Relationship between Physical Activity and Brain Atrophy Progression

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ABSTRACT

YUKI, A., S. LEE, H. KIM, R. KOZAKAI, F. ANDO, and H. SHIMOKATA. Relationship between Physical Activity and Brain Atrophy Progression. *Med. Sci. Sports Exerc.*, Vol. 44, No. 12, pp. 2362–2368, 2012. **Introduction**: Brain atrophy is associated with impairment in cognitive function and learning function. The aim of this study was to determine whether daily physical activity prevents age-related brain atrophy progression. **Methods**: The participants were 381 men and 393 women who had participated in both the baseline and the follow-up surveys (mean duration = 8.2 yr). Magnetic resonance imaging of the frontal and temporal lobes was performed at the time of the baseline and follow-up surveys. The daily physical activities and total energy expenditures of the participants were recorded at baseline with uniaxial accelerometry sensors. Multiple logistic regression models were fit to determine the association between activity energy expenditure, number of steps, and total energy expenditure variables and frontal and temporal lobe atrophy progression while controlling for possible confounders. **Results**: In male participants, the odds ratio of frontal lobe atrophy progression for the fifth quintile compared with the first quintile in activity energy expenditure was 3.408 (95% confidence interval = 1.205–9.643) and for the number of steps was 3.651 (95% confidence interval = 1.304–10.219). Men and women with low total energy expenditure were at risk for frontal lobe atrophy progression. There were no significant differences between temporal lobe atrophy progression and physical activity or total energy expenditure. **Conclusion**: The results indicate that physical activity and total energy expenditure are significant predictors of frontal lobe atrophy progression during an 8-yr period. Promoting participation in activities may be beneficial for attenuating age-related frontal lobe atrophy and for preventing dementia.
Key Words: LONGITUDINAL STUDY, MIDDLE AGED AND ELDERLY, ACCELEROMETRY SENSORS, MRI

Atrophy of brain structures is associated with impairment in cognitive function and learning function (the extreme case is Alzheimer disease) (21). Brain atrophy progresses with aging (17). The gray matter volume decreases by approximately 15%, from the 20s through the 70s (38). A previous study reported that a decline in cognitive function is associated with the progression rate of brain atrophy for 6 yr in normal elderly people (33). Thus, preventing brain atrophy may be a promising strategy for preventing cognitive impairment and decline.

Physical exercise appears to induce neurogenesis in the brain not only in animals but also in humans (11). The practice of juggling for 3 months increases the volume of gray matter in the bilateral midtemporal area and in the left posterior intraparietal sulcus in young people (10). Similarly, the increase in brain volume in the anterior cingulate gyrus and frontal pole caused by juggling occurs in elderly people (3). In particular, aerobic exercise appears to suppress global and regional brain atrophy to effectively increase brain volume (14). Relatively little brain structural atrophy is seen in elderly people with high aerobic capacity (7). Six months of aerobic exercise increases the volume of the frontal lobe, temporal lobe, and hippocampus (8). Aerobic capacity is correlated with the preservation of gray matter in the medial–temporal, parietal, and frontal areas in elderly people (18). Aerobic quick-step walking suppresses hippocampal atrophy and improves cognitive function in elderly people (15). These reports suggest the possibility that aerobic exercise prevents brain atrophy.

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We hypothesized that brain atrophy progression can be prevented in middle-age and elderly people with a high level of daily physical activity. Daily physical activities are correlated with aerobic capacity in middle-age and elderly people (2,6). In cross-sectional studies, high physical activity levels are related to larger superior frontal volumes (5). Increased physical activity is associated with greater average brain tissue volumes in the white matter of the corona radiata, extending into the parietal–occipital junction (19). Although daily physical activities may prevent brain atrophy progression, there has been no specific longitudinal analysis showing that daily physical activity maintained at a high level prevents brain atrophy. Recent longitudinal studies have reported that elderly people with high levels of daily physical activity have a low risk of decline in cognitive function (26,34). A demonstration of the prevention of brain atrophy progression by high levels of physical activity in a longitudinal study may support the association between daily physical activity and cognitive function.

The aim of this study was to determine whether high levels of daily physical activity prevent brain atrophy progression with aging. We assessed the progression of frontal and temporal lobe atrophy with aging using 8-yr follow-up surveys and magnetic resonance imaging (MRI) of middle-age and elderly people. We also recorded the amount of physical activity (activity energy expenditure and number of steps) and total energy expenditure using a uniaxial accelerometry sensor. We evaluated the association between brain atrophy progression and daily physical activity and total energy expenditure in 774 community-living, middle-age, and elderly Japanese people using longitudinal analysis.

METHODS

Participants. The participants in this study were derived from the National Institute for Longevity Sciences, Longitudinal Study of Aging (NILS-LSA), which involves ongoing population-based biennial examinations of a cohort of approximately 2300 persons. The participants in the NILS-LSA were randomly selected from resident registrations and stratified by both decade of age and sex. The NILS-LSA is a comprehensive and interdisciplinary study to observe age-related changes and consists of various gerontological and geriatric measurements, including medical examinations, blood chemical analysis, body composition, anthropometry, nutritional analysis, psychological tests, physical function, and physical activity. Details of the NILS-LSA have been described elsewhere (35).

The baseline participants of this study were 1526 middle-age and elderly people (773 men and 753 women) who completed the second wave examinations of NILS-LSA between April 2000 and May 2002. Of these, 942 (61.6%, 481 men and 461 women) participated in the 8-yr follow-up surveys (NILS-LSA sixth wave examination from July 2008 to July 2010). The dropouts were 584 participants (292 men and 292 women). In male and female participants, the age at baseline of the dropouts was significantly higher than that of the participants who completed both examinations (*t*-test, $P < 0.0001$). In male participants, the ratios of stroke and ischemic heart disease histories in dropouts were significantly higher than those in participants who completed both examinations (chi-square test: stroke, $P = 0.0002$; ischemic heart disease, $P = 0.0019$). In female participants, there were no differences in the ratios of stroke and ischemic heart disease histories between the dropouts and the participants who completed both examinations. In male and female participants, the ratio of diabetes histories in dropouts was significantly higher than that in participants who completed both examinations (chi-square test: men, $P = 0.0077$; women, $P = 0.0369$). There were no differences in the ratios of hypertension and hyperlipidemia histories between the dropouts and the participants who completed both examinations in men or women. There were no differences in the ratios of severe atrophy in the frontal and temporal lobe between the dropouts and the participants who completed both examinations in men or women.

Participants with severe atrophy in the second wave examination were excluded because severe atrophy was of a high-end grade that cannot be used to determine further atrophy progression. Participants in their 40s were also excluded because few participants of this age show brain atrophy progression. Participants with a current medical history of Parkinson disease, dementia, or open head surgery were also excluded. Finally, the participants for this study were 381 men and 393 women.

The study protocol was approved by the Ethics Committee of the National Center for Geriatrics and Gerontology, and written informed consent was obtained from all participants.

Brain MRI examination. Brain MRI was performed on participants at the second and sixth wave examinations using a 1.5-T scanner (Toshiba Visart, Tokyo, Japan) at the National Center for Geriatrics and Gerontology. Each participant's head was oriented in the scanner and stabilized during the scanning procedure by a head support. To establish slice orientation, the first scanning sequence consisted of a T1-weighted sagittal series (repetition time (TR) = 500 ms, echo time (TE) = 15 ms, 256 × 256 matrix) centered along the midline to define the orbitomeatal line. The second series of T1-weighted axial images (TR = 500 ms, TE = 15 ms, thickness = 8 mm, gap = 1.5 mm, 256 × 256 matrix) and T2-weighted axial images (TR = 4000 ms, TE = 120 ms, thickness = 8 mm, gap = 1.5 mm, 320 × 320 matrix) were oriented parallel to the orbitomeatal line. Fourteen slices were taken during each examination.

The presence and the degree of brain atrophy in the frontal and temporal lobes were assessed as no atrophy (I), mild atrophy (II), moderate atrophy (III), and severe atrophy (IV) (25,36). The participants were divided into two groups on the basis of results from the MRI in the second wave examination and sixth wave examination: the brain atrophy progression group (progress: degree of brain atrophy in the second wave < sixth wave) and the brain atrophy non-progression group.

Daily physical activities and total energy expenditure assessments. We recorded the daily physical activities and total energy expenditures of the participants at the second wave examinations using a uniaxial accelerometry sensor (Lifecorder; Suzuken, Aichi, Japan). Lifecorder can assess two types of activity energy expenditure by activity level: energy expenditure of activities (with body movements) and energy expenditure of minor activities (working at a desk or reading a book). In this study, the activity energy expenditure was estimated as the energy expenditure of both types of activities. The total energy expenditure was determined as the sum of basal metabolism, energy expenditure of activities, energy expenditure of minor activities, and thermic effects of food. Participants wore the Lifecorder constantly (except while sleeping or bathing) for a 7-d period. We calculated the mean activity energy expenditure, the number of steps, and the total energy expenditure from 5 d of records (the maximum and the minimum records were excluded).

Other parameters. Body height and weight were measured using a digital scale. Body mass index (BMI) was calculated as weight divided by height squared ($kg \cdot m^{-2}$). Body fat mass was assessed by dual x-ray absorptiometry (QDR-4500A; Hologic, Bedford, MA). Lifestyle factors (including alcohol intake, smoking habit, and education levels), medical history, and use of medications were assessed with questionnaires. These questionnaires were confirmed by a physician at the medical examinations. All prescribed and nonprescribed medications used during the previous 2 wk were documented and brought by the participants; the physicians confirmed and coded them. Users of antihypertensive, antilipemic, or hypoglycemic medications were considered participants with hypertension, hyperlipidemia, and diabetes histories, respectively.

Statistical analysis. The results are shown as the mean ± SD or mean ± SE. Differences in continuous and class variables between the progression and the nonprogression groups were assessed with *t*-tests and chi-square tests, respectively. Cochran–Mantel–Haenszel statistics were used to examine the relationship between the age group and the brain atrophy progression. Multiple logistic regression models were fit to determine the associations of activity energy expenditure, number of steps, and total energy expenditure variables with frontal and temporal lobe atrophy progression while controlling for the baseline decade of age group (38), BMI (19), education history (19), medical history (stroke, ischemic heart disease, hypertension, hyperlipidemia, and diabetes) (4,12,24), and current smoking and alcohol intake as possible confounders (9,37). Activity energy expenditure, number of steps, and total energy expenditure were modeled as sex-specific quintiles. Statistical testing was performed using the Statistical Analysis System release 9.1.3 (SAS Institute Inc., Cary, NC). Significant probability levels were considered to be less than 0.05.

RESULTS

Characteristics of the participants. Table 1 shows elementary statistics of the study variables in male and female participants. The mean follow-up durations of all participants were 8.2 ± 0.3 yr. There were no significant differences in baseline age, BMI, or number of steps between male and female participants. Body height and weight, alcohol intake, and education history were significantly higher in male participants than those in female participants (each, $P < 0.0001$). The percentage of body fat in female participants was significantly higher than that in male participants ($P = 0.0126$). The activity and total energy expenditures in men were significantly higher than those in women (each, $P < 0.0001$). There were no sex differences in the ratios of stroke, ischemic heart disease, and hypertension histories. The ratio of hyperlipidemia history in female participants was significantly higher than that in male participants ($P = 0.0060$). The ratios of diabetes history and smoking habits in male participants were significantly higher than that in female participants (diabetes history, $P = 0.0126$; smoking habits, $P < 0.0001$).

TABLE 1. The characteristics of participants at the time of the second wave examination of the NILS-LSA, 2000–2002.

	Male (n = 381)	Female (n = 393)	P
Mean follow-up (yr)	8.2 ± 0.3	8.2 ± 0.3	0.5777
Age (yr)	60.4 ± 7.3	60.8 ± 7.6	0.5421
Body height (cm)	164.7 ± 5.4	152.2 ± 5.2	<0.0001
Body weight (kg)	62.5 ± 7.1	52.7 ± 7.0	<0.0001
BMI ($kg \cdot nm^{-2}$)	23.0 ± 2.4	22.7 ± 2.9	0.1279
% body fat	21.0 ± 4.0	31.3 ± 4.9	<0.0001
Alcohol intake ($g \cdot d^{-1}$)	16.6 ± 20.9	2.7 ± 6.1	<0.0001
Education (yr)	12.3 ± 2.7	11.4 ± 2.3	<0.0001
Activity energy expenditure ($kcal \cdot d^{-1}$)	215.1 ± 78.5	175.1 ± 64.8	<0.0001
No. of steps per day	7993.2 ± 2588.0	7925.6 ± 2297.1	0.7011
Total energy expenditure ($kcal \cdot d^{-1}$)	1932.3 ± 168.5	1607.5 ± 150.0	<0.0001
With medical history, n (%)			
Stroke	14 (3.7%)	7 (1.8%)	0.1050
Ischemic heart disease	13 (3.5%)	19 (4.8%)	0.3203
Hypertension	40 (10.5%)	40 (10.2%)	0.8836
Hyperlipidemia	61 (16.0%)	94 (23.9%)	0.0060
Diabetes	32 (8.4%)	16 (4.1%)	0.0126
Smoking habit	102 (26.8%)	27 (6.9%)	<0.0001

Values are presented as mean ± SD. *P* values were obtained using the *t*-test for continuous data and the chi-square test for categorical data.

TABLE 2. The ratio of frontal and temporal lobe atrophy progression in participants from the second (2000–2002) to the sixth (2008–2010) wave examination of the NILS-LSA.

	Frontal Lobe Atrophy			Temporal Lobe Atrophy		
	Nonprogression	Progress	Trend *P*	Nonprogression	Progress	Trend *P*
Male, *n* (%)						
Age group						
50s	176 (95.1%)	9 (4.9%)	<0.001	156 (84.3%)	29 (15.7%)	<0.001
60s	112 (79.4%)	29 (20.6%)		87 (61.7%)	54 (38.3%)	
70s	38 (69.1%)	17 (30.9%)		38 (69.1%)	17 (30.9%)	
Total	326 (85.6%)	55 (14.4%)		281 (73.8%)	100 (26.3%)	
Female, *n* (%)						
Age group						
50s	191 (96.0%)	8 (4.0%)	<0.001	188 (94.5%)	11 (5.5%)	<0.001
60s	117 (90.0%)	13 (10.0%)		92 (70.8%)	38 (29.2%)	
70s	50 (78.1%)	14 (21.9%)		35 (54.7%)	29 (45.3%)	
Total	358 (91.1%)	35 (8.9%)		315 (80.2%)	78 (19.8%)	

The trend *P* values were obtained using the Cochran–Mantel–Haenszel test.

Progress of frontal and temporal lobe atrophy. Table 2 shows comparisons of the incidence of frontal and temporal lobe atrophy progression in each age group. Frontal lobe atrophy progression from the second wave examination to the sixth wave examination was present in 55 (14.4%) of 381 male participants and 35 (8.9%) of 393 female participants. The ratio of participants with frontal lobe atrophy progression in male participants was significantly higher than that in female participants ($P = 0.0213$). Aging raised the percentage of participants with frontal lobe atrophy progression in men and women (P trend <0.0001).

Temporal lobe atrophy progression from the second wave examination to the sixth wave examination was present in 100 (26.3%) of 381 male participants and 78 (19.8%) of 393 female participants. The ratio of participants with temporal lobe atrophy progression in male participants was significantly higher than that in female participants ($P = 0.0344$). Aging raised the percentage of participants with temporal lobe atrophy progression in men and women (P trend <0.0001).

Brain atrophy progression and physical activity level. Table 3 shows the activity energy expenditure, number of steps, and total energy expenditure in the frontal and temporal lobe atrophy progression and nonprogression groups. In the frontal lobe, activity energy expenditure ($P = 0.0095$), number of steps ($P = 0.0131$), and total energy expenditure ($P < 0.0001$) were significantly higher in the male nonprogression group than the progression group. In female participants, total energy expenditure was significantly higher in the nonprogression group than that in the progression group ($P = 0.0097$). There were no differences in the activity energy expenditure or number of steps between the female nonprogression and progression groups.

In the temporal lobe, there were no differences in the activity energy expenditure or number of steps between the nonprogression and the progression groups in male or female participants. The total energy expenditure was significantly higher in the nonprogression group than that in the progression group in male ($P = 0.0028$) and female ($P = 0.0096$) participants.

Risk of brain atrophy progression according to physical activity level differences. The results of multiple logistic regression analyses for risk of brain atrophy progression according to differences in the physical activity level in men and women are shown in Tables 4 and 5, respectively. In male participants, the odds ratio of frontal lobe atrophy progression for the comparison between the fifth quintile in activity energy expenditure and the first quintile was 3.408 (95% confidence interval (CI) = 1.205–9.643). The odds ratio of frontal lobe atrophy progression for the comparison between the fifth quintile in number of steps and the first quintile was 3.651 (95% CI = 1.304–10.219). The odds ratios of frontal lobe atrophy progression for the comparison between the fifth quintile in total energy expenditure and the first and third quintiles were 4.816 (95% CI = 1.037–22.376) and 4.639 (95% CI = 1.191–18.067), respectively.

In female participants, there were no significant differences between frontal lobe atrophy progression and physical activity parameters. The odds ratios of frontal lobe atrophy progression for the comparison between the fifth quintile in total energy expenditure and the first to the third quintiles

TABLE 3. Mean activity energy expenditure, number of steps, and total energy expenditure per day in each group.

	Frontal Lobe Atrophy			Temporal Lobe Atrophy		
	Nonprogression	Progress	*P*	Nonprogression	Progress	*P*
Male (*n*)	326	55		281	100	
Activity energy expenditure (kcal·d^{-1})	219.3 ± 4.4	189.7 ± 9.9	0.0095	217.3 ± 4.6	208.8 ± 8.1	0.3503
No. of steps per day	8128.0 ± 143.6	7194.3 ± 327.4	0.0131	7983.1 ± 155.1	8021.8 ± 256.6	0.8979
Total energy expenditure (kcal·d^{-1})	1947.0 ± 9.2	1845.22 ± 1.2	<0.0001	1945.6 ± 10.1	1895.0 ± 15.9	0.0097
Female (*n*)	358	35		315	78	
Activity energy expenditure (kcal·d^{-1})	176.4 ± 3.4	161.6 ± 10.1	0.1965	176.7 ± 3.7	169.4 ± 6.9	0.3664
No. of steps per day	7984.9 ± 121.8	7318.7 ± 365.6	0.1016	7997.4 ± 130.1	7699.5 ± 254.6	0.3043
Total energy expenditure (kcal·d^{-1})	1614.5 ± 7.9	1535.4 ± 21.8	0.0028	1616.5 ± 8.3	1567.7 ± 17.8	0.0096

Values are presented as means ± SE. The *P* values were obtained using the *t*-test.

TABLE 4. Adjusted odds ratios of frontal and temporal lobe atrophy progression in male participants distributed into quintiles of physical activity and total energy expenditure data.

	Odds Ratio, 95% CI				
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Frontal lobe (*n*)	76	76	76	76	77
Activity energy expenditure (kcal·d^{-1})	3.408, 1.205–9.643 (<143.2)	1.054, 0.321–3.462 (143.2 to <184.4)	1.623, 0.523–5.035 (184.4 to <226.2)	2.054, 0.691–6.904 (226.2 to <284.4)	1.00, referent (≥284.4)
No. of step per day	3.651, 1.304–10.219 (<5736.0)	1.216, 0.383–3.863 (5736.0 to <6955.0)	1.487, 0.471–4.689 (6955.0 to <8261.4)	2.403, 0.819–7.052 (8261.4 to <10,407.4)	1.00, referent (≥10,407.4)
Total energy expenditure (kcal·d^{-1})	4.816, 1.037–22.376 (<1771.4)	2.758, 0.652–11.672 (1771.4 to <1897.4)	4.639, 1.191–18.067 (1897.4 to <1983.4)	2.275, 0.553–9.358 (1983.4 to <2091.2)	1.00, referent (≥2091.2)
Temporal lobe (*n*)	76	76	76	76	77
Activity energy expenditure (kcal·d^{-1})	1.015, 0.473–2.178 (<143.2)	1.293, 0.617–2.708 (143.2 to <184.4)	0.800, 0.364–1.756 (184.4 to <226.2)	0.845, 0.390–1.833 (226.2 to <284.4)	1.00, referent (≥284.4)
No. of step per day	0.938, 0.435–2.024 (<5736.0)	1.100, 0.519–2.330 (5736.0 to <6955.0)	1.142, 0.538–2.425 (6955.0 to <8261.4)	1.123, 0.528–2.389 (8261.4 to <10,407.4)	1.00, referent (≥10,407.4)
Total energy expenditure (kcal·d^{-1})	1.045, 0.388–2.816 (<1771.4)	1.303, 0.554–3.065 (1771.4 to <1897.4)	1.229, 0.537–2.810 (1897.4 to <1983.4)	1.006, 0.439–2.307 (1983.4 to <2091.2)	1.00, referent (≥2091.2)

Odds ratios were controlled for age, BMI, education history, medical history (stroke, ischemic heart disease, hypertension, hyperlipidemia, and diabetes), current smoking, and alcohol intake in a multinomial logistic regression model.

were 12.363 (95% CI = 1.029–148.594), 12.743 (95% CI = 1.292–125.792), and 21.539 (95% CI = 2.381–194.839), respectively.

We also evaluated temporal lobe atrophy progression using the adjustment model, similar to the frontal lobe atrophy progression analysis. There were no significant differences between temporal lobe atrophy progression and physical activities or total energy expenditure (Tables 4 and 5) in any groups of participants.

DISCUSSION

Using longitudinal analyses, we showed that a high level of physical activity and total energy expenditure suppressed the frontal lobe atrophy progression that is induced by aging.

An inactive daily life appears to be a risk factor for frontal lobe atrophy progression. In male participants, those with the lowest activity energy expenditure (first quintile, <143.2 kcal) had a 3.408-fold risk of frontal lobe atrophy progression compared with those with the highest activity energy expenditure (fifth quintile, ≥284.4 kcal) (Table 4). Similarly, men with the fewest number of steps (first quintile, <5736.0 steps) had a 3.651-fold risk of frontal lobe atrophy progression compared with those with the most number of steps (fifth quintile, ≥10,407.4 steps) (Table 4). An activity energy expenditure of 143.2 kcal is equivalent to activity in 4 METs (e.g., raking the lawn and table tennis) for 33 min in 62.5-kg men (1). Thirty minutes of middle-intensity or greater activities per day, such as 5700 steps or more walking per day, may be necessary to reduce the risk of frontal lobe atrophy progression. In addition, daily physical activity decreases with aging (27). An increase in planned physical activities may be necessary to prevent frontal lobe atrophy progression in older people.

Not only the expenditure of energy with physical activity but also the energy metabolic rate of the whole body appears to be associated with frontal lobe atrophy. Low total energy expenditure tended to be a risk for frontal lobe atrophy in male and female participants (Tables 4 and 5). In a study of prosimians and anthropoid apes and humans, brain volume is correlated with basal metabolism (23). The amount of basal metabolism may determine frontal lobe atrophy progression. It is well known that basal metabolism decreases with aging (32). Age-related skeletal muscle loss (sarcopenia) may be a risk factor for frontal lobe atrophy progression due to decreasing basal metabolism. Physical activity may compensate for a reduction in basal metabolism in the elderly.

TABLE 5. Adjusted odds ratios of frontal and temporal lobe atrophy progression in female participants distributed into quintiles of physical activity and total energy expenditure data.

	Odds Ratio, 95% CI				
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Frontal lobe (*n*)	78	79	78	79	79
Activity energy expenditure (kcal·d^{-1})	1.442, 0.421–4.945 (<119.6)	1.422, 0.435–4.644 (119.6 to <148.4)	0.610, 0.148–2.520 (148.4 to <182.8)	1.233, 0.362–4.199 (182.8 to <226.4)	1.00, referent (≥226.4)
No. of step per day	1.559, 0.420–5.791 (<5825.2)	2.269, 0.627–8.209 (5825.2 to <7090.0)	0.826, 0.181–3.769 (7090.0 to <8374.0)	1.887, 0.505–7.053 (8374.0 to <9910.4)	1.00, referent (≥9910.4)
Total energy expenditure (kcal·d^{-1})	12.363, 1.029–148.594 (<1495.6)	12.743, 1.292–125.792 (1495.6 to <1570.2)	21.539, 2.381–194.839 (1570.2 to <1639.6)	4.261, 0.430–42.214 (1639.6 to <1722.0)	1.00, referent (≥1722.0)
Temporal lobe (*n*)	78	79	78	79	79
Activity energy expenditure (kcal·d^{-1})	0.978, 0.362–2.645 (<119.6)	1.023, 0.400–2.614 (119.6 to <148.4)	1.569, 0.591–4.162 (148.4 to <182.8)	1.547, 0.617–3.876 (182.8 to <226.4)	1.00, referent (≥226.4)
No. of step per day	0.879, 0.355–2.178 (<5825.2)	0.789, 0.311–2.005 (5825.2 to <7090.0)	0.825, 0.317–2.147 (7090.0 to <8374.0)	1.206, 0.489–2.974 (8374.0 to <9910.4)	1.00, referent (≥9910.4)
Total energy expenditure (kcal·d^{-1})	0.881, 0.260–2.984 (<1495.6)	1.127, 0.405–3.138 (1495.6 to <1570.2)	0.948, 0.337–2.668 (1570.2 to <1639.6)	1.285, 0.499–3.305 (1639.6 to <1722.0)	1.00, referent (≥1722.0)

Odds ratios were controlled for age, BMI, education history, medical history (stroke, ischemic heart disease, hypertension, hyperlipidemia, and diabetes), current smoking, and alcohol intake in a multinomial logistic regression model.

Although a low-activity energy expenditure and a low number of steps were risk factors for frontal lobe atrophy progression in male participants, they were not risk factors in female participants (Tables 4 and 5). Generally, there are many more men with brain atrophy than women (38). In this study, the ratios of frontal lobe atrophy progression were different between male and female participants (Table 2). Sex hormones may also affect the relationship between physical activity and frontal lobe atrophy. Androgens and estrogens are associated with brain volume (13,24), and the adaptability of the brain to physical activity may be higher in men than that in women.

In contrast to activity energy expenditure, total energy expenditure was associated with frontal lobe atrophy progression in both men and women. Basal metabolism is the maximal occupation ratio in total energy expenditure. The brain metabolic rate is included in the basal metabolism. In women, total energy expenditure including basal metabolism appears to be a better index of the risks for frontal lobe atrophy progression compared with physical activity parameters. However, because some of the odds ratios were exceedingly large in female participants, our logistic regression model may not have precisely estimated the risk of frontal lobe atrophy. There were 55 male participants with frontal lobe atrophy progression (Table 2), but only 35 female participants had frontal lobe atrophy progression (Table 2). These sex differences in the brain atrophy progression rate may have influenced estimation of the odds ratio. In women in particular, further investigations may be needed to determine the association of frontal lobe atrophy progression with total energy expenditure.

Brain atrophy is caused in part by obesity (19), metabolic syndrome, and its components (4,12). A high level of physical activity improves obesity and metabolic syndrome (29). Cross-sectional research suggests that prevention of obesity by physical activity causes the relationship between physical activity and brain volume (19). However, in this study, frontal lobe atrophy progression was associated with the physical activity level in logistic regression models that controlled for BMI. Physical activity or the total energy expenditure may be independent factors for preventing frontal lobe atrophy progression, regardless of obesity.

In this study, the activity energy expenditure, the number of steps, and the total energy expenditure were quantitative data collected by an accelerometer. The objectivity of our study is higher than that of past studies that estimated the physical activity level with a questionnaire (5,19).

A limitation of this study is the noninvasive approach using MRI. We could not elucidate the mechanism of frontal lobe atrophy progression induced by a low level of physical activity or total energy expenditure. In an animal study, the beta amyloid cumulative dose is active mass dependent in mouse brain (22). The death of neurons may be inhibited by physical activity. Some growth factors, such as nerve growth factor or brain-derived neurotrophic factor, contribute to neuronal survival or neurogenesis (31,39). The serum level of nerve growth factors fluctuates with physical exercise (16), and thus, exercise stimulus with physical activity may modify expression of nerve growth factors.

Exercise and physical activity have been reported to change the volume of every region of the brain, including the frontal lobe, the temporal lobe, the parietal lobe, and the hippocampus (3,5,8,19). Interestingly, our results showed associations between brain atrophy progression and physical activity or total energy expenditure only in the frontal lobe, but not in the temporal lobe. We hypothesize that the regional differences in brain atrophy progression were due to differences in the patterns of physical activities (including types, intensities, or frequencies). A previous study suggests that increased blood flow in the brain due to physical exercise promotes neurogenesis (30). Blood flow in the brain varies with exercise type and intensity (20,28). In this study, because the activity energy expenditure, the number of steps, and the total energy expenditure data were collected as the total amount per day with accelerometer sensors, the differences in the patterns of physical activities between participants were not determined. Further investigations that define these details may clearly uncover an association between physical activities and regional differences in brain atrophy progression.

In summary, using the longitudinal design of the NILS-LSA cohort, we evaluated the association between brain atrophy progression and daily physical activity and total energy expenditure in 774 community-living, middle-age, and elderly Japanese people with an 8-yr follow-up duration. Our data confirm that low levels of physical activity and total energy consumption are significant predictors of the risk for brain atrophy, and the effect of atrophy suppression is seen only in the frontal lobe. Promoting participation in physical activities may be beneficial in attenuating age-related frontal lobe atrophy and in preventing dementia.

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