MMSE score was maintained over time and did not show a decline in the exercise group. Therefore, good exercise habits may exert a positive and meaningful effect on cognitive function despite variations in the details of the specific exercises performed.

The exercise group had larger subcortical gray matter volumes at baseline. There are only a few reports on the relationship between exercise and subcortical gray matter volume. Two reports have shown that physical fitness is positively correlated with subcortical gray matter volumes, specifically, the caudate nucleus and the nucleus accumbens in elderly subjects [25] and the dorsal striatum in children [26]. Similar to previous studies, we found a relationship between good exercise habits and subcortical gray matter volumes. In particular, the bilateral volume of the nucleus accumbens was larger in the exercise group. Our results also suggest that a larger nucleus accumbens volume may prevent future cognitive decline in healthy elderly individuals.

The nucleus accumbens receives information from a variety of systems, such as the hippocampus, basolateral amygdala, and prefrontal cortex, which are associated with information processing, reward value, selective attention, and flexibility [27,28]. Recent studies have reported on the role of the nucleus accumbens in dementia and MCI. For example, cross-sectional studies showed that the MMSE score is related to the volume of the nucleus accumbens in patients with AD [29], and that the nucleus accumbens volume is smaller in subjects with MCI than in subjects with normal cognition [30]. Furthermore, longitudinal studies showed that the nucleus accumbens is reduced in size when examined several years after the development of AD in comparison to its size prior to the onset of AD [31,32]. The nucleus accumbens is also significantly smaller in patients with stable or progressive MCI than in healthy controls [33]. Yi et al. reported that a smaller nucleus accumbens volume is associated with an increased risk of progression from MCI to AD, as evidenced by Cox proportional hazards analysis [30]. Combined, these studies demonstrate an association between the volume of the nucleus accumbens and cognitive function or cognitive decline in patients with MCI as well as AD.

Our present study suggests that nucleus accumbens volume may correlate with cognition in elderly subjects, even if cognitive function is normal (i.e., in the absence of dementia or MCI). The MR images were acquired cross-sectionally in this study, therefore, it is unclear whether the small brain volumes observed are indicative of brain atrophy. If it is assumed that small brain volumes are related to brain atrophy in elderly subjects, the small volume of the nucleus accumbens may indicate that atrophy of this region occurs prior to the observance of MCI.

We analyzed our data using a validated automated algorithm. We attempted to further increase the accuracy of our analyses by examining each MR image and excluding those with artifacts, large white matter lesions, or structural changes (e.g., micro-cerebral infarction). In general, it is difficult to determine whether a reduced nucleus accumbens is due to age or pathological changes [34]. However, this study was designed to eliminate the influence of age.

The study design did not, however, elucidate a causal relationship, and it remains unclear whether exercise itself protected the volume of the nucleus accumbens or if subjects with greater nucleus accumbens volume tended to maintain exercise later in life. Future longitudinal

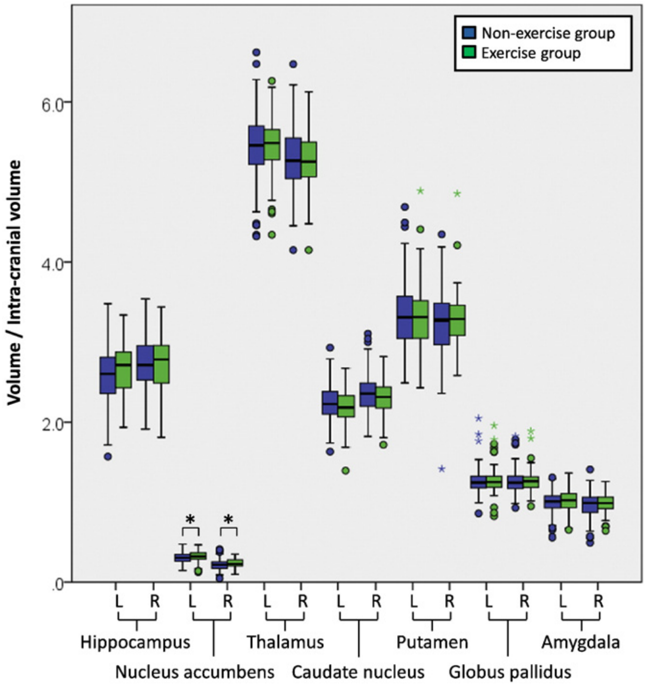

**Fig. 3.** Intracranial-volume-normalized volume of 7 left or right subcortical structures in the non-exercise group (green box) and the exercise group (blue box). Univariate regression analysis showed that the non-exercise group was significantly associated with a smaller bilateral nucleus accumbens volume (*$p < 0.05$). The box plots show the median value (thick line), the 25th percentile (lower line) and the 75th percentile (upper line). T-bars indicate the 10th and 90th percentile. Abbreviations: L, left; R, right.

studies are necessary to clarify the relationships between nucleus accumbens volume, exercise, and cognition.

## 5. Conclusion

The results of our population-based study of elderly Japanese subjects suggest that subjects with exercise habits have a greater volume of subcortical gray matter in the left hippocampus and bilateral nucleus accumbens than subjects lacking exercise habits. In addition, our results suggest that the left nucleus accumbens and right amygdala maybe predictive of future cognitive decline. Although further study is needed in order to better understand this relationship, the nucleus accumbens is considered to be a key structure involved in the prevention of dementia.

**Table 3**
Multiple regression of ΔMMSE and subcortical gray matter volumes adjusting age, sex and education level subcortical gray matter volumes; mean (SD) (%).

| Region | SB (95% CI) | p value |
|---|---|---|
| Lt. hippocampus | 0.104 (−0.386–1.824) | 0.201 |
| Rt. hippocampus | 0.101 (−0.417–1.834) | 0.216 |
| Lt. nucleus accumbens | 0.240 (2.799–14.088) | 0.004 |
| Rt. nucleus accumbens | 0.151 (−0.234–11.729) | 0.060 |
| Lt. thalamus | 0.017 (−0.890–1.103) | 0.833 |
| Rt. thalamus | 0.040 (−0.759–1.272) | 0.619 |
| Lt. caudate nucleus | 0.064 (−0.845–2.236) | 0.374 |
| Rt. caudate nucleus | −0.015 (−1.651–1.333) | 0.834 |
| Lt. putamen | −0.050 (−1.280–0.635) | 0.507 |
| Rt. putamen | −0.063 (−1.422–0.584) | 0.411 |
| Lt. globus pallidus | 0.019 (−2.092–2.743) | 0.791 |
| Rt. globus pallidus | −0.026 (−2.959–2.075) | 0.730 |
| Lt. amygdala | 0.044 (−1.800–3.335) | 0.556 |
| Rt. amygdala | 0.184 (0.680–6.081) | 0.014 |

Abbreviations: Lt.; left side, Rt.; right side, SB; standardized coefficient (β) of exercise habits, CI; confidence interval, ΔMMSE; Mini-Mental State Examination score change (a value obtained by subtracting the baseline MMSE score from the follow-up MMSE score).

## Competing interest statement

Drs. Yamamoto, Yamashita, Nakashita, Kishi, Tanaka, and Yamawaki have no conflicts of interest to declare.

Dr. Wada-Isoe has received honoraria for speaking engagements with DAIICHI SANKYO, Janssen Pharmaceuticals, Eisai, Takeda Pharma Corporation, ONO PHARMACEUTICAL, FUJIFILM RI Pharma, and Novartis Pharmaceuticals.

Dr. Nakashima has received honoraria for speaking engagements and research grants from TEIJIN Pharma TEIJIN PHARMA, DAIICHISANKYO, Eisai, GlaxoSmithKline K·K, ONO PHARMACEIUTICAL, Takeda Pharma Corporation, Otsuka Pharmaceutical, Mitsubishi Tanabe Pharma Corporation, Kyowa Hakko Kirin, FUJIFILM, Sumitomo Dainippon Pharma, Bayer Yakuhin, Boehringer Ingelheim, Japan Blood Products Organization, and the FP Pharmaceutical Corporation.

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**Table 2**
Multiple regression of subcortical gray matter volumes and exercise habits.

| Region | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|
| | SB (95% CI) | p value | SB (95% CI) | p value | SB (95% CI) | p value |
| Lt. hippocampus | 0.107 (−0.007–0.161) | 0.074 | 0.113 (0.006–0.157) | 0.036 | 0.118 (0.008–0.161) | 0.031 |
| Rt. hippocampus | 0.037 (−0.057–0.109) | 0.538 | 0.045 (−0.042–0.106) | 0.398 | 0.057 (−0.035–0.115) | 0.292 |
| Lt. nucleus accumbens | 0.122 (0.001–0.035) | 0.042 | 0.105 (0.000–0.031) | 0.047 | 0.108 (0.001–0.031) | 0.042 |
| Rt. nucleus accumbens | 0.156 (0.005–0.035) | 0.009 | 0.148 (0.006–0.033) | 0.006 | 0.147 (0.005–0.033) | 0.007 |
| Lt. thalamus | −0.001 (−0.095–0.093) | 0.983 | 0.036 (−0.058–0.114) | 0.520 | 0.043 (−0.053–0.121) | 0.444 |
| Rt. thalamus | −0.018 (−0.106–0.078) | 0.764 | 0.018 (−0.070–0.098) | 0.748 | 0.022 (−0.068–0.102) | 0.691 |
| Lt. caudate nucleus | −0.098 (−0.103–0.009) | 0.100 | −0.089 (−0.100–0.015) | 0.146 | −0.079 (−0.096–0.020) | 0.200 |
| Rt. caudate nucleus | −0.096 (−0.109–0.011) | 0.107 | −0.076 (−0.100–0.022) | 0.209 | −0.067 (−0.095–0.027) | 0.277 |
| Lt. putamen | 0.004 (−0.093–0.099) | 0.949 | 0.006 (−0.089–0.099) | 0.918 | 0.023 (−0.076–0.112) | 0.704 |
| Rt. putamen | 0.027 (−0.068–0.108) | 0.651 | 0.024 (−0.067–0.103) | 0.678 | 0.044 (−0.052–0.117) | 0.448 |
| Lt. globus pallidus | 0.065 (−0.017–0.058) | 0.281 | 0.095 (−0.007–0.067) | 0.108 | 0.102 (−0.005–0.070) | 0.089 |
| Rt. globus pallidus | 0.042 (−0.022–0.047) | 0.704 | 0.056 (−0.017–0.050) | 0.340 | 0.061 (−0.016–0.052) | 0.303 |
| Lt. amygdala | 0.049 (−0.020–0.048) | 0.414 | 0.043 (−0.020–0.044) | 0.461 | 0.038 (−0.022–0.043) | 0.515 |
| Rt. amygdala | 0.041 (−0.022–0.046) | 0.492 | 0.033 (−0.023–0.043) | 0.565 | 0.040 (−0.022–0.045) | 0.492 |

Model 1; crude model, Model 2; adjusted for age, sex and education level, Model 3; adjusted for age, sex, education level and hypertension. Subcortical gray matter volumes; mean (SD) (%). Abbreviations: Lt.; left side, Rt.; right side, SB; standardized coefficient (β) of exercise habits, CI; confidence interval.

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