Recently, a number of studies described the temporal patterns of functional decline before death, from either retrospective surveys of bereaved families or periodical observation of dying subjects [2, 3, 12–14]. These studies have described the different patterns of the time-course of disability before death in accordance with comorbid conditions and causes of death. No study has yet examined whether there are any modifiable factors related to the length of life with disability before death. If we could identify these factors, we could devise strategies to shorten morbidity and thus enhance the quality of the last months of life.

Our objective was therefore to examine whether there were any modifiable factors related to the length of life with disability before death. For this purpose, we conducted an interview survey of the family members of the deceased who had been enrolled earlier in a prospective cohort study.

Methods

Study Design

This study was a retrospective observation of the deceased who had been enrolled in a prospective cohort study. Study data were derived from the Ohsaki National Health Insurance (NHI) beneficiaries' cohort study, the design of which has already been reported in detail [15].

In 1994, we conducted a baseline survey of the NHI beneficiaries in a rural Japanese community. The response rate of those aged 70–79 years at baseline was 94.0%. From 1996 to 1999, we followed up the survival status of the participants (n = 10,216) and documented 781 deaths. With official permission from the government, we investigated the causes and dates of death of all the deceased. In accordance with the 10th edition of the International Classification of Diseases (ICD-10), we excluded 29 subjects who had died from external causes (ICD-10; V01-Y98). We then attempted to contact the family members of the remaining 752 subjects. We were unable to locate 44, but we contacted the family members of the remaining 708, explained the purpose of the study, and asked for participation in an interview survey to be conducted between February and March 2000. Finally, 655 families (93.0%) gave their consent to be interviewed.

This study was approved by the Ethics Committee of the Tohoku University Graduate School of Medicine.

Assessment of Lifestyle

In the baseline survey carried out in 1994, we assessed health-related lifestyle with a self-completion questionnaire. Body mass index (BMI) was calculated as the self-reported weight (kg)/height^2 (m) and then classified into three categories: <20, 20–25, >25. The criteria for BMI were developed from earlier studies showing their association with greater disability [16]. Tobacco smoking status was classified as current smoker, past smoker, or had never smoked. Subjects were asked: 'How long do you walk a day, on average?', and could choose one out of three options to answer: <30 min, 30 min to 1 h, and >1 h. The validity of the questionnaire on walking had already been established [17]. We also asked the subjects whether they were able to independently perform basic activities of daily living (ADL) tasks such as eating.

Outcome Measures

In 2000, we conducted structured interviews of families of the deceased regarding the disability status of the subjects before death. We asked whether they had been able to perform the four ADL tasks (eating, toileting, dressing, and bathing) at each of the following 6 time points before death: 1 week, 1 month, 3 months, 6 months, 1 year, and 3 years. The interviewers typically asked: 'Was he/she able to eat (or other task) by himself/herself 1 week (or other period) prior to death?'

We defined the length of life with disability before death as the duration from the time when a subject became unable to perform at least one of four ADL tasks independently to the time when he/she died.

Statistical Analysis

First, we examined the association between cause of death and the length of life with disability. We classified the underlying cause of death into four groups: death due to cancer (ICD-10; C00-97, D37-48), death due to stroke (I60-69), death due to ischemic heart disease (IHD) (I20-25), and others.

We then examined the relationship between health-related lifestyle and the length of life with disability before death. Since disability at baseline could influence baseline behaviors, in this analysis we limited to the 594 subjects who had been independent from the ADL angle at the time of the baseline survey. We arbitrarily defined 'long-term disability' as being disabled for more than 6 months before death, as this was the closest to the median value. To determine the associations between lifestyle and risk of long-term disability, we used a multivariate logistic regression after adjusting for sex, age at death, cause of death, baseline physical functioning status, and history of arthritis, osteoporosis, hypertension, or diabetes mellitus.

We also conducted stratified analyses of the relative risk of long-term disability before death according to cause of death – death from cancer, IHD or stroke, and other causes.

p values for tests of linear trends were estimated by using each category as a continuous variable. We used approximate variance formulas to calculate the 95% confidence interval (CI). All analyses were conducted with SAS software version 8.02 (SAS Institute, Cary, N.C., USA) [18].

Results

Among the deceased whose families gave their consent to cooperate with our interview survey (n = 655), 62.0% were men. The mean age at death was 78.4 years. The most common cause of death was cancer (32.5% of the total deaths), followed by stroke (18.9%) and IHD (9.3%). The distributions of causes of death among the study subjects was consistent with the national data for Japan: according to the Vital Statistics of Japan for 1998 among

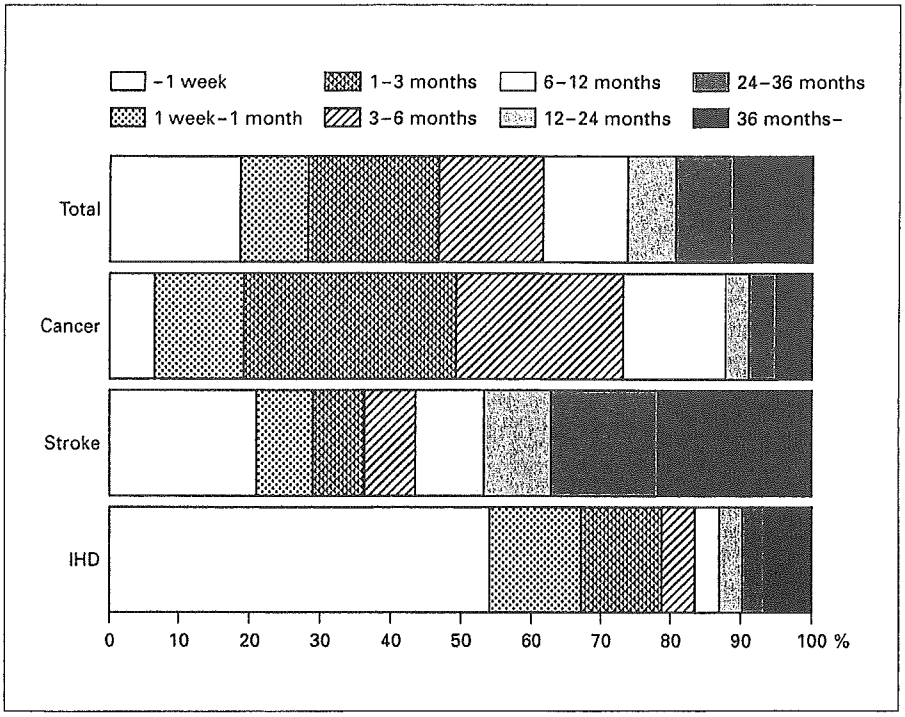

Fig. 1. Distribution of the length of life with disability before death.

those who had died aged 70–84 years, cancer accounted for 32.2% of deaths, stroke for 15.8%, and IHD for 8.5%.

Distribution of the Length of Life with Disability before Death

Among the study subjects, only 11.0% were disabled at 3 years prior to death, and 26.3% at 1 year prior to death. The frequency of disability then increased to 38.3% at 6 months, 53.1% at 3 months, 71.8% at 1 month, and 81.4% at 1 week prior to death. The frequency of disability in the subjects of this study was consistent with the Japanese national data.

The distribution of the length of life with disability before death by cause of death is shown in figure 1. The distribution varied significantly with cause of death. The median values for duration of disability were longest among those who died from stroke: the values were 3–6 months among all the deceased, less than 1 week among those who died from IHD, 3–6 months among those who died from cancer, and 6–12 months among those who died from stroke.

At 1 week prior to death, subjects who died from IHD were more active than those who died from any other causes. As many as 54.1% of those who died from IHD were independent until 1 week before death, whereas those values were only 6.6 and 21.0% in the subjects who died from cancer and stroke, respectively. Among those who died from stroke, 46.8% had been disabled for more than 12 months, whereas these values were only 13.1% among those who died from IHD and 12.2% among those who died from cancer.

Characteristics of the Deceased and Length of Life with Disability before Death

The relationships between the characteristics of the deceased and the risk of long-term disability are shown in table 1. Because disability at baseline could influence baseline behaviors, we limited this analysis to the 594 subjects who had been independent in all aspects of ADL at the time of the baseline survey. In this group, the mean age at death was 78.3 years and 377 (63.5%) were men. These lifestyle factors were assessed in 1994 and the subjects died between 1996 and 1999, so we were able to examine the relationships between lifestyle 2–5 years before death and the risk of long-term disability.

Because 6 months was the closest to the median value of the length of life with disability before death among the study subjects, we defined more than 6 months of life with disability before death as 'long-term disability'. The percentage of long-term disability varied with the cause of death: 23.5, 44.9, 8.9 and 39.4% for those who died

Table 1. Characteristics of the deceased and the risk of long-term (more than 6 months) disability before death

Characteristic		n	Long-term disability[1],%	Odds ratio[2]	95% CI	p value
Sex	Men	377	30.0	1.00	(Ref)	
	Women	217	35.5	0.83	0.50–1.39	0.48
Age at death	70–74	87	19.5	1.00	(Ref)	
	75–79	266	29.7	1.58	0.84–2.97	0.15
	80–	241	39.0	2.29	1.22–4.31	0.010
	Trend					0.0053
Cause of death	Cancer	204	23.5	1.00	(Ref)	
	Stroke	98	44.9	2.50	1.44–4.34	0.0011
	IHD	56	8.9	0.31	0.12–0.85	0.023
	Other	236	39.4	2.08	1.26–3.08	0.0028
BMI	<20.0	136	29.4	1.00	(Ref)	
	20.0–24.9	276	31.2	1.30	0.80–2.12	0.30
	≥25.0	119	40.3	2.08	1.16–3.72	0.014
	Trend					0.039
Tobacco smoking	Never smoked	197	37.1	1.00	(Ref)	
	Current smokers	167	30.5	1.06	0.60–1.85	0.85
	Past smokers	155	29.7	0.86	0.47–1.55	0.60
Walking, h/day	≥1.0	161	24.2	1.00	(Ref)	
	0.5–0.9	149	29.5	1.34	0.79–2.28	0.29
	<0.5	217	41.0	1.68	1.03–2.75	0.040
	Trend					0.028

CI = Confidence interval; IHD = ischemic heart diseases.

[1] Long-term disability denotes the period with disability before death longer than 6 months.

[2] Adjusted for sex, age at death (70–74, 75–79, and 80 years or older), cause of death, past history of hypertension, diabetes mellitus, osteoporosis and arthritis at baseline, and baseline physical functioning status (able to perform strenuous or moderate activities, able to walk one block or stairs, able to perform self-care or unable to do anything unaided).

from cancer, stroke, IHD and other causes, respectively. Compared with those who died from cancer, the odds ratio of long-term disability was 2.50 (95% CI 1.44–4.34) in those who died from stroke and 0.53 (0.12–0.85) in those who died from IHD. The odds ratio of long-term disability increased with age (p for trend = 0.053).

We examined the relationships between long-term disability before death and health-related lifestyles, including time spent walking, smoking status, and BMI. A shorter period spent walking and a higher BMI were significantly associated with risk of long-term disability before death after adjustment for sex, age at death, history of arthritis, osteoporosis, hypertension and diabetes mellitus, smoking status, physical functioning status, and cause of death. Compared with patients with BMI <20, the odds ratio of long-term disability was 1.30 (95% CI 0.80–2.12) in those with BMI 20–25 and 2.08 (1.16–3.72) in those with BMI >25 (p for trend = 0.039). The odds ratio of long-term disability significantly increased with a shorter time spent walking: compared with patients who walked >1.0 h/day, it was 1.34 (95% CI 0.79–2.28) in those who walked 0.5–0.9 h/day and 1.68 (1.03–2.75) for those who walked <0.5 h/day (p for trend = 0.028). There was no significant association between smoking history and disability. The above association was unchanged even when we changed the cut-off point for long-term disability to either 3 months or 1 year.

Because both obesity and physical inactivity are established risk factors for cardiovascular disease, the above association might be attributable to residual confounding of cardiovascular-related disability by cardiovascular risk factors. Therefore, we also examined the relationship be-

tween health-related lifestyle and the length of life with disability after stratifying by cause of death – death from cancer, IHD or stroke, and other causes. Compared with subjects with BMI <20, the odds ratio of long-term disability in those with BMI >25 were 2.88 (95% CI 1.01–8.23) for those who died from cancer, 1.54 (0.51–4.62) for those who died from IHD or stroke, and 1.50 (0.61–3.66) for those who died from other causes. Compared with those who had walked more than 1.0 h/day, the odds ratio of long-term disability among those who had walked for <0.5 h/day were 4.39 (1.57–12.29) in those who died from cancer, 2.11 (0.73–6.08) in those who died from IHD or stroke, and 0.93 (0.45–1.91) in those who died from other causes. The relationships between higher BMI and shorter time spent walking and increased risk of long-term disability before death were observed consistently across individual causes of death.

In separate models, we also examined the effect modification of the association among long-term disability before death and time spent walking, BMI, and smoking. None of the interactions tested was statistically significant (data not shown).

Discussion

Previous studies of the time-course of functional decline before death in the elderly have not identified any predictors of the length of life with disability [3, 12–14]. To clarify whether there are modifiable lifestyle factors influencing duration of disability before death, we conducted a retrospective observation of the deceased who had earlier been enrolled in a prospective cohort study. The results indicated that shorter time spent walking each day and higher BMI were significantly associated with long-term disability before death after adjustment for age at death, cause of death, and other potential confounding factors. To our knowledge, this is the first study to examine the association between a variety of lifestyle factors and duration of disability before death. Our study has some methodological strength. The subjects' lifestyles were surveyed when they lived independently and our findings were based on a prospective, population-based, representative cohort study. The follow-up rates of mortality incidence and participation of bereaved families in the study were high enough.

The characteristics of the deceased such as cause of death, age at death, and the length of life with disability were similar to the Japanese national data. The trajectory of functional disability of those who died from cancer was similar to that in the study of Lunney et al. [13], in which they reported the trajectories of functional disability for four categories (sudden death, cancer, organ failure, and frailty) using point-estimated incidence of disability before death. In our study, the time-course of disability before death varied with cause of death, and the duration of disability was greatest among those who died from stroke.

There were two potential limitations. First, information on duration of disability was obtained from proxies – a potential source of error or incorrect recollection. Second, we examined the lifestyles of subjects aged 70 years or more, but did not investigate when the subjects had started those lifestyles. Therefore, we did not determine whether the positive effect of healthy lifestyle on duration of disability before death was equally apparent in those who had recently improved their lifestyles and in those who had led healthy lives for many years.

We identified higher BMI and shorter time spent walking each day as predictors of long-term disability before death. The association between obesity and physical inactivity and disability was observed equally in each group of subjects, whether they died from cancer, stroke, IHD or other causes. This finding suggests that lifestyle factors such as BMI and daily walking may have important effects on the duration of disability, irrespective of the cause of death. There seems to be a possibility for patients to reduce their length of disability by lifestyle modification.

Although we identified only these two factors, there could be other modifiable factors for the length of disability before death. Further research is needed so that we may enhance the quality of the last months of life.

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Original Article

Influence of Leisure-Time Physical Activity on the Relationship between C-Reactive Protein and Hypertension in a Community-Based Elderly Population of Japan: The Tsurugaya Project

Kaijun NIU, Atsushi HOZAWA*,**, Kazuki FUJITA***, Kaori OHMORI*, Mitsuharu OKUTSU, Shinichi KURIYAMA*, Ichiro TSUJI*, and Ryoichi NAGATOMI

There are several studies indicating an association between C-reactive protein (CRP) and blood pressure (BP) in the Japanese population, but the influence of physical activity has not been considered. Therefore, we designed a cross-sectional survey to determine whether leisure-time physical activity (LTPA) modifies the relation between CRP and hypertension among Japanese elderly. Our study population comprised 643 subjects aged 70 years and over in whom CRP, home BP, and self-reported LTPA were measured. LPTA was categorized into three levels of intensity—walking, brisk walking, and sports—and a questionnaire was used to estimate the level in each patient. Hypertension was defined as a home systolic BP of 135 mmHg or over and/or home diastolic BP of 85 mmHg or over or current use of antihypertensive agents. LTPA levels were associated with both CRP and hypertension. After adjustment for factors affecting CRP and hypertension, and additional adjustment for LTPA levels, the odds ratio (95% confidence interval) of hypertension by CRP was 2.21 (range: 1.33–3.72), 1.99 (1.17–3.42), and 2.38 (1.36–4.21) times higher in subjects in the second, third, and fourth quartiles of CRP, as compared to subjects in the first quartile, respectively. A multiple regression model showed a positive and significant relation between log-transformed CRP and systolic BP after adjustment for potential confounding factors when participants taking antihypertensive medication were excluded. This is the first study to clarify that the positive significant relation between CRP and hypertension was independent of LTPA levels among Japanese elderly. (*Hypertens Res* 2005; 28: 747–754)

***Key Words*: C-reactive protein, leisure-time physical activity, hypertension, Japanese, community-dwelling population**

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Introduction

C-reactive protein (CRP) is a classical acute-phase marker and a member of the pentraxin family of innate immune response proteins (*1*, *2*). The concentration of CRP in serum is generally less than 2 μg/ml but increases by as much as 1,000-fold in response to stimuli such as tissue injury or inflammation (*3*). Following removal of the inflammatory stimulus, CRP levels decline rapidly. These features have made CRP useful as a clinical marker of an inflammatory process. Over the last several years, increasing evidence has suggested that inflammation mechanisms are important in the pathophysiology of hypertension (*4–7*). Furthermore, several studies have shown that serum CRP levels are associated with the development of hypertension (*8*, *9*).

At the same time, numerous studies have indicated that physical activity (PA), including leisure-time physical activity (LTPA), is inversely related to the prevalence of hypertension (*10*, *11*) or serum concentration of CRP (*12–19*). A more recent study has also demonstrated that inflammatory markers including CRP were lower in older adults with higher levels of exercise and non-exercise PA (*12*). Considering these studies together, it is natural to assume that PA would be a potent modifier of the relationship between CRP and hypertension. But to our knowledge, there are only three reports that have investigated the relationship between CRP and hypertension adjusted for the effect of PA (*20–22*), and their results are inconsistent. Furthermore, although there have been several studies that indicated an association between serum CRP level and blood pressure (BP) in Japanese, the influence of PA on this relationship has not been considered (*23–27*). Therefore, we considered that it would be worthwhile to examine whether the relation between CRP and hypertension is dependent of LTPA, and designed the present cross-sectional analysis in Japanese community-dwelling elderly individuals for this purpose.

Methods

Study Participants

Our study population was comprised of subjects aged 70 years and older who were living in the Tsurugaya area of Sendai, one of the major cities in the Tohoku area of Japan. At the time of the study in 2002, there were 2,730 individuals aged 70 years and older living in Tsurugaya. We invited all of these individuals to participate in a comprehensive geriatric assessment, which included medical status, physical function, cognitive function and dental status, and 1,178 of them did so, giving their informed consent for analysis of the data. The protocol of this study was approved by the Institutional Review Board of Tohoku University Graduate School of Medicine.

We excluded subjects whose high-sensitivity CRP had not been measured ($n=29$). Since we assessed hypertension using self-measured BP at home (home blood pressure [HBP]) data, subjects who did not measure HBP data more than 3 days during the 4-week study period were also excluded ($n=182$). This criterion was based on our previous observation that average BP values for the first 3 days did not differ significantly from those obtained during the entire study period (*28*, *29*). We also excluded those subjects whose serum CRP concentrations were higher than 10.0 mg/l ($n=24$), because those with acute inflammatory conditions were frequently found to have serum CRP levels ≥10.0 mg/l (*30*). Furthermore, we excluded subjects who did not complete the questionnaire items on LTPA ($n=109$). Finally, we excluded all potential subjects with notable comorbidity factors that might influence the frequency and degree of PA by a self-reported decline of physical function using the Medical Outcome Study (*31*) (physical functioning score ≤1; $n=77$) or arthritis ($n=114$). As a result of these exclusions, the final study population comprised 643 subjects (mean age, 75.5±4.4 years; men: 48.5%).

Measurements

Anthropometric measures (height, body weight) were recorded by a standardized protocol. HBP was measured with an HEM747IC device (Omron Life Science Co., Ltd., Tokyo, Japan), which uses the cuff-oscillometric method to generate a digital display of systolic and diastolic blood pressures (SBP and DBP). This device has been validated previously, and satisfies the criteria of the Association for the Advancement of Medical Instrumentation (*32*). We used the following procedure to ascertain the accuracy of the HBP measurement. First, physicians informed the population about HBP recording and taught them how to measure their own BP. The daily measurement was made within 1 h of awakening and before breakfast, with the subject seated and having rested for at least 2 min. In subjects receiving antihypertensive drugs, HBP was measured before taking the drugs. The HBP of an individual was defined as the mean of all measurements obtained for that person. The mean (±SD) number of HBP measurements was 15.9±10.5 (range, 3–49).

Blood samples were drawn from the antecubital vein of the seated subject with minimal tourniquet use. Specimens were collected in siliconized vacuum glass tubes containing sodium fluoride for blood glucose, and no additives for lipids and CRP analyses.

Total cholesterol (T-C), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) levels and blood glucose levels were measured by enzymatic methods (T-C, Denka Seiken, Tokyo, Japan; TG, Kyowa Medex, Tokyo, Japan; HDL-C, Daiichi Pure Chemicals, Tokyo, Japan; blood glucose, Shino-Test, Tokyo, Japan). Serum uric acid levels were determined according to a uricase method (*33*) with the Olympus autoanalyzer AU-5000 (Olympus Corp., Tokyo, Japan).

Table 1. Definition of Physical Activity Level

	Level 1	Level 2	Level 3	Level 4	Level 5	Level 6
N	147	131	148	71	80	66
Walking	None	Low	High	Any	Any	Any
Brisk walking	None	None	None	Low	High	Any
Sports	None	None	None	None	None	Low and High
Walking (*N*)						
None	147	0	0	25	49	30
Low	0	131	0	21	2	19
High	0	0	148	25	29	17
Brisk walking (*N*)						
None	147	131	148	0	0	41
Low	0	0	0	71	0	12
High	0	0	0	0	80	13
Sports (*N*)						
None	147	131	148	71	80	0
Low	0	0	0	0	0	58
High	0	0	0	0	0	8

High: at least 3–4 times per week for at least 30 min each time; Low: reporting some activity in the past year, but not enough to meet high levels; None: no leisure-time physical activity. *N*: number of subjects.

CRP levels were determined using an immunotechnique on a Behring BN II analyzer (Dade Behring, Tokyo, Japan). The BN II high-sensitivity assay utilizes a monoclonal antibody coated on polystyrene particles and fixed-time kinetic nephelometric measurements (*34*). The BN II nephelometer uses a 1:400 dilution to measure CRP concentrations between 3.5 and 210 mg/l. The assay has been approved by the US Food and Drug Administration for use in assessing the risk of cardiovascular and peripheral vascular disease.

Questionnaire of LTPA

LTPA was measured through a self-reported single-item question and corresponding response sets. The question asked whether the subject had performed any activities from the following categories in the previous 12 months: walking, brisk walking, or sports (*e.g.*, aerobics, tennis, swimming, jogging, *etc.*). If they had participated in a given activity, the frequency and duration spent in the activity were ascertained using the following categories: for frequency, 1) 1–2 times per month, 2) 1–2 times per week, 3) 3–4 times per week, or 4) almost every day; and for duration (per walk or workout), 1) 0–30 min, 2) 0.5–1 h, 3) 1–2 h, 4) 2–3 h, 5) 3–4 h, or 6) 4 h or more.

Statistical Analysis

Hypertension was defined as a home SBP of 135 mmHg or over and/or a home DBP of 85 mmHg or over or using antihypertensive agents (*35*, *36*). Based on the recently proposed cutoff point for CRP, we also categorized the study participants as having a low (less than 1.0 mg/l) or high level (at least 1.0 mg/l) of CRP (*37*, *38*). The high-sensitivity CRP value (ng/ml) was used for calculating the log-transformed CRP.

Among the levels of exercise intensity, sports were considered the highest, followed in order by brisk walking and walking. Each of the three types was further classified into three subcategories according to the frequency and duration of the walks or workouts as follows (*11*, *39*): 1) High, at least 3–4 times per week for at least 30 min each time; 2) Low, some activity in the past year, but not enough to meet the criteria for the high group; and 3) None, no LTPA. Finally, we used these categories and subcategories to define the following six levels of LTPA (Table 1): 1) Level 1, no sports, no brisk walking, no walking; 2) Level 2, no sports, no brisk walking, low amount of walking; 3) Level 3, no sports, no brisk walking, high amount of walking; 4) Level 4, no sports, low amount of brisk walking, any amount of walking; 5) Level 5, no sports, high amount of brisk walking, any amount of walking; 6) Level 6, any amount of sports, any amount of brisk walking, any amount of walking. Since only 8 subjects reported participating in a high amount of sports activity, we combined high- and low-level sports activity into a single category. Table 1 also shows the number of participants according to the LTPA levels.

Diabetes was defined as a free blood glucose level of 200 mg/dl or over or current use of antidiabetic medication. Hypercholesterolemia was defined as a level of total cholesterol of 220 mg/dl or over, or current use of non-statin lipid-lowering agents. Gout was defined as a serum uric acid level of 7.0 mg/dl or over or current use of antihyperuricemic medication. Information on smoking status, drinking status and histories of prior cardiovascular diseases (CVD) were obtained from the questionnaire survey. Current drinkers

Table 2. Association between High Sensitive C-Reactive Protein Levels and Cardiovascular Disease Risk Factors

	C-reactive protein (mg/l)				*p* value
	0.05–0.27	0.28–0.54	0.55–1.16	1.17–9.96	
No. of participants	160	161	161	161	
Age (years)	75.2±4.4	75.6±4.1	75.8±4.8	75.2±4.5	0.51
Sex (male %)	41.9	49.1	51.6	51.6	0.26
BMI (kg/m^2)	22.0±3.1	23.5±2.9	24.3±3.0	25.0±3.3	<0.01
Hypertension (%)	54.4	75.2	75.8	79.5	<0.01
SBP (mmHg)	132.7±18.4	139.2±17.2	141.6±18.8	144.6±19.1	<0.01
DBP (mmHg)	74.7±9.0	76.3±10.0	77.9±9.4	79.1±9.8	<0.01
Hypercholesterolemia (%)	30.0	33.5	36.7	38.5	0.40
HDL-C (mg/dl)	60.8±14.5	55.9±13.5	53.8±13.3	52.2±14.3	<0.01
Diabetes (%)	3.1	8.7	11.8	13.7	<0.01
Gout (%)	10.0	16.8	17.4	25.5	<0.01
Smoker					
Current smoker (%)	11.3	14.3	12.4	18.0	0.32
Ex-smoker (%)	22.5	32.3	37.2	37.3	0.01
Non-smoker (%)	63.1	52.8	48.5	44.7	<0.01
Alcohol consumption (g)	11.8±29.3	12.7±32.7	13.5±28.7	11.9±24.2	0.95
Use of statin drugs (%)	13.8	16.8	21.1	17.4	0.38
Use of aspirin drugs (%)	5.0	10.6	10.6	13.7	0.07
History of CVD (%)	11.9	14.9	14.3	19.3	0.02

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein-cholesterol; CVD, cardiovascular diseases. Variables are pressented as mean±SD. Hypertension: home SBP 135 mmHg or over and/or home DBP 85 mmHg or over or using antihypertensive agents.

Table 3. Correlation between Physical Activity and Blood Pressure or C-Reactive Protein

	Physical activity						*p* for trend
	Level 1	Level 2	Level 3	Level 4	Level 5	Level 6	
Walking	None	Low	High	Any	Any	Any	
Brisk walking	None	None	None	Low	High	Any	
Sports	None	None	None	None	None	Low and High	
N (total: 643)	147	131	148	71	80	66	
Hypertension (%)	75.5	77.9	74.3	69.0	57.5	60.6	<0.01
SBP (mmHg)	142.6±1.5	142.1±1.6	139.3±1.5	136.6±2.2	137.0±2.1	134.4±2.3	0.13
DBP (mmHg)	78.1±0.8	77.9±0.8	76.4±0.8	76.9±1.1	75.7±1.1	75.8±1.2	0.12
log-hsCRP (ng/ml)	6.5±0.1	6.5±0.1	6.3±0.1	6.3±0.1	6.2±0.1	6.2±0.1	0.14
High-CRP (%)	36.1	30.5	27.0	28.2	22.5	21.2	<0.01
Odds ratio (95% CI)							
Hypertension*	1.00	1.09 (0.61–1.96)	0.97 (0.56–1.67)	0.89 (0.47–1.73)	0.53 (0.29–0.97)	0.62 (0.33–1.19)	0.02
High-CRP*	1.00	0.70 (0.41–1.20)	0.64 (0.38–1.08)	0.70 (0.36–1.34)	0.57 (0.29–1.10)	0.49 (0.24–0.98)	0.04

N: number of subjects. SBP, systolic blood pressure; DBP, diastolic blood pressure; log-hsCRP, log-transformed high sensitivity C-reactive protein (CRP); CI, confidence interval. Variables are pressented as mean±SD. High-CRP: CRP≥1.0 mg/l. *Adjusted for age, sex, body mass index, and smoking status. High: at least 3–4 times per week for at least 30 min each time; Low: reporting some activity in the past year, but not enough to meet high levels; None: no leisure-time physical activity.

were further asked about drinking frequency, beverage types usually consumed, and amount consumed on a single occasion. From these responses, we calculated the average daily alcohol consumption in g. We also treated statin agents as independent confounding factors because they have been reported to lower CRP levels (*40*, *41*). The drug information was confirmed by a well-trained pharmacist.

The clinical and biochemical data of the subjects are presented as the means±SD, or as the median and interquartile range for variables with a skewed distribution or percentages.

Table 4. Adjusted Relationships of High Sensitive C-Reactive Protein Levels (Quartile) to Hypertension

	Level of C-reactive protein (mg/l)				*p* for trend
	0.05–0.27	0.28–0.54	0.55–1.16	1.17–9.96	
All					
N (total: 643)	160	161	161	161	—
N of hypertensives	87	121	122	128	—
Odds ratio (95% CI)					
Age- and sex-adjusted	1.00	2.57 (1.60–4.18)	2.67 (1.66–4.35)	3.41 (2.08–5.67)	<0.01
Multiple adjusted*	1.00	2.26 (1.36–3.78)	2.05 (1.21–3.50)	2.45 (1.41–4.31)	0.03
Multiple* and PA levels adjusted	1.00	2.21 (1.33–3.72)	1.99 (1.17–3.42)	2.38 (1.36–4.21)	0.04
	Level of C-reactive protein (mg/l)				*p* for trend
	0.05–0.29	0.30–0.57	0.58–1.34	1.35–9.96	
Participants without brisk walking or sports activity					
N (total: 426)	106	107	106	107	—
N of hypertensives	64	86	84	89	—
Odds ratio (95% CI)					
Age- and sex-adjusted	1.00	2.81 (1.52–5.32)	2.60 (1.42–4.89)	3.38 (1.80–6.55)	<0.01
Multiple adjusted*	1.00	2.46 (1.28–4.86)	1.98 (1.00–3.96)	2.48 (1.21–5.19)	0.11
	Level of C-reactive protein (mg/l)				*p* for trend
	0.05–0.23	0.24–0.51	0.52–0.93	0.94–9.25	
Participants with sports or brisk walking activity					
N (total: 217)	53	55	54	55	—
N of hypertensives	25	31	38	41	—
Odds ratio (95% CI)					
Age- and sex-adjusted	1.00	1.52 (0.71–3.33)	2.85 (1.28–6.51)	3.52 (1.56–8.27)	<0.01
Multiple adjusted*	1.00	1.30 (0.57–2.98)	2.00 (0.81–5.00)	2.67 (1.06–6.94)	0.04

N: number of subjects. PA, physical activity; CI, confidence interval. *Adjusted for age, sex, body mass index, hypercholesterolemia, high-density lipoprotein-cholesterol, gout, history of cardiovascular diseases, diabetes, smoking, alcohol consumption, use of aspirin,

Differences in variables among the CRP groups were examined by analysis of variance (ANOVA) for continuous variables, or by the χ^2 test for variables of proportion. Multiple logistic regression analysis and analysis of covariance (ANCOVA) were used to examine the relation of LTPA with hypertension, SBP, DBP, log-transformed CRP and high-CRP ($\geq$1.0 mg/l) after adjustment for age, gender, body mass index (BMI), and smoking status. *p* values for linear trends were calculated using the level of LTPA as a continuous variable. The odds ratio (OR) and 95% confidence interval (CI) of hypertension for increasing CRP levels with the lowest level as the reference was also calculated using multiple logistic regression analysis. When we calculated the OR, we used an age-sex adjusted model and a multivariate model adjusted for age, sex, BMI, hypercholesterolemia, HDL-C, gout, history of CVD, diabetes, smoking habits/history, alcohol consumption, use of aspirin, and use of statin drugs; the final multivariable model was further adjusted for LTPA levels. *p* values for linear trends were calculated using the median (mg/l) of CRP levels. Multiple linear regression analysis was used to establish the relationship between BP and CRP after adjustment for age, gender, BMI, hypercholesterolemia, HDL-C, gout, history of CVD, diabetes, smoking, alcohol consumption, and LTPA levels in the subjects who were not using antihypertensive agents, aspirin, and statin drugs. Values of $p<0.05$ were considered to indicate statistical significance. All statistical analyses were performed using the Statistical Analysis System (version 9.1 for Windows; SAS Institute Inc., Cary, USA).

Results

Association between High-Sensitivity CRP Levels and Cardiovascular Disease Risk Factors

Table 2 shows the association between high-sensitivity CRP levels (quartile) and CVD risk factors. Both SBP and DBP were significantly higher in the highest CRP quartiles. BMI was also significantly higher in the highest CRP quartile and the mean HDL-C was lower in the highest CRP quartile. Mean age and alcohol consumption did not significantly differ among the CRP groups. The proportion of subjects with hypertension, diabetes, gout, history of smoking (*i.e.*, ex-smokers), and subjects with a history of CVD was larger in the highest CRP quartile. The proportion of subjects with no history of smoking was significantly smaller in the lowest

Table 5. Results of Multivariate Modelling for log-Transformed C-Reactive Protein

	log-CRP (ng/ml) (n=318)	
	β coefficient (SEM)	p value
SBP	0.008 (0.003)	<0.01
Age	0.013 (0.014)	0.34
Sex	−0.086 (0.183)	0.64
BMI	0.090 (0.020)	<0.01
Hypercholesterolemia	0.275 (0.126)	0.03
HDL-C	−0.009 (0.005)	0.06
Gout	0.242 (0.170)	0.16
History of CVD	−0.114 (0.218)	0.60
Diabetes	0.241 (0.207)	0.25
Current smoker	0.492 (0.200)	0.01
Ex-smoker	0.291 (0.183)	0.11
Alcohol consumption	−0.003 (0.002)	0.20
PA Level 2	−0.038 (0.180)	0.83
PA Level 3	−0.237 (0.169)	0.16
PA Level 4	−0.287 (0.202)	0.16
PA Level 5	−0.096 (0.186)	0.61
PA Level 6	−0.073 (0.206)	0.72

log-CRP, log-transformed C-reactive protein; SBP, systolic blood pressure; BMI, body mass index; HDL-C, high-density lipoprotein-cholesterol; CVD, cardiovascular diseases; PA, physical activity.

CRP quartile. The gender ratio, the number of current smokers, and the rates of hypercholesterolemia, statin user, and aspirin use did not differ significantly among the CRP groups.

Correlation between LTPA Levels and BP or CRP

Table 3 shows the relationship between LTPA levels and the prevalence of hypertension, SBP, DBP, log-transformed high sensitivity CRP, or high-CRP after adjustment for age, gender, BMI and smoking status. In the crude model, increasing PA levels showed a significant inverse relationship with both the prevalence of hypertension (p for trend <0.01) and high-CRP (p for trend <0.01). Even after the adjustment for sex, age, BMI and smoking status, the significant inverse relation between PA levels and hypertension or high-CRP was unchanged (p for trend =0.02 and 0.04, respectively).

Relationships between High-Sensitivity CRP Levels (Quartile) and Hypertension

Adjusted relationships between CRP levels (quartile) and the prevalence of hypertension are shown in Table 4. The age- and sex-adjusted OR of hypertension increased from the lowest (reference) to the highest CRP quartiles in all subjects. These results were somewhat attenuated when we adjusted for other potential confounders: the ORs for hypertension of the second, third, and fourth CRP quartiles were 2.26 (95% CI: 1.36–3.78, p<0.01), 2.05 (95% CI: 1.21–3.50, p<0.01), and 2.45 (95% CI: 1.41–4.31, p<0.01), compared with the first group as a reference, and the frequency of hypertension was significantly higher in the high CRP group. When we additionally adjusted for the LTPA levels, which are potential confounding factors, the significantly positive association was unchanged: the ORs for hypertension of the second, third, and fourth CRP quartiles were 2.21 (1.33–3.72), 1.99 (1.17–3.42), and 2.38 (1.36–4.21), respectively. We also analyzed the relation between the CRP quartiles adjusted for hypertension and the subgroups, *i.e.*, participants who participated in sports or brisk walking (LTPA levels 4–6) and those who did not (LTPA levels 1–3). The relations between CRP and hypertension were mostly identical among these subgroups (p for interaction =0.95).

Multiple Regression Model Analysis of the Relationship between log-Transformed CRP and BP

To confirm the relationship between CRP and SBP values, we performed a multiple regression analysis among subjects who did not use antihypertensive medication, aspirin, or statin drugs. The multiple regression model showed a positive and significant relationship between log-transformed CRP and SBP after adjustment for potential confounding factors, including LTPA levels (Table 5). The SBP distinctly showed a significant relationship with log-transformed CRP (p<0.01). BMI, hypercholesterolemia, and current smoking were also positively related to log-transformed CRP. There was no significant interaction between LTPA levels and SBP for log-transformed CRP values (p for interaction =0.63).

Discussion

Hypertension is one of the most important modifiable risk factors for CVD in Western and Asian populations (*42*, *43*). It is well known that lifestyle changes (*e.g.*, diet, weight loss, exercise and smoking cessation, *etc.*) can reduce cardiovascular risk; in particular, regular PA reduces coronary and cardiovascular morbidity and mortality, independently from the other risk factors (*44*, *45*). PA is one of the most important independent contributors to the prevalence of hypertension (*10*, *11*). In this cross-sectional survey of Japanese community-dwelling elderly individuals, we found LTPA levels in daily life were inversely correlated with both serum CRP and the prevalence of hypertension.

Since the LTPA level was inversely related with both CRP and the prevalence of hypertension, we tested our hypothesis that the relation between CRP and hypertension would be dependent of LTPA levels. However, the positive significant relation between CRP and hypertension remained even after adjustment for the LTPA levels. Furthermore, there was a strong relation between the CRP and SBP values that was independent of the LTPA level among participants not taking antihypertensive or statin drugs or aspirin. Thus, we were able

to conclude for the first time that the relation between CRP and hypertension was independent of LTPA levels in a Japanese elderly population.

Several prospective studies have employed the amount of subjects' PA as one of the confounding factors in their multivariate analysis of the causal relationship between serum CRP and the development of hypertension and/or metabolic syndrome (*20–22*). In two of these studies (*21*, *22*), the amount of exercise did not attenuate the relationship between CRP and BP. The third prospective cohort study (*20*) also considered the influence of PA on the relation between CRP and BP, but in contrast to the other two studies, the results indicated that CRP was not a significant predictor of the development of hypertension or other metabolic syndromes. Although the reason for these discrepancies remains unclear, our data are similar to the first two studies, which indicated that CRP may be related to hypertension independent of PA levels.

In this study, we used HBP measurement. HBP makes it possible to obtain multiple measurements over a long observation period under relatively controlled conditions (*46*, *47*). It has been reported that multiple measurements eliminate observer bias and regression dilution bias; therefore, HBP measurements are more reliable than conventional BP measurements taken in medical settings (office BP) (*46–48*). We also adjusted for a considerable number of confounding factors. In this way, we were able to confirm the positive and significant relation between log-transformed CRP and SBP in subjects who were not using antihypertensive agents.

This study had several limitations. First, most of the participants were sufficiently active to participate in the survey. Therefore, we lacked the participation of those who were physically dependent or disabled due to metabolic syndromes or hypertension, leading to underestimation of the relation between CRP and hypertension. Second, since this study was a cross-sectional study, we could not conclude that CRP causes hypertension or that hypertension leads to increased CRP among subjects aged 70 years and over. Third, we did not directly measure the exercise intensities of walking, brisk walking and sports. Still, one may easily discriminate one's own "brisk walking" from ordinary walking. We therefore believe that the categorization of relative walking intensity based on the subjects' own perceptions was reliable. It is well known that ratings of perceived exertion correspond well to exercise intensity as measured by oxygen uptake (*49*).

In conclusion, we have demonstrated that among elderly subjects 70 years and older the higher LTPA levels were associated with reductions of serum CRP levels and hypertension prevalence, but that the positive significant relation between CRP and hypertension was independent of LTPA levels.

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Preliminary communication

Male elderly subthreshold depression patients have smaller volume of medial part of prefrontal cortex and precentral gyrus compared with age-matched normal subjects: A voxel-based morphometry

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Abstract

Background: The brain morphological changes in subthreshold depression (sD) have not been clarified. We examined the structural difference in regional gray matter volume between community-dwelling elderly subjects with sD and age-matched nondepressed normal subjects by voxel-based morphometry (VBM) based on magnetic resonance imaging (MRI).
Methods: Thirty-four community-dwelling elderly subjects with sD and 109 age-matched nondepressed normal subjects were studied by MRI. We defined subjects with sD as those who showed a Geriatric Depression Scale score of 15 or higher and a Mini Mental State Examination score of 22 or higher, and do not fulfill the criteria of major depressive disorder (MDD) in the Diagnostic and Statistical Manual for Mental Disorders IV. We collected brain magnetic resonance images of 34 subjects with sD and 109 age-matched normal subjects, and analyzed the difference in regional gray matter volume between these two groups by VBM.
Results: Male subjects with sD had significantly smaller volumes of the medial part of the bilateral frontal lobes and the right precentral gyrus than normal male subjects.
Limitations: We have not clarified the discrepancy in the results of gender difference.
Conclusions: Our study revealed that even community-dwelling elderly male subjects with sD show bilateral prefrontal gray matter volume reduction, which was reported to be observed in elderly patients with MDD, although there is no significant

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volume reduction in the hippocampus, which was also reported to be observed in MDD. Our study may contribute to clarifying the mechanism underlying brain pathological changes in sD.

Keywords: Voxel-based morphometry; Subthreshold depression; Gray matter; MRI

1. Introduction

Depression is one of the most common mental disorders in the elderly. It is associated with a decline in both well-being and daily functioning and with a high risk of functional impairment, a high risk of mortality, and a high rate of service utilization. A number of large-scale epidemiological studies have been carried out to further clarify the prevalence of late-onset depression (Blazer, 1989; Wells et al., 1989; Gurland, 1992; Beekman et al., 1997, 1999). However, the prevalence of depression in a community determined by check lists such as the Geriatric Depression Scale (GDS) (Brink et al., 1982; Yesavage et al., 1982) is higher than that by diagnostic criteria such as the Diagnostic and Statistical Manual for Mental Disorders IV (DSM-IV) (American Psychiatric Associataion, 1994). GDS has been used as a screening test for depression among the elderly population, and used widely among community-dwelling and institutionalized elderly populations (Mui et al., 2003). Subjects selected on the basis of their responses to a questionnaire have significant depressive symptoms but these subjects do not necessarily fulfill the criteria for major depressive disorder (MDD). This state is defined as "subthreshold depression (sD)" (Preisig et al., 2001; Cuijpers and Smit, 2004). This state is clinically important because individuals with sD have an increased risk of subsequent MMD (Cuijpers et al., 2004). There are many brain morphometric studies of MDD. It was reported that elderly patients with MDD show volume reduction in the prefrontal cortex (Kumar et al., 2000; Ballmaier et al., 2004), and hippocampus (Sheline et al., 1999; Mervaala et al., 2000; Steffens et al., 2000; Bell-McGinty et al., 2002). However, it has not been clarified whether neuroanatomical abnormalities occur in the community-dwelling elderly with sD. In addition, if indeed the abnormalities occur in the elderly with sD, it has not been clarified whether the affected regions are the same as those in patients with MDD.

In recent years, voxel-based morphometry (Ashburner and Friston, 2000), which enables the global assessment of brain structures without a priori identification of the region of interest, has been developed. This approach is not biased toward any one brain region and permits the identification of potential unsuspected brain structural abnormalities.

The purpose of this study was to detect the difference in regional gray matter volume between community-dwelling elderly subjects with sD and nondepressed normal subjects by voxel-based morphometry (VBM).

2. Methods

2.1. Study populations

The Tsurugaya Project study is a comprehensive geriatric assessment (CGA) of the elderly population, which includes the assessment of the medical status, depressive symptoms, and physical and cognitive functions of the elderly. The study involved 2730 subjects aged 70 years or older in 2002 who were living in Tsurugaya district, Sendai City, Japan. We sent the CGA guide information to all of them. The number of subjects who participated in the study was 1198 among whom 1179 gave their written informed consent. The subjects responded to a mailed questionnaire that was sent in June 2002, which provided information concerning their educational level (year), history of diseases, activities in daily life, physical status, smoking and drinking habits, self-rated status of health, chronicle of pain, and propensity to fall. The subjects also responded to oral interviews by psychologist and geriatrists based on a questionnaire, including the Rome II Modular Questionnaire 8, GDS, and MMSE as part of CGA. We asked the subjects whether they would be willing to

undergo magnetic resonance (MR) imaging of their brains. More than 80% of the subjects responded positively.

In this study, we defined subjects with sD as those who showed GDS scores of 15 and higher and MMSE scores of 22 and higher. Among the 1111 subjects who completed GDS and MMSE, 51 (10.9%) male and 138 (21.4%) female subjects fulfilled the sD criteria out of 467 male and 644 female subjects, respectively. Among the 189 subjects, 58 subjects gave their consent to undergo brain MR imaging. Psychiatrists conducted medical interviews and examinations of these subjects. Six women were diagnosed as having MDD according to the DSM-IV criteria, and were excluded from this study. We also excluded those who had present or past history of a neuropsychiatric illness or taking medications for it and who had history of any brain tumors, any cerebrovascular diseases, or head traumas. Finally, the subjects with sD consisted of 13 men (age: 70–75, mean ± SD, 72.92 ± 1.71; GDS: 16–25, 19.77 ± 3.22; MMSE: 25–30, 27.85 ± 1.62) and 21 women (age: 69–75, 71.81 ± 1.69; GDS: 15–24, 17.43 ± 2.20; MMSE: 23–30, 28.28 ± 1.79). We defined normal subjects as those who showed GDS scores of less than 10 and MMSE scores of 28 and higher. In addition, we excluded those who had a history of any brain tumors, cerebrovascular diseases, head traumas, or neuropsychiatric diseases. There were 79 males and 96 females who fulfilled the criteria of normal and gave their consent to undergo brain MR imaging. From these subjects, we selected male and female normal subjects separately by random sampling. The normal group consisted of 55 men (age: 70–75, 72.38 ± 1.60; GDS: 0–9, 5.15 ± 2.39; MMSE: 28–30, 29.18 ± 0.80), and 54 women (age: 69–75, 71.96 ± 1.86; GDS: 1–9, 5.39 ± 2.48; MMSE: 28–30, 29.02 ± 0.86). We obtained brain MR images of subjects with sD and normal subjects.

The study was approved by the Ethics Committee of Tohoku University School of Medicine. Written informed consent to participate in this study was obtained from each subject.

2.2. MR image acquisition

Brain MR images were taken from each subject using the same type of 0.5 T MR scanner (Signa contour, GE-Yokogawa Medical Systems, Tokyo) with three different pulse sequences: (1) 124 contiguous, 1.5-mm-thick axial planes of three-dimensional T1-weighted images (spoiled gradient recalled acquisition in steady state: repetition time (TR), 40 ms; echo time (TE), 7 ms; flip angle, 30°; voxel size, 1.02 × 1.02 × 1.5 mm); (2) 63 contiguous, 3-mm-thick axial planes of gapless (using interleave) proton probability weighted images/T2-weighted images (dual echo fast spin echo: TR, 2860 ms; TE, 15/120 ms; voxel size, 1.02 × 1.02 × 3 mm). Prior to further computational procedures, all MR images were filmed in a conventional format and inspected by experienced radiologists.

2.3. Image analyses

The image analysis of local volume changes of the gray matter was carried out by statistical parametric mapping (SPM) (SPM99, Wellcome Department of Cognitive Neurology, London, UK) (Friston et al., 1995) in Matlab (Math Works, Natick, MA, USA). All T1-weighted images were transformed to the same stereotactic space by registering each of the images to the same template image. The template image we used was the ICBM 152 template (Montreal Neurological Institute), which was derived from 152 normal subjects and approximates the Talairach space (Talairach and Tournoux, 1988). This first step of spatial normalization was performed by 12-parameter affine transformation. Next, nonlinear normalization was performed, and normalized images were then segmented into the gray matter, white matter, cerebrospinal fluid (CSF) spaces, and nonbrain partitions. The nonbrain partitions were removed. The normalized, segmentated images were modulated by the method of Good et al. (2001). The modulation step was performed to correct volume changes. The normalized, segmented, and modulated images were smoothed convoluting a 12-mm full-width at half-maximum isotropic Gaussian kernel.

2.4. Statistical analyses

The smoothed gray matter images were analyzed using SPM99. To detect regionally specific differences between subjects with sD and normal subjects, a two-sample t-test was performed between the two groups. The significance level was set at $p < 0.05$, for multiple

comparison, corrected. In addition, we performed the analysis of covariance (ANCOVA) between the two groups with the MMSE score as a confounding variable to adjust for the effect of cognitive function. The resulting images following SPM image analysis were superimposed on structural MR images on horizontal slices, which were the average images of all the subjects' normalized segmentated gray matter images, to facilitate correlation with anatomic structures.

3. Results

Table 1 shows that there was no significant difference in age between the subjects with sD and normal subjects for both men (Mann–Whitney U test, $p=0.278$) and women (Mann–Whitney U test, $p=0.919$). The subjects with sD had significantly higher GDS scores than normal subjects for both men (Mann–Whitney U test, $p<0.001$) and women (Mann–Whitney U test, $p<0.001$). The male subjects with sD had significantly lower MMSE scores than normal male subjects (Mann–Whitney U test, $p=0.004$). The male subjects with sD had a significantly lower educational level than normal male subjects (Mann–Whitney U test, $p=0.041$). However, there were no significant differences in MMSE score (Mann–Whitney U test, $p=0.086$) and educational level (Mann–Whitney U test, $p=0.734$) between the two groups for women.

Table 2 shows the gray matter regions and the coordinate of the Talairach stereotaxic space that showed significantly smaller volumes in the male subjects with sD than in normal male subjects.

Fig. 1 shows the gray matter regions that had significantly smaller volumes in the male subjects with sD than in normal male subjects. The left side of the image represents the left side of the brain. Color scales indicate the t-score. The number at the bottom of the left side of each image indicates the value of the z-axis in the Talairach stereotaxic space. The medial part of the bilateral superior frontal gyri and the right precentral gyrus show significantly smaller volumes in the male subjects with sD than in normal male subjects. To adjust for the effect of cognitive functions, we performed ANCOVA between the two groups with the MMSE score as a confounding variable. Although almost the same regions as described above were detected, these regions did not reach the statistical significance level for multiple comparisons, corrected ($p=0.078$ for the right precentral gyrus, $p=0.145$ for the right superior frontal gyrus, $p=0.250$ for the light superior frontal gyrus). There was no significant structural difference in the gray matter between the normal female subjects and female subjects with sD.

Table 2
Gray matter regions and coordinate of Talairach space showing significantly smaller volume in male subjects with sD than in normal male subjects

Location	x	y	z	t	p (corrected)
R superior frontal gyrus	6	58	14	4.91	0.028
L superior frontal gyrus	−2	54	28	4.89	0.030
L superior frontal gyrus	−4	56	22	4.82	0.037
L superior frontal gyrus	−4	56	18	4.80	0.040
R precentral gyrus	58	8	30	4.75	0.046

4. Discussion

This study provides the first detailed account of differences in gray matter volume between subjects with sD and age-matched normal subject determined by voxel-based morphometry. Another characteristic

Table 1
Subject characteristics and clinical measures

	Men			Women		
	Normal	Depression	p	Normal	Depression	p
Age (range, mean ± SD)	70–75, 72.38 ± 1.30	70–75, 72.92 ± 1.71	NS	69–75, 71.96 ± 1.86	69–75, 71.81 ± 1.69	NS
MMSE (range, mean ± SD)	28–30, 29.18 ± 0.80	25–30, 27.85 ± 1.62	<0.05	28–30, 29.02 ± 0.86	23–30, 28.28 ± 1.79	NS
GDS (range, mean ± SD)	0–9, 5.15 ± 2.39	16–25, 19.77 ± 3.22	<0.001	1–9, 5.39 ± 2.48	15–24, 17.43 ± 2.20	<0.001
Duration of education [year] (range, mean ± SD)	8–25, 14.4 ± 3.73	8–16, 12.2 ± 5.47	<0.05	8–18, 11.6 ± 2.26	8–16, 11.5 ± 2.44	NS

NS: not significant.

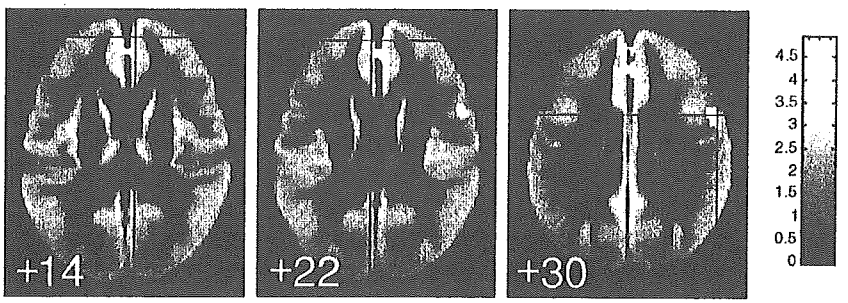

Fig. 1. Gray matter regions showing significantly smaller volumes in male subjects with sD than in normal male subjects. The left side of the image represents the left side of the brain. Color scales indicate the t-score. The number at the bottom of the left side of each image indicates the value of the z-axis in the Talairach stereotaxic space. To clarify the extent of the regions, we showed data, the significance level of which was set at $p<0.001$, for multiple comparison, uncorrected.

of this study is the narrow age window of the subjects, which minimizes the aging effect of gray matter loss in the cerebral cortices on sD-dependent changes. The analysis revealed that the male subjects with sD had significantly smaller volumes of the medial part of the bilateral frontal lobes and the right precentral gyrus than age-matched normal subjects.

Our observation that subjects with sD have a smaller prefrontal lobe was consistent with that of previously reported studies of patients with MDD (Kumar et al., 2000; Ballmaier et al., 2004). In addition, previous studies showed that patients with late-onset minor depression have a smaller prefrontal lobe volume than age-matched nondepressed subjects (Kumar et al., 1997, 1998), although in these studies only the prefrontal and temporal cortices were analyzed and voxel-based morphometry was not used.

However, our results are partially inconsistent with those of previous studies in the point that our study showed that there was no significant hippocampal volume reduction in subjects with sD compared with normal subjects. In one previous study, voxel-based morphometry was carried out on patients with MDD compared with normal subjects; it revealed volume reductions of the prefrontal cortex and hippocampus in patients with MDD (Bell-McGinty et al., 2002). Previous studies also showed hippocampal volume reduction in patients with MDD compared with normal subjects (Sheline et al., 1999; Mervaala et al., 2000; Steffens et al., 2000; Bell-McGinty et al., 2002). One of these studies also showed that the reduction correlated with the duration of depression, but not with patient's age (Sheline et al., 1999). It is believed that an increase in cortisol level, which is caused by long-term stress, causes neuronal loss in the hippocampus caused by excitotoxic damage (Carroll et al., 1981; Sapolsky et al., 1985). Thereby, it will be reasonable to consider that the reduction in hippocampal volume may correlate with the progression and duration of depression. Although our present study showed that there was no significant hippocampal volume reduction in depressive subjects, the study populations of previous studies of MDD were different from those of our study in the aspect of the stage of depression. The subjects with sD of our study were all community-dwelling elderly people and their symptoms were less severe than those of patients with MDD. In addition, as described in the Methods section, only 58 (30.7%) subjects with sD gave their consent to undergo MR imaging out 189 subjects who fulfilled the criteria of sD, while more than 80% of 922 normal subjects gave their consent. Therefore, the subjects with sD who gave their consent in this study might have less severe depressive symptoms than the subjects with sD who did not gave their consent to undergo MR imaging, although the GDS score was not significantly different between the two groups. This will be one of the reasons why hippocampal volume reduction was not detected in our study. From these aspects, it is considered that early-stage depression correlates with volume reduction of the prefrontal cortex, and the hippocampus may be affected with the progression of depression.

The gray matter volume reduction in the male subjects with sD was observed, but not in the male normal subjects. The GDS scores of male subjects with sD were significantly lower than those of male normal subjects. In addition, the MMSE scores of

male subjects with sD were also significantly lower than those of male normal subjects. To adjust for the effect of cognitive functions, we performed ANCOVA between the two groups with the MMSE score as a confounding variable. Although almost the same regions showing volume reduction were detected, these regions did not reach the statistical significance level when the correction of multiple comparisons was performed. However, previous studies showed an association between depressive symptoms and dementia or cognitive decline (Yaffe et al., 1999; Paterniti et al., 2002). In addition, depressive symptoms predict cognitive decline in elderly people with initially normal functioning, independent of educational level and previous cognitive functioning (Wilson et al., 2004). Therefore, it is difficult to separate the effect of cognitive decline from sD. However, the regions that we observed to show volume reduction in this study are not affected in patients with mild cognitive impairment, who had a significant gray matter volume loss in the hippocampal region and the cingulate gyri (Chetelat et al., 2002). Therefore it is reasonable to conclude that the regions that we observed to show volume reduction in this study are those that are specifically affected in patients with sD.

There was no significant brain structural difference between the female subjects with sD and normal female subjects, although there was a significant difference in gray matter volume reduction between the male subjects with sD and male normal subjects. One possible explanation for this finding is the difference in the stage of depression between the female subjects with sD and male subjects with sD because the GDS scores of male subjects with sD were significantly higher than those of female subjects with sD. Another possible explanation is the sex difference per se. To clarify the differences in the findings between the male and female subjects, further analysis of the two groups with matched scores of GDS and MMSE is needed.

In this study, we adopted a GDS score of 15 as the cut-off point for subjects with sD. Usually, a GDS score of 11 is set as the cut-off point for depression. One previous study showed that the mean GDS score for mildly depressed patients is 15.05 (Yesavage et al., 1982). When the cut-off point for depression was set at a GDS score of 14, clinical depression could be diagnosed well with a sensitivity of 80% and a specificity of 100% (Brink et al., 1982). The subjects with sD in this study included 3 male and 7 female subjects with a minor depressive episode, which included only two to four symptoms of the DSM-VI major depressive episode. Consequently, the subjects with sD in this study are considered to be at a high risk of major depression, although the group might consist of a heterogeneous population including subjects with depressive disorder that is not otherwise a specific partial remission of major depression, those with anxiety disorder with depression, adjustment disorder with depression, and those without DSM-IV mental disorder but with depressed feelings.

The limitation of this study is that this is a cross-sectional study; therefore, it cannot assess the impact of sD on the extent of later-life brain atrophy. Only a longitudinal study can solve these problems. In addition, as described above, we have not clarified the discrepancy in the results between male subjects with sD and female subjects with sD. To clarify them, further analysis of the two groups with matched scores of GDS and MMSE is needed. In addition, there are potential problems in the use of voxel-based morphometry. In essence, this method, originally intended for use in the analysis of large samples, requires smoothing of the images, with the loss of resolution for small structures (such as the hippocampus), and the large number of comparisons requires corrections that greatly reduce the power of the study.

The identification of regions that are affected in elderly subjects with sD is very important in understanding the mechanism underlying brain pathological changes in sD, because sD is a significant risk indicator for MDD (Cuijpers and Smit, 2004) and depressive symptoms predict cognitive decline (Wilson et al., 2004).

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