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Abstract A physically active lifestyle is important across the entire life span. However, little is known about life-long participation in regular exercise among older people. The purpose of the present study was to describe regular exercise throughout a person's lifetime and evaluate the impact of exercise earlier in life on participation in exercise at age 60 and over. The participants were 984 community-dwelling older people aged 60 to 86 years. Each participant's life was divided into five age categories: 12-19, 20-29, 30-39, 40-59, and 60 years and over. The association between exercise at an earlier age and that at 60 years and over was assessed using logistic regression analysis adjusted for potential confounders. Men had exercised throughout their lives more than women. Among women, participation in exercise during their 20s and 30s showed a sharp decline. The preference for exercise differed according to age and gender. Among men, the most common patterns of exercise throughout life were exercise during all the age categories, and starting exercise at age 60 and over; whereas in women the most common pattern was no exercise at all. The adjusted odds ratio of exercise at 40-59 years for exercise at age 60 and over was 5.85 (95% confidence interval: 3.82-8.96) among men and 6.89 (4.23-11.23) among women. Regular exercise in the younger age categories affected exercise at age 60 and over among men, but not among women. Regular exercise at 40-59 years was a strong predictor of exercise at 60 years and over in both men and women.

Keywords : regular exercise, older people, life course, random sampling data

Introduction

Physical activity is an important health behavior across the course of one's life. The benefits of physical activity in preventing health decline and physical function loss have been demonstrated, especially for frail and aged people¹. The Ministry of Education, Culture, Sports, Science and Technology in Japan reported that the participation rate of older people in physical activity and fitness has slightly increased in the past decade^{2,3}. However, more than 40 % of older people aged 70 years and older did not participate in any exercise during the past year⁴. Insufficient physical activity remains a public health concern among older people in Japan.

Engaging in sports activities in childhood and adolescence is known to predict physical activity in adulthood⁵. A low level of physical activity in early life has been found to predict physical inactivity in adulthood⁶. However,

most longitudinal studies have demonstrated that sports activities in early life have an effect on physical activity in young adulthood^{5,6}. It remains unclear whether sports activities in early life are associated with physical activity at an older age. Some studies have found that a history of physical activity was associated with current physical activity in older people^{7,8}. In an earlier study we found that the experience of exercise in adolescence was associated with a higher level of leisure-time physical activity in middle-aged and elderly Japanese women⁹. However, little basic descriptive data exists on individual variation in participation in exercise throughout the life span and the impacts of early exercise on physical activity in later life among community-dwelling Japanese older people.

The purpose of the present study was to describe regular exercise throughout the life course and evaluate the effect of early exercise on the participation in exercise at the age of 60 years and over.

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Methods

Study population. The investigation is a part of the 4th survey of the National Institute for Longevity Sciences - Longitudinal Study of Aging (NILS-LSA), which is a follow-up study on the causes of geriatric diseases and health problems in older people. The NILS-LSA was based on data obtained from interviews and laboratory examinations of medical, nutritional, psychological, and physical fitness variables. The details of the study can be found elsewhere¹⁰. The initial survey of the NILS-LSA involved 2,267 men and women aged 40-79 years, including almost 300 men and 300 women for each decade (40s, 50s, 60s and 70s). The participants were gender- and decade age-stratified random samples of the residents of Obu-shi and Higashiura-cho, Aichi Prefecture, in central Japan. The participants were drawn from resident registrations in cooperation with local governments. All subjects lived or had lived at home in the community. The participants in the present study comprised 523 men and 461 women aged 60-86 years. All the NILS-LSA procedures were already approved by the Ethical Committee of the National Center for Geriatrics and Gerontology, and all of the participants signed a written informed consent.

Measures and Procedures. Regular exercise was assessed using a questionnaire and an interview. The questionnaire was based on a questionnaire developed by the Japanese Lifestyle Monitoring Group¹¹. The participants were asked for the type, time, frequency and duration of their regular exercise from the age of 12 years to the present with the question "What physical activities or sports have you participated in during these age categories?" The participants reported the types of physical activities and sports they had engaged in from a list of alternatives. These were coded as 1) light activities such as walking, gymnastic exercise and gardening, 2) moderate activities such as brisk walking, dancing and swimming for pleasure, 3) vigorous activities with increased breathing and sweating such as jogging and playing tennis, 4) exhausting activities such as various competitive sports. Frequency of participation was defined as how often they participated in physical activities or sports per week. The duration of each activity was calculated with 1 year as the basic unit. Physical activities or sports that were engaged in for at least 20 minutes, once a week and over 1 year, excluding physical education at school, were defined as regular exercise. Life span was divided into five age categories: 12-19, 20-29, 30-39, 40-59 and 60 years and over. The age categories of 40 and over included more years with reference to previous studies^{7,8}, showing physical activity to be stable in middle age¹².

If participants engaged in a number of regular exercises during the same period, the exercise with the longer duration was selected. Interviews were performed by trained staff.

Potential confounders, included age, education, marital

status (never married, married, separated, divorced and be-reaved), annual income (6,500,000 yen or less vs. more than 6,500,000 yen) and chronic conditions including smoking status (never, former and current), self-rated health (excellent, very good, good, fair and poor) and prevalent diseases (hypertension, ischemic heart disease, diabetes, osteoporosis, arthritis and cancer), were investigated using a questionnaire and interview by a physician. Height and weight were measured using a digital scale. Body mass index was calculated by weight divided by height squared (BMI; kg/m²). Body fat mass was assessed by dual X-ray absorptiometry (DXA; QDR-4500A, Hologic, USA). Work-related physical activity was estimated using the same questionnaire developed by the Japanese Lifestyle Monitoring Group¹¹. Work activities were assigned an intensity coefficient of 1.5, 2.5, 4.5 and 7.5 METs (metabolic equivalents) for sedentary work, work done standing or walking, moderately strenuous work and strenuous work, respectively. The work activity scores were calculated by multiplying the intensity coefficients by the total number of minutes spent on the activity over the last 12 months.

Statistical analysis. The statistical significance of the differences in social and health conditions were analyzed by the Cochran-Mantel-Haenszel test for categorical variables and Student's t-test for continuous variables according to participation in regular exercise at age 60 and over. The participation rate in regular exercise was calculated as the percentage of participants who engaged in exercise in each age category. Gender differences in the participation rate in each age category were analyzed using Pearson's chi-squared test. The relationship between regular exercise in the younger age categories and at age 60 and over was evaluated using multiple logistic regression analysis. Both the unadjusted model and the model adjusted for all potential confounders were analyzed. The analyses were performed for men and women separately, as the gender difference in the participation rate in regular exercise was considerable. Statistical testing was performed using the Statistical Analysis System (SAS), release 9.1.3 (SAS Institute Inc. NC, USA). Probability levels of less than 0.05 were considered to be significant.

Results

Table 1 shows the characteristics of the participants by gender according to participation in regular exercise at age 60 and over. The mean age of the study population was 70.0±6.6 years in men and 69.8±6.7 years in women. Age, weight, BMI, annual income, work-related physical activity, smoking, self-rated health, hypertension and arthritis for men; and height, education, work-related physical activity for women were associated with regular exercise at age 60 and over (p<0.05).

The participation rates in regular exercise for age categories 12-19, 20-29, 30-39, 40-59 and 60 years and over

Table 1. Characteristics of the participants according to regular exercise at age 60 and over for men and women

		Men		p-value	Women		p-value
		Regular exercise			Regular exercise		
		Yes n=342	No n=181		Yes n=263	No n=193	
Age	years	70.4 ± 6.3	69.2 ± 7.2	0.048	69.7 ± 6.4	70.2 ± 7.0	0.503
Height	cm	163.6 ± 5.7	162.7 ± 5.9	0.108	150.5 ± 5.6	149.1 ± 6.2	0.010
Weight	kg	62.3 ± 9.0	59.2 ± 8.3	<0.001	51.8 ± 7.7	51.7 ± 8.7	0.829
BMI	kg/m ²	23.3 ± 2.8	22.3 ± 2.8	<0.001	22.9 ± 3.0	23.2 ± 3.4	0.246
Body fat	%	22.9 ± 4.4	22.5 ± 4.6	0.395	32.4 ± 5.1	32.6 ± 5.5	0.688
Education	years	11.9 ± 2.9	11.7 ± 3.0	0.513	11.1 ± 2.3	10.6 ± 2.5	0.033
Marital status	%			0.097			0.295
Never		0.0	2.2		3.1	3.7	
Married		94.4	91.2		71.7	64.0	
Separation		0.6	0.6		0.4	0.0	
Divorce		0.6	0.6		1.9	4.2	
Bereavement		4.5	5.5		23.0	28.0	
Annual income	%						
6,500,000 yen and higher		24.8	35.2	0.013	25.8	29.4	0.401
Work-related physical activity	METs*min* 10 ⁻³	130.8 ± 135.9	170.7 ± 151.7	0.002	183.0 ± 85.5	206.8 ± 109.0	0.010
Smoking	%			<0.001			0.910
Never		24.8	20.3		93.9	94.2	
Former		58.1	47.3		2.3	2.6	
Current		17.1	32.4		3.8	3.1	
Self-rated health	%			0.001			0.287
Excellent		6.5	0.6		3.8	5.2	
Very good		33.3	24.7		21.7	15.6	
Good		52.2	63.2		65.0	66.2	
Fair		7.7	9.9		9.1	12.5	
Poor		0.3	0.6		0.4	0.5	
Prevalent diseases	%						
Hypertension		44.5	31.3	0.003	40.7	41.2	0.921
Ischemic heart diseases		6.2	9.3	0.188	7.2	6.8	0.852
Diabetes		11.5	11.0	0.860	7.2	5.2	0.385
Osteoporosis		1.2	3.3	0.093	16.4	17.2	0.827
Arthritis		4.4	11.5	0.002	11.8	17.2	0.102
Cancer		6.2	6.6	0.859	5.7	9.4	0.136

Continuous variables are presented as means ± standard deviation (SD), and categorical variables are presented as percentages. The differences between groups were analyzed by Student's t-test for continuous variables and by Cochran-Mantel-Haenszel test for categorical variables. Bold represents significant p-value (<0.05). BMI, Body mass index. METs, Metabolic equivalents

are shown Table 2. The percentage of men who had regular exercise was significantly higher than that of women in all of the age categories (p<0.05), except for 40-59 years. Among women, a large drop in the percentage reporting participation in exercise was found during the ages of 20-29 and 30-39 years.

The popular type of exercise reported for the different age categories is presented in Tables 3a and 3b. The most popular activities and sports differed both by gender and

by age category. Men frequently reported team sports such as baseball and softball up to 40-59 years of age. In women, volleyball was frequently reported up to 30-39 years of age, while dancing and gymnastics exercise were more likely to be reported among those over 20 years of age. At age 60 and over, walking was the most popular exercise among both men and women.

All the possible patterns of participation in regular exercise from age 12 to the present were examined. Thirty-two

different patterns were identified (Figure 1). In men, the most common patterns were participation in regular exercise during all the age categories (12.6%) and participation in regular exercise at age 60 and over (12.6%). In women, the most common pattern was no regular exercise in any age category (21.1%), followed by participation in regular exercise at age 40 and over (14.3%).

Table 4 shows that participating in regular exercise at age 60 and over is related to participation in regular exercise across one's life span. The participants who had exercised at younger age categories were more likely to participate in exercise at age 60 and over for both men and women.

The odds ratios (OR) and 95% confidence intervals (CI) for those who regularly exercised at age 60 and over are shown in Table 5. Although, among men, the results of the unadjusted model for the age category 12-19 years

was of borderline statistical significance (OR1.42, 95% CI 0.99-2.05), the odds ratio for participating in exercise at age 60 and over was higher for men who had regular exercise during each age category. The highest odds ratio was 4.63 (95%CI 3.07-6.98) among men who had regular exercise at 40-59 years. In women, regular exercise in the earlier age categories did not correlate with exercise at age 60 and over. However, the odds ratio for participating in exercise at age 60 and over was about six times higher among those who had regular exercise at 40-59 years (OR 5.85, 95%CI 3.82-8.96). After adjusting for age (continuous variable), BMI (continuous variable), education (continuous variable), annual income (6,500,000 yen or less/more than 6,500,000 yen), work-related physical activity (1SD), smoking (never/ former/ current), self-rated health (excellent/ very good/ good/ fair/ poor) and chronic diseases (Yes/ No), the associations remained in both men and women. Regular exercise at 40-59 years was strongly associated with exercise at age 60 and over in both men (OR 5.96, 95%CI 3.72-9.57) and women (OR 6.89, 95%CI 4.23-11.23).

Table 2. Participation rate in regular exercise across the life course

age (years)	Men (n=523)		Women (n=461)		p-value
	n	%	n	%	
12-19	311	59.5	198	43.0	<0.001
20-29	173	33.1	29	6.3	<0.001
30-39	155	29.8	62	13.5	<0.001
40-59	233	44.6	203	44.0	0.871
60 and over	342	65.4	263	57.1	<0.001

Numbers and percentages are shown for those who participated in regular exercise divided into five age categories. Pearson's chi-squared test. df=1.

Discussion

The present study described regular exercise throughout a person's life and evaluated the impact of early regular exercise on participation in exercise at age 60 and over.

Previous longitudinal studies suggest that physical activity in early life tracks to later life^{5,6}. However, most studies have tracked physical activity from childhood and adolescence to young adulthood and the coefficients re-

Table 3a. Popular types of regular exercise across the life course among men (n=523)

age (years)	1st		2nd		3rd	
		%		%		%
12-19	Baseball	16.6	Track & Field	11.9	Judo	8.4
20-29	Baseball	11.9	Softball	4.6	Table tennis	4.0
30-39	Golf	7.6	Softball	6.5	Baseball	5.9
40-59	Golf / Walking *		16.1		Softball	7.6
60 and over	Walking	34.4	Brisk walking	18.4	Golf	13.2

Percentages are shown for those who participated in the exercise. *, Both golf and walking share in 1st place with the same percentage.

Table 3b. Popular types of regular exercise across the life course among women (n=461)

age (years)	1st		2nd		3rd	
		%		%		%
12-19	Volleyball	15.8	Softball	7.8	Table tennis	6.1
20-29	Volleyball	1.7	Dancing	1.3	Tennis	0.9
30-39	Volleyball	3.5	Walking	2.8	Tennis, Dancing or Softball	1.5
40-59	Walking	13.9	Gymnastics exercise	8.7	Dancing	8.5
60 and over	Walking	24.7	Gymnastics exercise	15.4	Brisk walking	9.5

Percentages are shown for those who participated in the exercise.

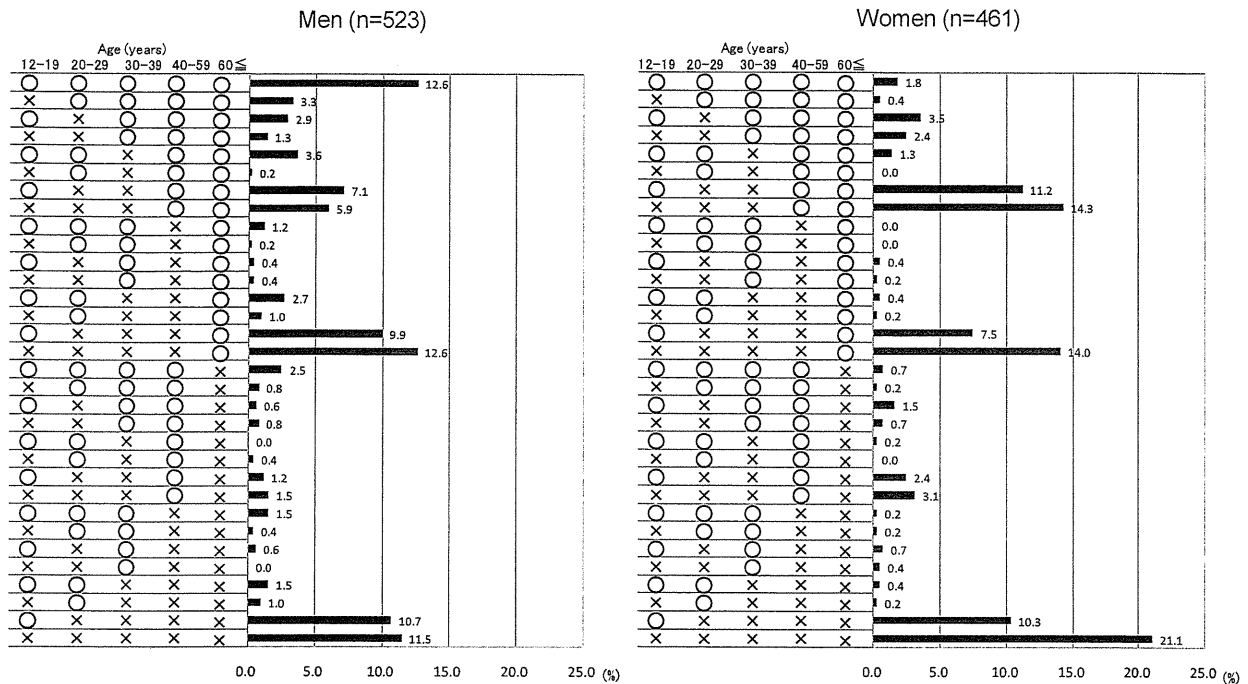


Fig. 1 Participation pattern in regular exercise across the life course for men and women, separately
 Regular exercise status: (○) = participants who engaged in regular exercise, (×) = participants who did not engage in regular exercise

Table 4. Distribution of participation in regular exercise at age 60 and over according to participation in regular exercise across the life course

age (years)	Regular exercise	Men (n=342)		Women (n=263)	
		n	%	n	%
12-19	No	130	61.3	144	54.8
	Yes	212	62.0	119	60.1
20-29	No	213	60.9	244	56.5
	Yes	129	74.6	19	65.5
30-39	No	225	61.4	223	56.0
	Yes	117	75.5	40	64.5
40-59	No	148	51.3	104	40.3
	Yes	194	83.3	159	78.3

Numbers and percentage are shown for those who engaged in regular exercise at age 60 and over.

ported have been only low or moderate⁵). In another study, the correlation between the time points studied was found to weaken over time¹³). Only a few studies have examined whether physical activity in early life tracks to an older age. Retrospective findings that past physical activity predicts physical activity in older people^{7,8}) can help to explain the positive association between experiences of exercise and physical activity later in life. However, basic descriptive data on individual exercise history throughout life is lacking for the community-dwelling older people in Japan. Assessing life-long regular exercise and the contribution of past exercise experience to engagement in regular exercise later in life are the underlying considerations when promoting an active lifestyle throughout a person's life.

Our finding that men are more physically active than women throughout their lives is partially supported by pre-

Table 5. Odds ratio and 95% confidence interval for those who had regular exercise at age 60 and over

	Model 1				Model 2			
	Men		Women		Men		Women	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Regular exercise								
At 12-19 years of age	1.42	0.99 - 2.05	1.30	0.89 - 1.90	1.69	1.10 - 2.58	1.06	0.71 - 1.60
At 20-29 years of age	2.03	1.35 - 3.05	1.43	0.65 - 3.14	1.87	1.21 - 2.90	1.26	0.55 - 2.87
At 30-39 years of age	2.02	1.32 - 3.09	1.47	0.84 - 2.58	2.00	1.27 - 3.15	1.29	0.69 - 2.41
At 40-59 years of age	4.63	3.07 - 6.98	5.85	3.82 - 8.96	5.96	3.72 - 9.57	6.89	4.23 - 11.23

OR, odds ratio; CI, confidence interval. Model1: unadjusted, Model2: adjusted for age, BMI, education, income, work-related physical activity, smoking, self-rated health, chronic diseases. Bold represents significant p-value (<0.05)

vious studies^{14,15}. Women may perceive more traditional, social and environmental barriers than men to engaging in exercise^{8,15}. For instance, exercise has been considered “not ladylike”¹⁶. These aspects may in part be responsible for the lower rate of participation in exercise throughout life among women. Furthermore, a large drop in participation in exercise was observed among women in their 20s and 30s. The transition from adolescence to adulthood is a period of general decline in physical activity¹⁷. Some life changes, such as getting married and having children, affect physical activity in young adulthood in women more than in men⁹. National data in Japan show that the age of first marriage for men was 26.9 years and for women 24.2 years in 1970¹⁸. The most common age range for giving birth is 20-39 years¹⁹. After the fourth decade of life, most people’s family and job situations seem to be established and stable. Retirement, in turn, tends to increase physical activity²⁰. These life events may be associated with regular exercise. Further research on the relationship between life events and exercise is needed to clarify this issue.

The most popular activities and sports changed between the earlier and later age categories; there was also a gender difference in popular types of activities throughout life. Previous studies have reported a high frequency of ball games among men across ages 14 to 31 years²¹. Dance and gymnastics were more popular with women^{15,22}. Our finding supports the previous gender difference in the traditional preferences for specific types of exercise. From the perspective of age, team sport activities were common in adolescence and young adulthood, and individual sports in middle age and older. A possible explanation of the shift is that social situations and lifestyle change according to age, for instance, it is more difficult for a large number of adults to get together, whereas individual sports can be performed in one’s own time²¹. Individual sports are sometimes labeled lifetime sports²³ and adult-like activities¹⁷. Previous studies have reported walking and gardening as the most common activities among older adults²⁴. To maintain their exercise levels, people may have to choose specific types of exercise as their lifestyles change with aging²⁵. We may consider that older people who engage in regular exercise in our study are those who are able to find suitable activities to match their life changes.

In this study, we tracked regular exercise from adolescence to age 60 and over, and described the individual variation in participation in exercise. A number of participants reported participating in regular exercise at some time in their life, although reports of consistent engagement in regular exercise across several decades were scarce. We have already shown cross-sectionally in Table 2 that the prevalence of regular exercise in the 20s and 30s was low. Figure 1 illustrates the findings as individual transitions of regular exercise throughout life. Although the percentage in each pattern was small, and the patterns of exercise frequency seemed to be similar in both men and women, we found that among men the most frequent

pattern was participation in regular exercise at all the life stages; whereas among women the most frequent pattern was no regular exercise at all. Results suggest that encouragement and support for older women should be provided by health professionals as well as the community, since participation in exercise may induce a major behavioral change among older women. There may be a need to tailor health promotion messages and interventions according to gender and personal exercise history.

After fully adjusting for confounding factors such as age, BMI, education, annual income, smoking, work-related physical activity, self-rated health, and chronic diseases, both men and women who had participated in regular exercise during 40-59 years of age had a 5 to 7-fold higher rate of participation in exercise at age 60 and over. This result suggests that participation in exercise during 40-59 years of age predicts exercise at age 60 and over. Our findings are in line with those of some previous studies^{7,8}. Frändin et al. , who studied age groups from the age of 10 years, found that physical activity during earlier life was not correlated with physical activity at the age of 76, except for the last age period 66-76 years⁷. Other studies also found the last age group to be better predictors than earlier ones^{8,26}. The short interval may be one of the causes for the strong relationship between regular exercise at 40-59 years of age and that at age 60 and over. A number of studies have suggested that childhood is usually considered the best time for socialization into physical activity⁸, for encouraging physical activity in adults through the developing of habits²⁵ and for promoting exercise-related feelings of pleasure and joy⁷. Furthermore, sports activities may have an effect on motor and coordination skills that may be of value later in life²¹. We believe that the positive effects of exercise in early life are associated with physical activity in older life. In fact, regular exercise during all the age categories studied affected exercise at age 60 and over among men. However, demographic, psychological, behavioral, social and environmental factors are associated with adulthood participation in physical activity²⁷. These multiple factors may decrease the positive effect of earlier exercise at older ages. Health problems were reported to be the most common barrier to increasing physical activity²⁸. We found that the effect of regular exercise at 40-59 years of age on participation in exercise at age 60 and over increased among women who had a history of hypertension in the sub-analyses (data not shown). Chronic health problems may also have influenced the motivation for physical activity as a part of clinical care. Our finding that regular exercise during 40-59 years of age was associated with that at age 60 and over was true for a lot of people who had not engaged in regular exercise earlier in their lives. The motivation to engage in regular exercise in the fourth and fifth decades of life may have important implications for promoting increased physical activity in older age.

This study has several limitations. The first limitation

is that our study was a retrospective study and the regular exercise data were based on self-reports. Possible memory failure and potential recall bias may have influenced the results. In addition, we were not able to take into account the short-term substitution of one exercise for another as regular exercise was defined as an activity lasting one year. Therefore our study may underestimate regular exercise as an indicator of physical activity. Secondly, social and environment factors, which have been indicated as predictors of physical activity, were not widely examined in our study. Environmental factors are among the important factors promoting participation in physical activity¹⁶. Recent studies suggested that environmental problems, such as poorly lit streets or noisy traffic, are correlated with inactivity²⁹. Further studies are needed to confirm the association between regular exercise and a comprehensive range of factors. Finally, the definition of regular exercise in this study was lower than the well-known recommendation of physical activity for adults by the American College of Sports Medicine³⁰. However, we previously found that continuation of regular exercise by the same definition as used in this study was associated with higher muscle strength and power in both elderly men and women³¹. A number of older people are physically inactive. "Tojikomori", being housebound, which has been defined in recent studies as going outdoors once or less than once a week, is a serious concern in relation to older people³². Pate et al. suggest that an active lifestyle does not require a regimented, vigorous exercise program³³. To avoid causing undue stress coming from misconceptions, it may be sufficient just emphasizing to older people the importance of being physically active as opposed to having to maintain a disciplined workout schedule.

The strengths of the present study include a large number of randomized community-dwelling people and regular exercise data tracked from age 12 to 60 years and over. These data provide important information for demonstrating the value of life-long physical activity. The participants had a face-to-face interview by trained staff, which increases the reliability of the answers and reduces missing data in the questions. We were able to take into account essential social and health condition data such as education, smoking and disease as confounders. Our study described individual variation in regular exercise throughout the various stages of a person's life and showed the positive impact of experiences of exercise in earlier life on regular exercise in later life; and thus lays a good foundation for persuading the general population of the importance of maintaining physical activity throughout life.

Conclusion

The present study found that men engaged in regular exercise more than women throughout their lifetime. Exercise preferences differed depending on age and gender. Among women, those reporting no regular exercise were

the largest group. Among men, regular exercise earlier in life positively affected regular exercise at age 60 years and over. Regular exercise in middle age markedly increased participation in exercise later in life regardless of social and health conditions among both men and women.

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地域在住中高年者の微量ミネラルおよびビオチンの摂取量

加藤 友紀, 大塚 礼, 今井 具子
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Vitamin D Deficiency in Elderly Women in Nursing Homes: Investigation with Consideration of Decreased Activation Function from the Kidneys

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OBJECTIVES: To determine the approximate percentage of women in nursing homes who have vitamin D deficiency and to investigate whether, in assessing vitamin D status in elderly women, there are problems with measuring only 25 hydroxy-vitamin D₃ (25(OH)D₃) and whether decreased vitamin D activation as a result of poor renal function needs to be considered.

DESIGN: Cross-sectional study.

SETTING: Forty-eight nursing homes in Japan.

PARTICIPANTS: Four hundred three women with a mean age of 86.5 living in nursing homes who had participated in a clinical trial for hip protectors and were not bedridden.

MEASUREMENTS: At the start of the trial, in addition to general biochemical data, 25(OH)D₃, 1,25-dihydroxy-vitamin D₃ (1,25(OH)₂D₃), intact parathyroid hormone (intact PTH), calcium (Ca), phosphorus (P), bone alkaline phosphate (BAP), cross-linked N-telopeptide of type I collagen (NTx), and osteocalcin were measured in participants' blood, and statistical analysis was performed.

RESULTS: 25(OH)D₃, which is thought to reflect vitamin D status in the body, was surveyed and found to have a mean value of 16.7 ng/mL. 25(OH)D₃ was less than 16 ng/mL in 49.1% of all participants. Creatinine clearance (CCr) was less than 30 mL/min in 20.1% of participants. Participants with serum 25(OH)D₃ less than 16 ng/mL and CCr less than 30 mL/min had significantly higher levels of intact PTH and serum NTx. Participants with a CCr less than 30 mL/min had significantly lower levels of 1,25(OH)₂D₃.

CONCLUSION: Frail elderly adults living in nursing homes with poor renal function had lower 1,25(OH)₂D₃ and higher intact PTH levels and were thus thought to have poorer vitamin D activating capacity. Supplementation with cholecalciferol may be insufficient in people who have poor renal function. *J Am Geriatr Soc* 60:251–255, 2012.

Key words: 25-hydroxy-vitamin D₃; 1,25-dihydroxy-vitamin D₃; nursing homes

The importance of vitamin D for bones has been indicated in previous studies.^{1,2} Frail elderly adults with limited ability to perform activities of daily living (ADL) who enter a nursing home are at high risk for low vitamin D as a result of poor nutrition and lack of sunlight. Vitamin D deficiency is an important risk factor for osteoporosis and fractures from falls in elderly adults.^{3–5} When assessing serum 25 hydroxy-vitamin D₃ (25(OH)D₃) levels to define vitamin D deficiency, many reports have adopted a cutoff of 20 ng/mL.^{6–8} It has also been reported that individuals with hip fracture or those with a history of falls have low 25(OH)D₃ levels.^{9,10} Secondary hyperparathyroidism from poor renal function in elderly adults must also not be overlooked.¹¹ The group that is probably at the highest risk of falls and fractures is elderly women living in nursing homes who are not completely bedridden but have a mobility level of at least being able to move about in a wheelchair with assistance. The participants in this study were such a group of people, who had previously participated in a fracture prevention trial using hip protectors.¹² Vitamin D levels, renal function, and the relationship between the two were investigated in these women, and the approximate percentage of these nursing home residents who needed supplemental vitamin D was considered.

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METHODS

Participants were 403 women aged 70 and older (range: 70–103) who lived in 48 nursing homes from whom consent was obtained for participation in a fracture prevention trial using hip protectors.¹² They had a mobility level of at least being able to move about in a wheelchair with assistance. A history of bilateral hip fracture was a condition for exclusion. Written informed consent was obtained from all participants. The Ethics Committee of the National Center for Geriatrics and Gerontology approved the study. Blood was collected from participants as the 48 nursing homes in the southern part of central Japan were visited in turn between January 2005 and May 2008. At the start of the trial, in addition to general biochemical data, 25(OH)D₃, 1,25-dihydroxy-vitamin D₃ (1,25(OH)₂D₃), intact parathyroid hormone (PTH), calcium (Ca), phosphorus (P), bone alkaline phosphate (BAP), cross-linked N-telopeptide of type I collagen (NTx), and osteocalcin were measured using participants' blood, and statistical analysis was performed. 25(OH)D₃ was measured using the radioimmunoassay double antibody method. Frail elderly adults have little muscle, and even if creatinine (Cr) is in the normal range, it cannot be concluded that renal function is normal. For a simpler assessment of renal function, we estimated Cr clearance (CCr) with adjustments for age and body weight using the widely adopted Cockcroft-Gault formula.¹³

Statistical Analyses

SPSS (version 17.0, SPSS, Inc., Chicago, IL) was used in the statistical analysis. Adjustment was made for age as a control variable in partial correlation. Two-tailed significance probability <.05 was taken to be significant. The Student *t*-test was used to test for differences between the mean values of the two groups, with *P* < .05 taken to indicate significance. The Bonferroni test was used to compare the mean values in the groups, using a general linear model adjusted for age. *P* < .05 was taken to indicate a significant difference.

RESULTS

Participants were aged 70 to 103 (mean 86.5). Mean 25(OH)D₃ level, which is an indicator of vitamin D level, was low (16.7 ng/mL). The mean values for the following tests were: 1,25(OH)₂D₃, 44.4 ± 17.5 pg/mL; intact PTH, 57.4 ± 38.7 pg/mL; BAP, 32.4 ± 13.2 U/L; osteocalcin, 7.8 ± 3.8 ng/mL; and NTx, 17.6 ± 9.7 nmol bone collagen equivalent/L. The percentile distribution in the 25(OH)D₃ distribution is shown in Figure 1. When 25(OH)D₃ concentration of less than 20 ng/mL was taken to indicate vitamin D deficiency, 78.1% of participants were found to be vitamin D deficient.

To further investigate 25(OH)D₃, the partial correlation was first examined adjusted for age. There were significant positive correlations between 25(OH)D₃ and 1,25(OH)₂D₃ (correlation coefficient (*r*) = 0.149, *P* = .003), albumin (*r* = 0.185, *P* < .001), total cholesterol (*r* = 0.165, *P* = .001), blood urea nitrogen (*r* = 0.116, *P* = .02), Ca (*r* = 0.153, *P* = .002), and P (*r* = 0.100,

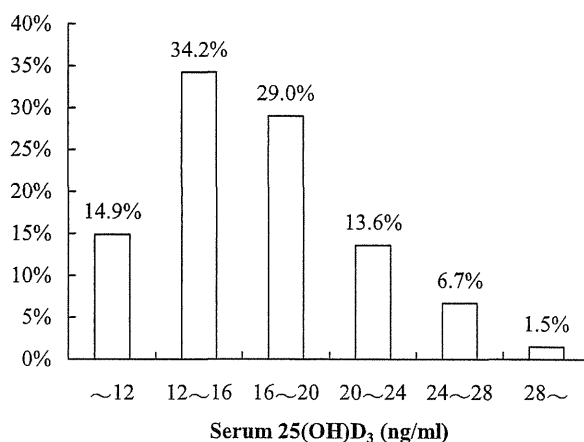


Figure 1. Percentile distribution of serum 25 hydroxy-vitamin D₃ (25(OH)D₃) concentrations. 25(OH)D₃ level was < 20 ng/mL in 78.1% and < 16 ng/mL in approximately half.

P = .04). Significant negative correlations were shown with serum NTx (*r* = -0.153, *P* = .002) and intact PTH (*r* = -0.178, *P* < .001). It was then decided to further investigate intact PTH, which had shown a high correlation. Mean intact PTH levels in the group with a serum 25(OH)D₃ concentration less than 12.0 ng/mL, 12.0 to 15.9 ng/mL, and 16.0 ng/mL or higher were 72.3 pg/mL, 60.4 pg/mL, and 51.1 pg/mL, respectively. Mean intact PTH level was significantly higher in participants with a serum 25(OH)D₃ concentration less than 12.0 ng/mL (*P* < .001) and 12.0 to 15.9 ng/mL (*P* = .02) than in those with a concentration of 16.0 ng/mL or higher. Participants younger than 85 were then compared with those aged 85 and older to determine whether the various data differed depending on age (Table 1). Significant differences were seen in 25(OH)D₃, 1,25(OH)₂D₃, and intact PTH. Because 1,25(OH)₂D₃, a form of activated vitamin D, also decreases with age, it was decided to investigate 1,25(OH)₂D₃. First, in the age-adjusted partial correlation, 1,25(OH)₂D₃ showed the strongest negative correlation with Cr (*r* = -0.323, *P* < .001). This finding suggests that renal function strongly affects 1,25(OH)₂D₃. The relationship between 1,25(OH)₂D₃ concentration and estimated CCr is shown in Table 2. 1,25(OH)₂D₃ concentration was significantly lower in participants with CCr less than 30 mL/min. Similarly, intact PTH concentration was significantly higher in participants with CCr less than 30 mL/min, in whom 1,25(OH)₂D₃ concentration was significantly lower (Table 2). A tendency was seen for 25(OH)D₃ levels to be higher with lower CCr, and a significant difference was seen between groups with CCr of less than 30 and 45 mL/min or greater (*P* < .05, general linear model Bonferroni test). To improve understanding of how participants were distributed according to 25(OH)D₃ concentration and CCr value, they were divided into four groups with 25(OH)D₃ concentrations of less than 16 and 16 ng/mL and greater and CCr of less than 30 and 30 mL/min and greater. Concentrations of 1,25(OH)₂D₃, intact PTH, and serum NTx of the groups were then compared (Table 3). Of 198 participants with 25(OH)D₃ concentrations of less than 16 ng/mL, 36 (18.4%) had poor renal function (CCr < 30 mL/min), and of 205 participants with

Table 1. Comparison of Mean Data Values According to Age

Characteristic	Normal Range	Mean ± Standard Deviation		P-Value
		<85 (n = 139)	≥ 85 (n = 264)	
Age	—	79.1 ± 3.8	90.4 ± 3.7	<.001
Height, cm	—	145.2 ± 7.5	142.8 ± 7.2	.003
Weight, kg	—	44.1 ± 8.3	41.6 ± 7.5	.003
Body mass index, kg/m ²	—	20.7 ± 4.4	20.0 ± 3.3	.28
25 hydroxy-vitamin D ₃ , ng/mL	—	17.5 ± 4.9	16.3 ± 4.7	.01
1,25-dihydroxy-vitamin D ₃ , pg/mL	20–60	47.5 ± 18.1	42.7 ± 16.9	.008
Intact parathyroid hormone, pg/mL	10–65	51.6 ± 27.4	60.4 ± 43.2	.03
Albumin, g/dL	3.9–4.9	3.9 ± 0.3	3.9 ± 0.4	.01
Total protein, g/dL	6.5–8.2	6.9 ± 0.5	6.9 ± 0.5	.26
Total cholesterol, mg/dL	120–220	207.6 ± 38.0	195.9 ± 36.3	.003
Blood urea nitrogen, mg/dL	8–20	17.8 ± 6.5	18.7 ± 7.7	.25
Creatinine, mg/dL	0.5–0.8	0.66 ± 0.3	0.72 ± 0.4	.13
Creatinine clearance (Cockcroft-Gault formula), mL/min	—	55.2 ± 18.6	38.9 ± 12.7	<.001
Glomerular filtration rate (modified diet in renal disease formula), mL/min	—	73.9 ± 25.0	65.4 ± 22.1	.001
Calcium, mg/dL	8.7–10.1	8.8 ± 0.4	8.8 ± 0.5	.25
Phosphorus, mg/dL	2.5–4.5	3.6 ± 0.4	3.6 ± 0.5	.21
Aspartate aminotransferase, U/L	10–40	19.2 ± 6.2	19.7 ± 6.2	.39
Alanine aminotransferase, U/L	5–45	13.2 ± 7.5	11.5 ± 6.0	.02

Table 2. Comparison of 1,25-Dihydroxy-Vitamin D₃ (1,25(OH)₂D₃), Intact Parathyroid Hormone (PTH), and 25 Hydroxy-Vitamin D₃ (25(OH)D₃) Concentrations According to Creatinine Clearance (CCr)

CCr, mL/min	Mean (Standard Error)		
	1,25(OH) ₂ D ₃ , pg/mL	Intact PTH, pg/mL	25 Hydroxy-Vitamin D ₃ , ng/mL
<30.0 (n = 82)	33.0 (1.9)*	80.1 (4.3)*	17.9 (5.2)
30.0–44.9 (n = 160)	45.8 (1.3)	52.7 (3.0)	17.0 (4.9)
≥ 45 (n = 161)	48.8 (1.4)	50.5 (3.2)	15.9 (4.4)

* P < .05, general linear model Bonferroni test.

25(OH)D₃ concentrations of 16 ng/mL and higher, 45 (22.0%) had poor renal function. These percentages were approximately the same, but concentrations of intact PTH and NTx were significantly higher in the group with 25(OH)D₃ of less than 16 ng/mL and CCr of less than 30 mL/min. In addition, in the group with CCr of less than 30 mL/min, 1,25(OH)₂D₃ concentration was significantly lower than in the group with CCr of 30 mL/min and higher, regardless of 25(OH)D₃ concentration.

DISCUSSION

Table 4 summarizes the reports on 25(OH)D₃ concentration in elderly cohorts.^{14–20} A comparison of reports in which participants were living in institutions and reports in which participants were living independently revealed lower levels of 25(OH)D₃ in residents of institutions, who are thought to have greater difficulty with activities of

Table 3. Comparison of 1,25-Dihydroxy-Vitamin D₃ (1,25(OH)₂D₃), Intact Parathyroid Hormone (PTH), and Cross-Linked N-Telopeptide of Type I Collagen (NTx) Concentrations According to Creatinine Clearance (CCr) and 25 Hydroxy-Vitamin D₃ (25(OH)D₃) Concentration

CCr, mL/min	Mean (Standard Error)	
	25(OH)D ₃ , ng/mL	
	<16	≥ 16
<30		
1,25(OH) ₂ D ₃ , pg/mL	29.0 (2.7)*	36.3 (2.5)*
Intact PTH, pg/mL	104.8 (6.1)*	60.7 (5.4)
NTx, nmolBCE/L	28.3 (1.6)*	18.9 (1.4)
≥ 30		
1,25(OH) ₂ D ₃ , pg/mL	45.2 (1.2)	49.3 (1.3)
Intact PTH, pg/mL	55.1 (2.8)	48.1 (2.9)
NTx, nmolBCE/L	17.1 (0.7)	15.3 (0.7)

1,25(OH)₂D₃ levels were significantly lower in participants with CCr lower than 30 mL/min than those with CCr of 30 mL/min and higher. Mean intact PTH and NTx concentrations in participants with CCr lower than 30 mL/min and 25(OH)D₃ of less than 16 ng/mL were significantly higher than in the other participants.

* P < .05, general linear Bonferroni test.

daily living. Experts have proposed that 25(OH)D₃ concentrations of 20 to 32 ng/mL, or roughly 30 ng/mL, are the minimum necessary concentration to prevent fractures.²¹ A recent meta-analysis also reported that concentrations of 75 to 100 nmol/L balanced the benefits and risks of the health of elderly people.²² Many studies take PTH to be an indicator of the cutoff value for 25(OH)D₃ concentration.^{6–8} When PTH is taken as an indicator, a 25(OH)D₃ concentration of 20 ng/mL is taken as the cutoff

Table 4. Past Reports of 25 Hydroxy-Vitamin D₃ (25(OH)D₃) Levels in Elderly Cohorts

Study Participants	n	Age, Mean	25(OH)D ₃ , ng/mL, Mean	References
Nursing home (Japan)	133	84.6	11.9	14
Nursing home or housebound (United States)	116	81	12.6	15
Nursing home (this study, Japan)	425	86.4	16.8	—
Nursing home (United States)	35	74	17.4	16
Independent women (Canada)	186	73	15.6	17
Independent women (France)	440	80	17.0	18
Community-dwelling elderly women (Japan)	2,007	75.4	24.2	19
Independent women (United States)	500	71	29.6	20

in many reports.^{6–8} In the participants in this study, 78.1% had 25(OH)D₃ levels less than 20 ng/mL. Another study reported that 25(OH)D₃ of 20 ng/mL and greater is needed when intact PTH is taken as the indicator and that 28 ng/mL and greater is needed when bone density in the femoral neck is taken as the indicator.⁶ From the present results, the cutoff value for 25(OH)D₃ as an indicator of intact PTH was thought to be 16 ng/mL; 49.1% of participants had 25(OH)D₃ of less than 16 ng/mL (Figure 1). In general, people with poor renal function have lower levels of 1,25(OH)₂D₃, an activated form of vitamin D, as a result of poor vitamin D activating capacity. Moreover, secondary hyperparathyroidism from poor renal function is not unusual in elderly people.¹¹ In the present results as well, there was a strong negative correlation between 1,25(OH)₂D₃ and CCr ($r = -0.323$, $P < .001$), which suggests that renal function strongly affects 1,25(OH)₂D₃. As shown in Table 2, intact PTH levels were significantly higher and 1,25(OH)₂D₃ significantly lower with a CCr of less than 30 mL/min. From this it can be conjectured that vitamin D activation in the kidneys may decrease in cases of secondary hyperparathyroidism from poor renal function. In addition, as shown in Table 3, the percentage of people with poor renal function (CCr < 30 mL/min) was nearly the same in participants with 25(OH)D₃ levels greater and less than 16 ng/mL. Women with such vitamin D activating capacity made up 20.1% of all participants, although according to guidelines published in the United States in 2003²³ for bone metabolism disorders in individuals with chronic kidney disease, if PTH is measured and found to be high in people undergoing dialysis and those with chronic renal failure with less than 60% renal function, it is recommended that serum 25(OH)D₃ be measured and vitamin D₂ be administered if it is less than 30 ng/mL. Considering these guidelines, a greater number of people would probably be judged to have poor renal function, although there are limitations to this investigation. All CCr values were derived through calculation, not from actual measurements of CCr or glomerular filtration

rate (GFR). Cystatin C was not measured either. The Cockcroft-Gault formula was first used to calculate CCr, but the Modification of Diet in Renal Disease (MDRD) formula²⁴ was also used to investigate CCr. The correlation between CCr calculated using the Cockcroft-Gault formula and GFR calculated using the MDRD formula was high ($r = 0.769$, $P < .001$). Moreover, in the group with GFR of less than 50 mL/min ($n = 84$, 20.8%), a significant difference, similar to that in the results obtained with the Cockcroft-Gaults formula, was seen. Thus, although CCr obtained from calculations is not ideal, it seems to be reliable. In addition, intact PTH level may be a useful indicator in establishing a cutoff value for 25(OH)D₃ in frail elderly adults such as the present participants. Moreover, because plainly higher intact PTH levels were shown in participants with poor vitamin D activation in the kidneys, intact PTH may have an important role in considering vitamin D supplementation in frail elderly adults. Many experts recommend vitamin D supplementation with cholecalciferol when 25(OH)D₃ level drops below 30 to 32 ng/mL. A recent Institute of Medicine report²⁵ recommends supplementation when 25(OH)D₃ is less than 20 ng/mL, but it does not specifically address frail elderly adults. Vitamin D is not activated efficiently even with cholecalciferol supplementation in frail elderly adults, such as the present participants, who seem to have poor activation of vitamin D. Theoretically, therefore, it would seem that supplementation with a form of activated vitamin D such as paricalcitol or alfacalcidol may be beneficial in the case of frail elderly adults with poor renal function.

CONCLUSION

In this study, 25(OH)D₃ levels were found to be low in women living in nursing homes who were at least able to move about in a wheelchair with assistance. Approximately 50% to 80% of participants were thought to be vitamin D deficient, although this depends somewhat on the cutoff value used for 25(OH)D₃. In addition, approximately 20% of all participants were thought to have decreased vitamin D activating capacity in the kidneys. Such poor vitamin D activation capacity in the kidneys was present in a similar 20% of people whose 25(OH)D₃ level was above the cutoff level (16 ng/mL). An unexpectedly large number of women in nursing homes thus had poor vitamin D activation secondary to poor renal function. For vitamin D supplementation, therefore, it may be necessary to make a comprehensive judgment with measurements of intact PTH and CCr or GFR and 1,25(OH)₂D₃ rather than cholecalciferol supplementation based simply on 25(OH)₃ level.

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Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

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Relationship between Atrophy of the Medial Temporal Areas and Cognitive Functions in Elderly Adults with Mild Cognitive Impairment

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Key Words

Entorhinal cortex · VSRAD · Voxel-based morphometry · Wechsler Memory Scale · Stroop test

Abstract

Aim: The current study sought to determine which types of cognitive function are related to atrophy of the bilateral medial temporal areas including the entorhinal cortex (MTA-ERC) in elderly adults. **Methods:** The subjects were 96 elderly adults (mean age 75.3 years) with mild cognitive impairment. Subjects underwent Wechsler Memory Scale-Revised, logical memory I and II (WMS-R, LM I and II), Rey complex figure retention tests after 3 and 30 min (RCF-3 min and RCF-30 min), digit span backward (DSB), digit symbol-coding (DSC), Stroop Color and Word Test-Interference List (SCWT-IL) as well as magnetic resonance imaging (MRI) and were divided into elderly adults without or with mild to moderate MTA-ERC atrophy, and those with severe atrophy. **Results:** In all subjects, MTA-ERC atrophy showed significant relationships with age ($r = 0.43$), education ($r = -0.25$), WMS-R, LM I ($r = -0.21$), DSC ($r = -0.32$), and SCWT-IL ($r = 0.32$). The mild to moderate atrophy group showed significant relationships between MTA-ERC atrophy and age ($r = 0.34$), DSC ($r = -0.28$),

and SCWT-IL ($r = 0.25$). In contrast, in the severe atrophy group, MTA-ERC atrophy was correlated significantly with RCF-3 min ($r = -0.70$) and RCF-30 min ($r = -0.74$). The linear regression model included demographic variables and cognitive tests; two variables to survive the step-wise analysis were age ($\beta = 0.374$) and SCWT-IL ($\beta = 0.247$) in all subjects. Age ($\beta = 0.301$), and RCF-30 min ($\beta = -0.521$) and age ($\beta = 0.460$) remained as a significant variable in the mild to moderate atrophy and severe atrophy groups, respectively. **Conclusion:** Executive function tests such as SCWT-IL may be useful as a screening tool to identify mild to moderate MTA-ERC atrophy and a decline in the RCF test may suggest severe MTA-ERC atrophy in elderly adults with MCI.

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Introduction

There is increasing evidence for baseline structural magnetic resonance imaging (MRI) correlates of cognitive impairment in elderly adults exhibiting mild cognitive impairment (MCI) and Alzheimer's disease (AD) [1–4]. To date, the most reliable and well-documented finding is an association between impaired memory ability

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and medial temporal lobe atrophy, which is particularly robust in the hippocampus and entorhinal cortex (ERC) [5]. Several studies have reported that hippocampal and ERC atrophy can predict conversion to AD [6–9], as well as memory decline in MCI and AD [10, 11]. Although memory deficits constitute the hallmark feature of MCI, many patients exhibit deficits in other cognitive domains, such as mild anomia [12, 13], reductions in semantic fluency [14] and executive dysfunction, characterized by impaired working memory, inhibition, set-shifting, and phonemic fluency [15, 16]. The pathological hallmarks of AD (e.g. neurofibrillary tangles and senile plaques) have been found in the ERC in the earliest phase of disease, leading to an overall neuronal loss of 32% compared with control subjects [17]. An MRI investigation of the ERC reported a 37% decrease in patients who went on to develop AD, in comparison with control subjects [18]. These findings indicate that a strong relationship exists between *in vivo* measures of ERC atrophy in the early stages of AD.

The region of interest (ROI) method and more automated methods such as voxel-based morphometry (VBM) are the most common MR analysis techniques used for examining brain atrophy. Automated analytical methods such as VBM enable objective examination of anatomical group differences in controls, MCI patients, and AD patients across the whole brain. With this statistical parametric mapping technique, researchers are able to evaluate group differences in gray matter, white matter, and cerebrospinal fluid (CSF) volume with high spatial resolution. Whole-brain VBM has the important advantage of not requiring a priori assumptions about the size, location, or shape of the brain ROI(s). Furthermore, VBM allows the quantification of brain changes that are not easily revealed by visual inspection, such as atrophy that is not fully encompassed by sulcal boundaries between structures.

Recent research has led to the development of a voxel-based specific regional analysis system for Alzheimer's disease (VSRAD), which enables the examination of atrophy of the bilateral medial temporal areas including the entorhinal cortex (MTA-ERC) using VBM [19–21]. The VSRAD has been shown to achieve high accuracy (87.8%) in discriminating patients in the very early stages of AD with MCI from normal control subjects using Z-scores [21]. Atrophy of the MTA-ERC was indicated by VSRAD to exhibit a clear functional relationship with blood flow changes in the hippocampus, thalamus and temporal lobe, which were suggested to be closely related to inter-regional anatomical and physiological connections [22]. In cognitive function, Nagata et al. [23] reported that Z-

scores of the VSRAD was associated with executive function, although there was no relationship between Z-scores and memory function which was assessed by the Mini-Mental State Examination (MMSE) in the amnesic MCI and early AD patients. These authors suggested that detailed examination such as the Wechsler Memory Scale was required to reveal the relationship between MTA atrophy and memory function. Moreover, it is currently unclear which aspects of cognitive function including memory and executive function are related to the atrophy of the MTA-ERC identified by VSRAD in elderly adults with MCI.

In the current study, we measured volumetric MRI and performance in a range of cognitive domains, including logical memory, visual memory, working memory, processing speed, and executive function in elderly adults with MCI. Overall, we sought to determine which aspects of cognitive performance were associated with MTA-ERC atrophy in elderly adults with MCI.

Methods

Subjects

Subjects in this study were recruited from two volunteer databases ($n = 1,543$), which included elderly individuals (65 years and over) selected either by random sampling, or when they attended a medical check-up in Obu, Japan. 528 prospective subjects with a Clinical Dementia Rating (CDR) of 0.5, or who complained of memory impairment, were recruited in the first eligibility assessments. 165 subjects responded to the second eligibility assessments, and 125 out of 165 subjects completed the neuropsychological tests which included language and memory tests, attention and executive function tests, clinical diagnosis, activities of daily living (ADL), educational level, and MRI scanning. Out of 125 subjects, 25 were excluded and the remaining 100 subjects met definition of MCI using Petersen criteria [24]. All MCI subjects had objective impairments in either episodic memory and/or executive functioning at least 1.5 standard deviations below the age-adjusted mean for at least one of the neuropsychological tests. Final classification of subjects was based on the above factors and consensus of a team of neuroscientists. Exclusion criteria included CDR 0, or 1–3, a history of neurological, psychiatric, and cardiac disorders or other severe health issues, use of donepezil, impairments in basic ADL, and participation in other research projects. 96 elderly adults remained after these exclusions (mean age 75.3 ± 6.8 years, range 65–93, men $n = 48$, 50%), and were included in the final analysis. Table 1 shows the characteristics of the subjects.

The purpose, nature, and potential risks of the experiments were fully explained to subjects. All subjects gave written, informed consent before participating in the study. The study protocol was approved by the Ethics Committee of the National Center for Geriatrics and Gerontology.

Table 1. Characteristics of subjects (mean \pm SD)

Age, years	75.3 \pm 6.8
Male, %	50
Education, years	10.6 \pm 2.5
Body mass index	23.0 \pm 3.1
Cognitive functions	
MMSE, points	26.5 \pm 2.5
WMS-R, LM I, points	14.4 \pm 7.1
WMS-R, LM II, points	10.0 \pm 7.4
RCF-3 min, points	15.5 \pm 6.3
RCF-30 min, points	14.9 \pm 6.7
DSB, points	5.2 \pm 1.6
DSC, points	46.1 \pm 15.9
SCWT-IL, s	21.1 \pm 17.2
Medication, yes, %	
Hypertension	44.8
Heart disease	5.2
Diabetes mellitus or hyperlipidemia	20.9
Total number \pm SD	2.3 \pm 2.1

WMS-R, LM = Wechsler Memory Scale-Revised, Logical Memory; RCF = Rey complex figure retention test; DSB = digit span backward; DSC = digit symbol coding; SCWT-IL = Stroop Color and Word Test-Interference List.

MRI

MRI was performed with a 1.5-T system (Magnetom Avanto; Siemens, Germany). Three-dimensional volumetric acquisition with a T₁-weighted gradient echo sequence was then used to produce a gapless series of thin sagittal sections using a magnetization preparation rapid-acquisition gradient-echo sequence (repetition time 1,700 ms, echo time 4.0 ms, flip angle 15°, acquisition matrix 256 \times 256, 1.3 mm slice thickness).

The MRI images acquired from the subjects were formatted to gapless, transaxial images, followed by extraction of the gray matter images using SPM2. Anatomical standardization was used to fit each individual brain to the standard template MRIs in the common coordinate system of the MNI T₁ MRI template [25, 26]. The segmented gray matter images were then subjected to affine and non-linear standardization using a template of prior gray matter.

The anatomically standardized gray matter images were then smoothed again using an isotropic Gaussian kernel 12 mm in full width at half maximum, to determine the partial volume effect and create a spectrum of gray matter intensities. Gray matter intensities were equivalent to the weighted average of gray matter voxels located in the volume fixed by the smoothing kernel. Regional intensity was considered equivalent to gray matter concentration. We compared the gray matter image of each patient with the mean and standard deviation (SD) of gray matter images of healthy volunteers using voxel-by-voxel Z-score analysis. In the final step, the Z-score was calculated according to the following equation: (Z-score = ((control mean) - (individual value))/control SD). The Z-score thus reflected the degree of atrophy in bilateral MTA-ERC. Higher Z-scores indicated clearer MTA-ERC atrophy.

Cognitive Tests

Speech therapists conducted all of the memory tests, and a speech therapist recalculated all of the results. The Wechsler Memory Scale-Revised, logical memory I and II (WMS-R, LM I and II) [27], Rey complex figure retention tests after 3 and 30 min (RCF-3 min and RCF-30 min), digit span backward (DSB) and digit symbol-coding (DSC) subset of the Wechsler Adult Intelligence Scale III [28], and Stroop Color and Word Test-Interference List (SCWT-IL) [29] were included as cognitive tests.

Modified versions of the logical memory subtest from the WMS-R and RCF were used to assess logical and visual memory ability, respectively. In the WMS-R, two short stories (story a and b) were read aloud to the subject, who was instructed to recall details of the stories immediately (LM I) and after 30 min (LM II) [27]. We calculated the total score, i.e. sum score of story a and b, of WMS-R in LM I and LM II. In the RCF, subjects were requested to copy the RCF figure (construction ability) and reproduce it after 3- and 30-min delays. One rater independently scored the RCF using the system described by Osterrieth and Rey [30] and translated by Corwin and Bylsma [31]. DSB and DSC were used to assess working memory and processing speed, respectively. DSB required subjects to repeat a series of verbally presented digits of increasing length in backward order. In the DSC, subjects copied symbols that are paired with numbers. Using the key provided at the top of the exercise form, the participant drew the symbol under the corresponding number. The score of DSC was the number of correct symbols drawn within 120 s. In the SCWT-IL as a test of executive function, subjects were presented with a series of color words. Our test version consisted of two subtasks. The first subtask showed color words in random order (red, blue, yellow, green) printed in black ink. The second subtask contains color words printed in an incongruous ink color, for example, the word *yellow* printed in red ink. The subjects were instructed to read the words and name the ink color of the printed words as quickly and as accurately as possible in the two subsequent subtasks. The score was measured as the total time taken to complete the task with 24 words [32]. The time limit to complete a subtask was set at 120 s. An interference measure was calculated by subtracting the average time needed to complete the first subtask from the time needed to complete the second subtask.

Analysis

The relationships between atrophy of the MTA-ERC and cognitive measurements were examined with Pearson correlations. The independent associations between MTA-ERC atrophy and cognitive ability with each demographic (i.e. sex, age, and educational level) and diagnosis (aMCI and non-aMCI) variables were tested using a linear regression model with a step-wise analysis. To examine differences in MTA-ERC atrophy level, subjects were divided into the following two groups according to the Z-score: (1) mild to moderate atrophy group (Z-score: 0–1.99) and (2) severe atrophy group (Z-score: 2.00 and over) in the MTA-ERC, according to the results of the VSRAD [23]. Pearson correlations and the linear regression model with a step-wise analysis were used to examine the relationships between MTA-ERC atrophy and cognitive tests in each group. SPSS 18.0 software (SPSS Inc., Chicago, Ill., USA) was used for all data management and statistical analysis. The statistical threshold was set at a $p < 0.05$.

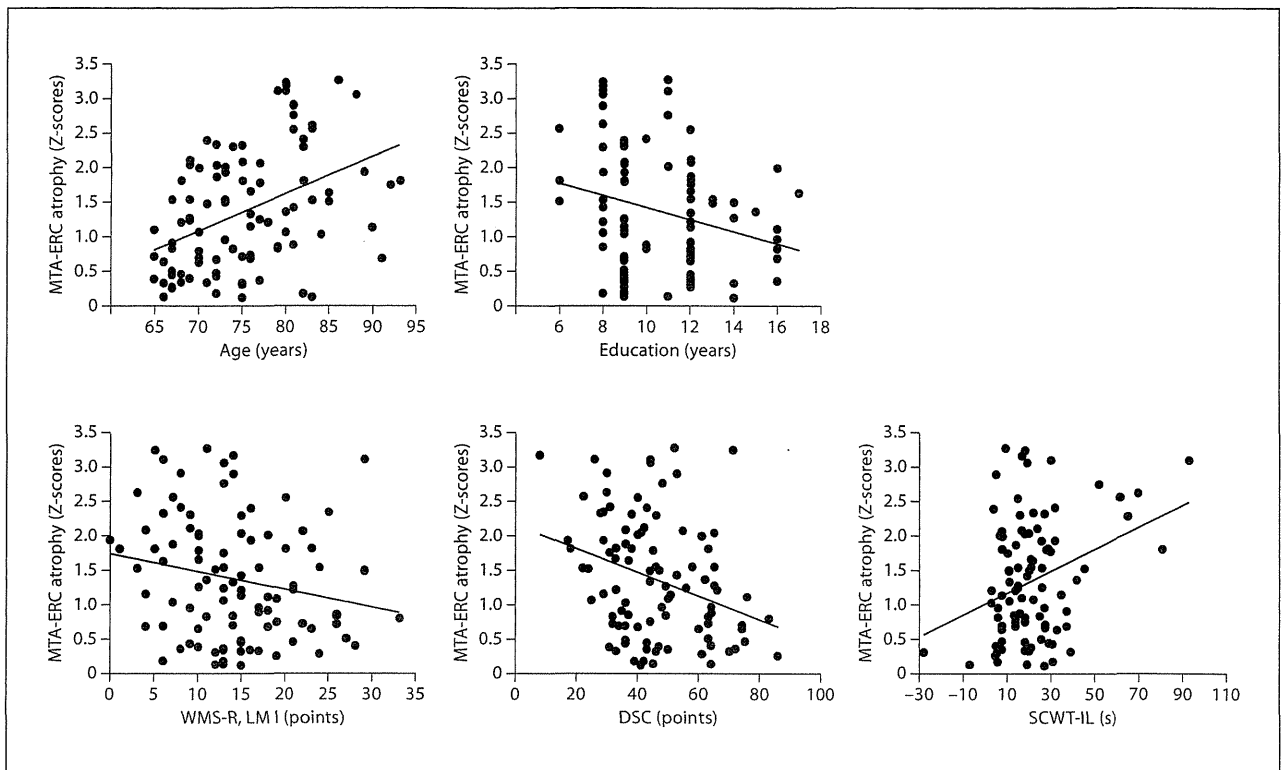


Fig. 1. Relationship between the Z-score of MTA-ERC and age, education, and cognitive test scores. MTA-ERC atrophy was correlated significantly with age ($r = 0.43$, $p < 0.001$), educational level ($r = -0.25$, $p = 0.012$), WMS-R, LM I ($r = -0.21$, $p = 0.040$), DSC ($r = -0.32$, $p = 0.002$), and SCWT-IL ($r = 0.32$, $p = 0.002$).

Table 2. Pearson correlation coefficients between MTA-ERC atrophy and age, educational level, and cognitive measurements

	All subjects (n = 96)		Mild to moderate atrophy group (n = 72)		Severe atrophy group (n = 24)	
	r	p value	r	p value	r	p value
Age	0.43	<0.001	0.34	0.003	0.71	<0.001
Education	-0.25	0.012	0.01	0.921	-0.26	0.224
WMS-R, LM I	-0.21	0.040	-0.17	0.155	-0.06	0.774
WMS-R, LM II	-0.09	0.370	0.03	0.812	-0.22	0.308
RCF-3 min	-0.16	0.119	-0.10	0.396	-0.70	<0.001
RCF-30 min	-0.13	0.201	-0.11	0.386	-0.74	<0.001
DSB	-0.15	0.134	-0.12	0.298	-0.14	0.511
DSC	-0.32	0.002	-0.28	0.016	-0.05	0.825
SCWT-IL	0.32	0.002	0.25	0.031	0.18	0.404

For abbreviations, see table 1.

Fig. 2. Relationship between the Z-score of MTA-ERC and processing speed and executive function in the mild to moderate atrophy and severe atrophy groups. The upper panel shows scatter plots between MTA-ERC atrophy and DSC and the lower panel shows scatter plots between MTA-ERC atrophy and SCWT-IL. Correlations of the mild and moderate and severe atrophy groups are shown in panels **a** and **b**, respectively. MTA-ERC atrophy was correlated significantly with DSC ($r = -0.28$, $p = 0.016$) and SCWT-IL ($r = 0.25$, $p = 0.031$) in the mild and moderate atrophy group.

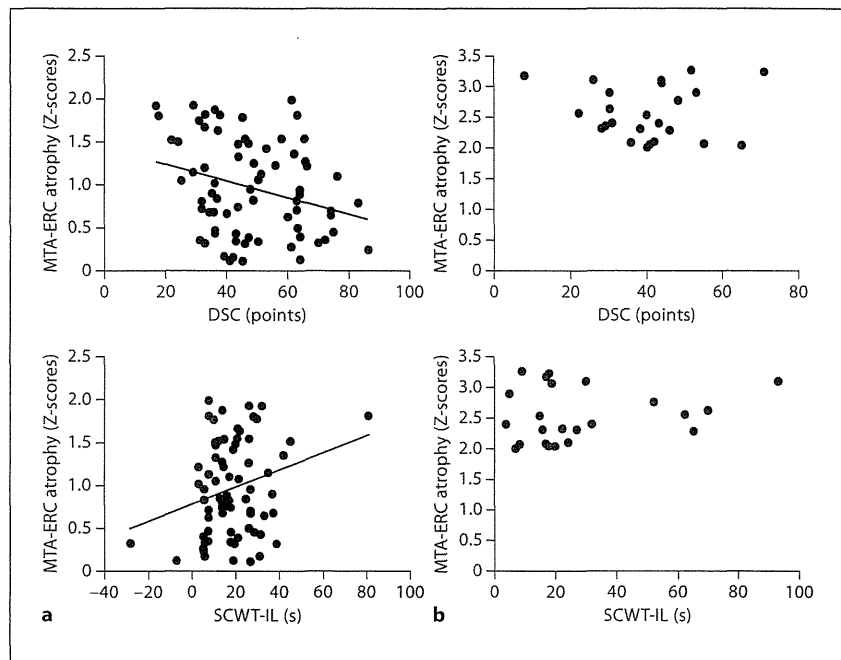


Table 3. Multivariate regression analysis between MTA-ERC atrophy and age, educational level, and cognitive measurements

	β	t value	p value	R^2
All subjects				
Age	0.374	4.0	<0.001	0.236
SCWT-IL	0.247	2.6	0.01	
Mild to moderate atrophy group				
Age	0.301	2.6	0.011	0.091
Severe atrophy group				
RCF-30 min	-0.521	-3.8	0.001	0.706
Age	0.460	3.4	0.003	

For abbreviations, see table 1.

Results

In all subjects, Z-score showed significant relationships with age ($r = 0.43$, $p < 0.001$), education ($r = -0.25$, $p = 0.012$), WMS-R, LM I ($r = -0.21$, $p = 0.040$), DSC ($r = -0.32$, $p = 0.002$), and SCWT-IL ($r = 0.32$, $p = 0.002$) (fig. 1; table 2). There were no significant relationships between Z-score and WMS-R, LM II, RCF-3 min, RCF-30 min, and DSB (table 2). In linear regression model, two variables to survive the step-wise analysis were age ($\beta =$

0.374 , $p < 0.001$) and SCWT-IL ($\beta = 0.247$, $p < 0.010$) (table 3).

Of the 96 MCI elderly adults tested, the mild to moderate atrophy and severe atrophy groups included 72 (75%) and 24 (25%) subjects, respectively. In the Pearson correlation analysis, the mild to moderate atrophy group showed significant relationships between Z-score and age ($r = 0.34$, $p = 0.003$), DSC ($r = -0.28$, $p = 0.016$), and SCWT-IL ($r = 0.25$, $p = 0.031$) (fig. 2; table 2). In contrast, Z-scores were correlated significantly with RCF-3 min ($r = -0.70$, $p < 0.001$) and RCF-30 min ($r = -0.74$, $p < 0.001$) in the severe atrophy group (fig. 3; table 2).

A multivariate regression model indicated that age ($\beta = 0.301$, $p = 0.011$) remained as the only significant variable in the mild to moderate atrophy group (table 3). DSC and SCWT-IL did not reach significance in this group. In the severe atrophy group, two variables to survive the step-wise analysis were RCF-30 min ($\beta = -0.521$, $p = 0.001$) and age ($\beta = 0.460$, $p = 0.003$) (table 3).

Discussion

It is well established that structures in the medial temporal lobe, particularly the hippocampus and ERC, are essential for normal memory function [33]. There is evi-