frontal lobe atrophy progression compared to those with the most number of steps (5th quintile; ≥10,407.4 steps) (Table 4). An activity energy expenditure of 143.2 kcal is equivalent to activity in 4 metabolic equivalents (METs; e.g., raking the lawn, table tennis) for 33 minutes in 62.5-kg weight males (1). Thirty minutes of middle-intensity or greater activities per day, such as 5,700 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.

24. 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 prosimiae 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.

25. Although 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 males with brain atrophy than females (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 males than females.

26. In contrast to activity energy expenditure, total energy expenditure was associated with frontal lobe atrophy progression in both males and females. Basal metabolism is the maximal occupation ratio in total energy expenditure. The brain metabolic rate is included in the basal metabolism. In females, total energy expenditure including basal metabolism appears to be a better index of the risks for frontal lobe atrophy progression than 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 females in particular, further investigations may be needed to determine the association of frontal lobe atrophy progression with total energy expenditure.

27. 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.

28. In this study, 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).

29. 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.

30. Exercise and physical activity have been reported to change the volume of every region of the brain, including the frontal lobe, temporal lobe, parietal lobe, and 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, number of steps, and 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.

31. 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-aged and elderly Japanese people with an 8-year 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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Table 1. The characteristics of participants at the time of the 2nd wave examination of the National Institute for Longevity Sciences-Longitudinal Study of Aging (NILS-LSA), 2000-2002.

	Male (n = 381)	Female (n = 393)	p value
Mean follow-up (years)	8.2 ± 0.3	8.2 ± 0.3	0.5777
Age (years)	60.4 ± 7.3	60.8 ± 7.6	0.5421
Body height (cm)	164.7 ± 5.4	152.2 ± 5.2	<.0001
Body weight (kg)	62.5 ± 7.1	52.7 ± 7.0	<.0001
BMI (kg/m^2)	23.0 ± 2.4	22.7 ± 2.9	0.1279
% of body fat	21.0 ± 4.0	31.3 ± 4.9	<.0001
Alcohol intake (g/day)	16.6 ± 20.9	2.7 ± 6.1	<.0001
Education (years)	12.3 ± 2.7	11.4 ± 2.3	<.0001
Activity energy expenditure (kcal/day)	215.1± 78.5	175.1 ± 64.8	<.0001
Number of steps (/day)	7993.2 ± 2588.0	7925.6 ± 2297.1	0.7011
Total energy expenditure (kcal/day)	1932.3 ± 168.5	1607.5 ± 150.0	<.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%)	<.0001

Means ± SD. The 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 2nd (2000-2002) to the 6th (2008-2010) wave examination of the NILS-LSA.

		Frontal lobe atrophy		trend p value	Temporal lobe atrophy		trend p value
		Non-progression	Progress		Non-progression	Progress	
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.

Table 3. The mean activity energy expenditure, number of steps, and total energy expenditure per day in each group.

	Frontal lobe atrophy		p value	Temporal lobe atrophy		p value
	Non-progression	Progress		Non-progression	Progress	
Male (n)	326	55		281	100	
Activity energy expenditure (kcal/day)	219.3 ± 4.4	189.7 ± 9.9	0.0095	217.3 ± 4.6	208.8 ± 8.1	0.3503
Number of steps (/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/day)	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/day)	176.4 ± 3.4	161.6 ± 10.1	0.1965	176.7 ±3.7	169.4 ± 6.9	0.3664
Number of steps (/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/day)	1614.5 ± 7.9	1535.4 ± 21.8	0.0028	1616.5 ± 8.3	1567.7 ± 17.8	0.0096

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				
	Quintile1	Quintile2	Quintile3	Quintile4	Quintile5
Frontal lobe (n)	76	76	76	76	77
Activity energy expenditure (kcal/day)	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)
Numbers of step (/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 < 10407.4)	1.00, Referent (≥ 10407.4)
Total energy expenditure (kcal/day)	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/day)	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)
Numbers of step (/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 < 10407.4)	1.00, Referent (≥ 10407.4)
Total energy expenditure (kcal/day)	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, body mass index, education history, medical history (stroke, ischemic heart disease, hypertension, hyperlipidemia, diabetes), current smoking, and alcohol intake in a multinomial logistic regression model.

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				
	Quintile1	Quintile2	Quintile3	Quintile4	Quintile5
Frontal lobe (n)	78	79	78	79	79
Activity energy expenditure (kcal/day)	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)
Numbers of step (/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/day)	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/day)	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)
Numbers of step (/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/day)	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, body mass index, education history, medical history (stroke, ischemic heart disease, hypertension, hyperlipidemia, diabetes), current smoking, and alcohol intake in a multinomial logistic regression model.

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