

temporal cortex. Thus, preventing the progression of arteriosclerosis may be important for preventing a decrease in gray matter volume in healthy elderly subjects. *Hum Brain Mapp* 00:000–000, 2012. © 2012 Wiley Periodicals, Inc.

**Key words:** gray matter; high-sensitivity C-reactive protein; magnetic resonance imaging; elderly; voxel-based morphometry; DARTEL

## INTRODUCTION

Recent studies have shown that chronic inflammation plays a crucial role in the development of atherosclerosis [Ross, 1999]. High-sensitivity C-reactive protein (hsCRP) is a sensitive marker of systemic low-grade inflammation [Pearson et al., 2003] and is associated with plaque progression and instability in large arteries [Hashimoto et al., 2001; Yamagami et al., 2004]. Additionally, hsCRP is useful to predict several diseases such as stroke and cardiovascular diseases [Pearson et al., 2003; Teunissen et al., 2003; Yaffe et al., 2003]. Increased serum concentrations of hsCRP have been associated with poor memory [Teunissen et al., 2003], poor global cognitive performance [Pearson et al., 2003], and vascular dementia [Ravaglia et al., 2007]. Several higher cognitive functions have been shown to be associated with regional gray matter volume, for example, episodic memory with hippocampus gray matter [Kramer et al., 2007], working memory with dorsolateral prefrontal cortex gray matter [Takeuchi et al., 2010], semantic memory with temporal pole gray matter [Taki et al., 2011], and executive function with lateral prefrontal cortex gray matter [Kramer et al., 2007; Zimmerman et al., 2006]. Therefore, it is plausible that there is a correlation between hsCRP level and regional gray matter volume. Investigating the correlation between hsCRP level and regional gray matter volume is important because a significant correlation would indicate that cognitive decline owing to atherosclerosis is derived from a reduction in gray matter volume, and that medical treatment for atherosclerosis is important not only to prevent the decrease in cognitive function but also to prevent a decrease in gray matter volume.

However, few studies have tested the correlation between hsCRP level and brain structure. A recent study focused on the correlation between hsCRP level and white matter microstructure in healthy adults, and showed that a higher hsCRP level was related with reduced fractional anisotropy of the frontal lobe, the corona radiata, and the corpus callosum [Wersching et al., 2010]. Another study showed that hsCRP level was related with hippocampal volume in patients with type 2 diabetes mellitus [Anan et al., 2011]; nondemented patients with type 2 diabetes mellitus and a higher hsCRP level and showed more hippocampal atrophy compared with those with a normal hsCRP level. Although these findings suggest a significant correlation between hsCRP and regional gray matter volume of the hippocampus, that study focused on patients with type 2 diabetes mellitus, who show atrophy of sev-

eral gray matter regions including the hippocampus [Korf et al., 2007]. That study also focused only on hippocampal volume, not regional gray matter volume. Therefore, it has not yet been clarified whether there is a significant correlation between hsCRP and regional gray matter volume in healthy subjects using a whole-brain analysis.

The purpose of this study was to investigate the correlation between hsCRP level and regional gray matter volume using brain magnetic resonance imaging (MRI) of 109 community-dwelling healthy elderly subjects within a narrow age window. We applied the brain-image analysis technique of voxel-based morphometry (VBM) [Ashburner and Friston, 2000]. VBM analysis enables a global analysis of brain structures without a priori identification of a region of interest. This approach permits the identification of unsuspected potential brain structural abnormalities. We hypothesized that the gray matter volume of regions fed by the middle cerebral artery would be negatively correlated with hsCRP level because symptomatic atherosclerotic disease is mostly observed in the middle cerebral artery [Kim et al., 2005]; therefore, it was thought that the middle cerebral artery would be more vulnerable to atherosclerosis compared with other intracranial arteries such as the anterior cerebral artery.

## METHODS

### Study Population

The subjects were selected from participants in the Tsurugaya Project, a comprehensive geriatric assessment (CGA) of the elderly population, which includes assessments of medical status, depressive symptoms, and physical and cognitive functions. Recruitment of subjects was described previously [Taki et al., 2011]. Briefly, the project enrolled 2,730 subjects aged 69 years or older living in Tsurugaya district, Sendai, Japan. The subjects responded to interviews by psychologists and geriatrists based on questionnaires, including the Rome II Modular Questionnaire 8, Geriatric Depression Scale (GDS; <http://www.stanford.edu/~yesavage/GDS.html>) [Brink et al., 1982; Yesavage et al., 1982], and the Mini-Mental State Examination (MMSE) [Folstein et al., 1975] as part of the CGA. Next, we asked the subjects whether they were willing to undergo an MRI of their brains. We defined healthy subjects as those who showed GDS scores <10 and MMSE scores of 28 or higher. Additionally, we excluded subjects with a history of brain tumors, cerebrovascular diseases,

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TABLE I. Subject clinical characteristics

	Men (Range, mean ± SD)	Women (Range, mean ± SD)	P
Age (years old)	70–75, 72.4 ± 1.3	69–75, 72.0 ± 1.9	0.187
MMSE <sup>a</sup> (max. 30)	28–30, 29.2 ± 0.8	28–30, 29.0 ± 0.9	0.321
GDS <sup>b</sup> (max. 30)	0–9, 5.2 ± 2.4	1–9, 5.4 ± 2.5	0.632
Duration of education (year)	8–25, 14.4 ± 3.7	8–18, 11.6 ± 2.3	<0.001
Systolic blood pressure (mm Hg)	81–167, 132.6 ± 16.7	105–203, 137.8 ± 20.3	0.163
Diastolic blood pressure (mm Hg)	50–104, 77.1 ± 10.8	63–104, 78.4 ± 10.2	0.544
hsCRP <sup>c</sup> (mg/dL)	0.05–21.7, 1.46 ± 3.1	0.09–34.3, 2.00 ± 4.7	0.491
Total cholesterol (mg/dL)	113–259, 191.8 ± 32.1	146–311, 191.8 ± 32.1	<0.001
Triglyceride (mg/dL)	62–495, 179.8 ± 100.0	58–272, 148.6 ± 59.8	0.050
HDL-C <sup>d</sup> (mg/dL)	32–104, 50.1 ± 13.7	29–113, 59.6 ± 14.8	<0.001

<sup>a</sup>Mini-Mental State Examination.

<sup>b</sup>Geriatric Depression Scale.

<sup>c</sup>High-sensitivity C-reactive protein.

<sup>d</sup>High-density lipoprotein cholesterol.

head trauma, or any neuropsychiatric disease. In total, 79 men and 96 women fulfilled the criteria of “healthy” and gave their consent to undergo brain MRI. From these subjects, we selected healthy male and female subjects separately by random sampling and obtained their brain MRIs. We also obtained hsCRP levels from the blood in each subject. As a result, the study subjects consisted of 55 men and 54 women. The characteristics of the subjects were reported previously [Taki et al., 2011].

Written informed consent was obtained from each subject after a full explanation of the purpose and procedures of the study prior to brain MRI according to the declaration of Helsinki (1991). Approval for these experiments was obtained from the institutional review board of Tohoku University.

### Measurement of Serum hsCRP

Blood was extracted from the antecubital vein after an overnight fast. All subjects underwent routine laboratory tests, including assays for serum total cholesterol, serum triglycerides, serum high-density lipoprotein cholesterol, and serum low-density lipoprotein cholesterol. hsCRP concentrations 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 [Ledue et al., 1998]. The detection limit of this assay is 0.02 mg/L. Clinical characteristics of the subjects are summarized in Table I.

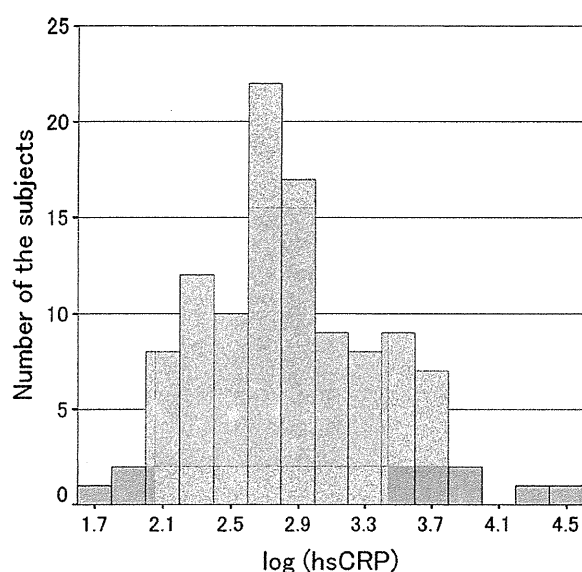
### Image Acquisition

Brain MRI was acquired from each subject using two 0.5-T MRI scanners of the same model (Signa Contour, GE-Yokogawa Medical Systems, Tokyo, Japan). The scanner was rou-

tinely calibrated using the same standard GE phantom. No major hardware upgrades occurred during the period. All subjects were scanned with identical pulse sequences: 124 contiguous, 1.5-mm-thick axial planes of three-dimensional T1-weighted images (spoiled gradient recalled acquisition in steady state: repetition time, 40 ms; echo time, 7 ms; flip angle, 30; voxel size, 1.02 × 1.02 × 1.5 mm).

### Image Analysis

We applied VBM to conduct the image analyses. Specifically, we used the Statistical Parametric Mapping 8 software (SPM8, Wellcome Department of Cognitive Neurology, London, United Kingdom) for the structural segmentation, longitudinal registration, and group statistics, and the “Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL)” [Ashburner, 2007] deformation framework for intersubject spatial normalization. As DARTEL produces more accurate registration [Klein et al., 2009], it allows improved sensitivity such as that needed to assess the correlation between regional gray matter volume and hsCRP. Practically, all of the T1-weighted images were first segmented using the New Segmentation algorithm in SPM8 [Ashburner and Friston, 2005] and their resulting gray matter maps were rigidly registered onto their common mean image. Then, the DARTEL toolbox was used to estimate a best set of smooth, pure nonlinear and reversible deformation sets from each subject’s tissue map to a common, custom template. To achieve this goal, DARTEL uses an iterative process: by computing constrained warping fields from all subject data to the current average at each step, successive and increasingly sharp average templates are generated, as well as corresponding warping fields for each subject. Finally, our resulting custom template was itself matched to the Montreal Neurological Institute (MNI) space using



**Figure 1.**

The distribution of log-transformed hsCRP P-levels.

an affine-only registration to map our custom coordinate space to the more standard MNI space [Bergouignan et al., 2009]. We applied modulation, which compensated for the volume change induced by warping [Good et al., 2001], to preserve the amount of gray matter in the process. Finally, the warped gray matter images were smoothed by convolving an 8-mm full-width at half-maximum isotropic Gaussian kernel.

### Statistical Analysis

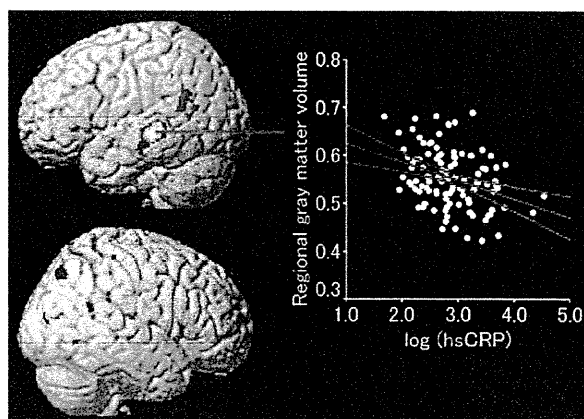
A multiple regression analysis was performed to investigate the correlation between hsCRP level and regional gray matter volume after adjusting for age, gender, and intracranial volume. The intracranial volume was calculated by summing the gray matter volume, white matter volume, and CSF space volume derived in the abovementioned image preprocess step. Intracranial volume adjustment was performed using intracranial volume as an independent variable as described below. As the distribution of hsCRP levels was highly deviated from a normal distribution, the hsCRP data were log transformed to achieve a normal distribution. Age, gender, intracranial volume, and log-transformed hsCRP levels were used as independent variables, and regional gray matter volume was used as the dependent variable. We set the significance level at  $P < 0.05$  by controlling false-discovery rate when performing multiple tests of topological features (i.e., clusters of voxels) and with random field theory when performing multiple tests [Chumbley et al., 2010; Morrell et al., 2010].

## RESULTS

The distribution of log-transformed hsCRP levels is shown in Figure 1. A significant negative correlation was observed between regional gray matter volume of the posterior and lateral aspects of the left temporal cortex and hsCRP levels after adjusting for age, gender, and intracranial volume ( $x, y, z = -60, -33, -2; t = 4.46, r = -0.345, P = 0.014$ ; Fig. 2). This result indicates that individuals with mild inflammation, which is related with arteriosclerosis, show a decrease in regional gray matter volume in the posterior and lateral aspects of the left temporal cortex. If the statistical threshold was set to a more liberal condition ( $P < 0.001$ , uncorrected), a correlation between regional gray matter volume and hsCRP level was observed in the bilateral posterior and lateral aspect of the temporal cortex and temporo-parieto-occipital regions after adjusting for age, gender, and intracranial volume. In no region did gray matter show a significant positive correlation with hsCRP level.

## DISCUSSION

This is the first study to show a significant negative correlation between regional gray matter volume and hsCRP level in healthy elderly subjects. A significant negative



**Figure 2.**

Gray matter regions that had a significant negative correlation with the log-transformed hsCRP P-levels and regional gray matter volume after adjusting for age, gender, and intracranial volume. Upper: Correlation results were superimposed onto right and left lateral-view structural magnetic resonance images. Lower: Relationship between high-sensitivity C-reactive protein P-levels and regional gray matter volume (Talairach coordinates,  $x = -60, y = -33, z = -2$ ). Color scales indicate the t-scores. We show the multiple comparisons data ( $P < 0.001$ , uncorrected) to clarify the extent of the regions. The 95% confidence interval of the regression line is also shown.

correlation was observed in the posterior and lateral aspects of the left temporal cortex. Although the mechanism for the correlation between regional gray matter volume and hsCRP is not well clarified, it is thought that atherosclerosis is associated with gray matter volume loss because hsCRP is a sensitive marker of systemic low-grade inflammation such as that seen in atherosclerosis [Pearson et al., 2003]. Atherosclerosis may be related to a variety of vascular pathologies, including carotid artery wall thickening [De Michele et al., 2002], vascular and coronary endothelial dysfunction [Brook et al., 2001; Sorisky, 2002; Williams et al., 2002], peripheral resistance, and arterial stiffness [Yki-Jarvinen and Westerbacka, 2000]. Therefore, it was thought that atherosclerosis may predispose a patient to a progressive decrease in cerebral blood flow [Nobili et al., 1993; Rodriguez et al., 1987] and alter the supply of oxygen and other nutrients to neurons, leading to chronic ischemia and tissue loss. Additionally, the lower limit of cerebral blood flow autoregulation is shifted to the right on the blood pressure axis to maintain a constant cerebral blood flow in the hypertensive state [Strandgaard, 1976]. This state is vulnerable to minor hypotensive episodes and easily leads to ischemia. From these phenomena, atherosclerosis may result in neuronal loss and gray matter volume decline.

We showed that the volume of the posterior and lateral aspects of the left temporal cortex was significantly and negatively correlated with hsCRP level. As hypothesized, this region is fed by the middle cerebral artery [Martin and Neuroanatomy, 2003]. As symptomatic atherosclerotic disease is mostly observed in the middle cerebral artery [Kim et al., 2005], it is thought that the middle cerebral artery is more vulnerable to atherosclerosis compared with other intracranial arteries such as the anterior cerebral artery. Additionally, the left lateral temporal lobe is significantly and negatively correlated with the rate of brain perfusion and age [Van Laere et al., 2001]; therefore, it may be particularly vulnerable to aging by the atherosclerotic interaction in the left lateral temporal lobe. Furthermore, we showed that the gray matter regions of the rather posterior aspect of the brain showed a tendency toward correlation with regional gray matter volume and hsCRP level in the liberal threshold analysis. Posterior circulation fed by the bilateral vertebral arteries shows vulnerability to atherosclerosis [Baker and Iannone, 1959; Strassburger et al., 1997]. Thus, it is thought that the gray matter regions of the posterior aspect of the brain had a tendency toward correlation with regional gray matter volume and hsCRP level.

Although a recent study suggested a significant correlation between hsCRP level and regional gray matter volume of the hippocampus [Anan et al., 2011], we did not find this correlation. This inconsistency may be derived from differences in subject characteristics, as that study focused not on healthy subjects but on patients with type 2 diabetes mellitus, who show atrophy in several gray matter regions such as the hippocampus [Korf et al., 2007].

Therefore, it is possible that diabetes mellitus itself may have affected the results of the correlation between hippocampal volume and hsCRP level. Additionally, although we applied VBM, which enables a global analysis of brain structures without a priori identification of a region of interest, Anan and colleagues focused only on the hippocampus. Thus, the inconsistency in the results was thought to be derived from both the subject characteristics and the methodology applied. In addition, although another study showed that higher hsCRP levels were related to reduced fractional anisotropy of the frontal lobe [Wersching et al., 2010], we did not find a significant correlation between regional gray matter volume in the frontal lobe and hsCRP level. Although there is also a negative correlation between gray matter volume in several regions in the dorsal frontal lobe and hsCRP level if a more liberal threshold such as  $P < 0.01$ , uncorrected for multiple comparisons is used (data not shown), we cannot deny the possibility that mechanism(s) of the correlation between hsCRP level and gray matter, and white matter structure, may be different. Further studies may help elucidate correlations between brain structure and hsCRP levels.

The present study had several limitations. First, it was a cross-sectional study. Thus, although we have shown a relationship between hsCRP level and gray matter volume, we cannot clarify a causal relationship between hsCRP level and gray matter volume. Longitudinal studies are needed to clarify this issue. Second, we cannot exclude the possibility that our sample may have included subjects with mild cognitive deficits or even early-stage dementia because we used only the MMSE and GDS to screen for what our study defined as "healthy" subjects. To reduce this possibility, we set strict inclusion criteria for healthy elderly subjects by requiring that the MMSE score be 28 or higher. Third, we used two 0.5-T MRI scanners, and although we adjusted the pulse sequences to collect optimized images, the sensitivity of the results may be lower than could be obtained using a 1.5-T MRI scanner, which is more commonly used. Fourth, we did not collect other measures of atherosclerosis, such as plaque thickening or calcification of the internal carotid or middle cerebral artery. Therefore, further studies may be needed to show the correlation between the extent of atherosclerosis and gray matter volume decline.

In summary, we analyzed the correlation between hsCRP level and brain regional gray matter volume in 109 community-dwelling healthy elderly subjects. We found a significant negative correlation between regional gray matter volume of the posterior and lateral aspects of the left temporal cortex and hsCRP level after adjusting for age, gender, and intracranial volume. Our results suggest that individuals with mild inflammation, which is related with arteriosclerosis, show a decrease in regional gray matter volume in the posterior and lateral aspects of the left temporal cortex. Therefore, preventing the progress of arteriosclerosis may help to prevent decreases of gray matter volume in healthy elderly subjects.

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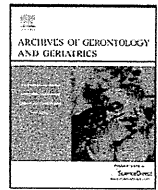
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## C-reactive protein (CRP) is a predictor of high medical-care expenditures in a community-based elderly population aged 70 years and over: The Tsurugaya project

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### ABSTRACT

Because CRP is a strong independent predictor of various diseases, it was hypothesized that CRP may be a useful predictor or treatment target for medical-care expenditures. The aim of this study was to investigate the relationship between CRP and medical-care expenditures in a community-dwelling elderly population. This prospective cohort study was conducted including 925 Japanese subjects aged  $\geq 70$  years. A high-sensitivity CRP assay was used by applying the nephelometric method. Hospitalizations, outpatient visits, and expenditures were ascertained through computerized linkage with claims lodged between August 2002 and March 2008 with the Miyagi National Health Insurance (NHI) Association. Since medical-care expenditures were not normally distributed, the category of high medical-care expenditures ( $>75$ th percentile of medical-care expenditures: inpatient expenditures  $> \$494$ /month; outpatient expenditure  $> \$522$ /month; total expenditures  $> \$1103$ /month) was used to examine the relation of CRP levels with medical-care expenditures. Multiple logistic regression analysis was used to examine the relationship between CRP cutoff points (low concentrations:  $< 1.0$  mg/L; intermediate concentrations:  $1.0$ – $3.0$  mg/L; or high concentrations:  $\geq 3.0$  mg/L) and medical-care expenditures during 6 year-follow up period. After adjustment for potential confounding factors, a positive association of CRP with hospitalization, and total expenditures ( $p$  for trend =  $0.03$  and  $0.02$ , respectively) was found. An elevated baseline CRP level is an independent predictor of increases in prospective medical-care expenditures among community-dwelling elderly. Further study is required to clarify whether reducing CRP by intervention is a cost-effective measure.

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### 1. Introduction

CRP has received substantial attention in recent years as a promising biological predictor of atherosclerotic disease (Pearson et al., 2003). An evolving body of work suggests that even small increases in CRP within the normal range are predictive of future

vascular events in apparently healthy, asymptomatic individuals (Ridker et al., 2002). A number of prospective studies have also demonstrated that high baseline levels of CRP are a strong independent predictor of cardiovascular risk (Koenig et al., 1999), recurrent events and/or increased mortality in patients with ischemic stroke (Di Napoli et al., 2001), peripheral vascular disease (Ridker et al., 2001) cancer (Heikkila et al., 2007), and all-cause mortality (Cao et al., 2007). CRP is also correlated with abdominal obesity and metabolic syndrome, and an elevated level increases the risk of developing type 2 diabetes (Barzilay et al., 2001; Pradhan et al., 2001).

Total medical-care expenditures in Japan reached 33 trillion yen (approximately \$290 billion) in 2006 (Accessed October 05,

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2007). The ratio of medical-care expenditures to the total national income has increased in recent years, and exceeded 9% in 2006 (Accessed October 05, 2007). In the Japanese census reports of 2006, the proportion of the population aged  $\geq 65$  years was 20.7% (Accessed October 04, 2007). A breakdown by age group shows that medical-care expenditures for people aged  $\geq 65$  years accounted for 51.0% of the total expenses, with an approximately 4.1-fold difference in per capita medical expenditures between older and younger generations (Accessed October 05, 2007). A reduction in medical-care expenditures for the elderly population through health promotion and disease prevention is therefore a recognized public objective. Because CRP levels are strongly associated with several diseases, CRP status might be a useful predictor of medical-care expenditure in clinical or subclinical practice. However, to our knowledge, no previous studies have assessed the relationship between CRP and medical-care expenditures in a community-dwelling elderly population.

The present report describes the results of a prospective cohort study designed to investigate the relationship between CRP and medical-care expenditures in the Japanese elderly population.

## 2. Materials and methods

### 2.1. Study participants

The subjects of the present study were participants of the Tsurugaya project, a population-based longitudinal study designed to clarify the various medical problems associated with geriatric health. The Tsurugaya project is described in detail elsewhere (Niu et al., 2006; Kikuchi et al., 2007). The medical expenditures data were derived from the prospective evaluation of National Health Insurance beneficiaries between August 2002 and March 2008. In 2002, there were 2730 individuals who were  $\geq 70$  years of age in the Tsurugaya area, a residential zone within Sendai City, a major city in northern Japan. We invited all of these individuals to participate in a comprehensive geriatric assessment, in which physical, mental, and social functioning were examined to assess for the presence of early deterioration that may result in the need for long-term care and thus to promote healthy aging. Of those invited, 1178 gave written informed consent to be included in the structured survey. Of these 1178, 969 subjects who agreed to have NHI disclose medical care expenditures, coverage of these expenditures under the NHI system, and medical-care utilization from claim history files were initially included. The protocol of this study was approved by the Institutional Review Board of the Tohoku University Graduate School of Medicine.

Subjects whose CRP had not been measured ( $n = 18$ ) were excluded. Patients with a CRP  $> 10.0$  mg/L ( $n = 26$ ) were also excluded because serum CRP concentrations  $\geq 10.0$  mg/L are often indicative of acute inflammatory conditions (Pepys and Hirschfeld, 2003). As a result of these exclusions, the final study population was comprised of 925 subjects [mean  $\pm$  standard deviation; age:  $76.2 \pm 4.7$  years; men: 43.1%]. Moreover, no acute inflammatory symptoms were observed in these subjects at baseline.

### 2.2. Measurement of CRP

CRP concentrations were determined using an immunotechnique on a Behring BN II analyzer (Dade Behring, Tokyo, Japan). The BN II high sensitivity assay utilizes monoclonal antibody-coated polystyrene particles and fixed-time kinetic nephelometric measurements (Ledue et al., 1998).

### 2.3. Assessment of medical care expenditures and mortality data

We prospectively collected data on medical care use, expenditures, and mortality for all individuals in the cohort study. NHI claims history files were obtained from the Miyagi NHI Association. The files included the number of outpatient visits, the number of days of inpatient care, and charges for outpatient and inpatient care. Incidentally, NHI covers almost all medical care, including diagnostic tests, medication, and surgery, in Japan. When a beneficiary was withdrawn from the NHI, the date and reason were coded on an NHI withdrawal history file. This file identified the survival and emigration status for each subject. Both the NHI claims and withdrawal history files were linked with our baseline survey data file, based on the beneficiary's ID number as the key code.

Monthly medical expenditures for each subject were calculated by dividing the total medical expenditures throughout the observation period by the number of months observed. We used monthly values rather than cumulative values to avoid underestimating medical expenditures for subjects who died or emigrated during the follow-up period. To compare outcomes to those of other countries, the expenditures were converted to US dollars by using a multiplication factor of 80.

### 2.4. Assessment of other variables

Anthropometrics (height, body weight) were recorded by a standardized protocol. Body mass index (BMI) was calculated as weight (kg)/height<sup>2</sup> (m<sup>2</sup>). Blood pressure (BP) was measured at home with an HEM7471C device (Omron Life Science Co. Ltd., Tokyo, Japan), which uses the cuff-oscillometric method to generate a digital display of systolic and diastolic pressures. The mean of  $15.0 \pm 10.7$  (mean  $\pm$  SD) BP measurements were used as the BP values. Participants who did not measure their home BP on at least 3 days were treated as having missing information on BP.

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 albumin, lipids, or CRP analyses.

Total cholesterol (T-C), high-density lipoprotein cholesterol (HDL-C) concentrations, and blood glucose concentrations were measured by enzymatic methods (T-C, Denka Seiken, Tokyo, Japan; HDL-C, Daiichi Pure Chemicals, Tokyo, Japan; blood glucose, Shino-Test, Tokyo, Japan). Information on smoking status, drinking status, use of medication and histories of prior cardiovascular disease (CVD, including ischemic heart disease and stroke), cancer, renal disease, liver disease, and arthritis were obtained from the questionnaire survey. All individuals were told to bring their regular medications to the trial setting, and these were checked and recorded by a well-trained pharmacist. The 30-item Geriatric Depression Scale (GDS) (Niino et al., 1991), was used to assess depressive symptoms. Cognitive functioning was measured with the Mini-Mental State Examination (MMSE) (Folstein et al., 1975). Furthermore, socioeconomic status (SES) is one of the most powerful predictors of health. In this paper, educational attainment was assessed as an indicator of SES by determining the age at completion of schooling and was divided into 3 categories:  $\leq 9$  y, 9–12, or  $> 12$  y (Fujino et al., 2005).

### 2.5. Definitions of variables

We categorized the study participants on the basis of the recently proposed cutoff points for CRP as having low concentrations ( $< 1.0$  mg/L), intermediate concentrations (1.0–3.0 mg/L), or high concentrations ( $\geq 3.0$  mg/L) (Pearson et al., 2003).



Hypertension was defined as a home systolic BP of  $\geq 135$  mm Hg and/or a home diastolic BP of  $\geq 85$  mm Hg or the use of antihypertensive agents (Chobanian et al., 2003). Diabetes was defined as a casual blood glucose concentration of  $\geq 200$  mg/dL or current use of antidiabetic medication. Hypercholesterolemia was defined as a concentration of T-C of  $\geq 220$  mg/dL or current use of non-statin lipid-lowering agents. We treated statin agents as independent confounding factors because they have been reported to lower CRP concentrations (Ridker, 2001).

Physical activity (PA) was classified into 6 levels based on a self-reported single-item question on whether the participant carried out any PA in the past year. PA was then classified into three categories (high, levels 5 and 6; moderate, levels 3 and 4; low, levels 1 and 2), based on frequency and duration in the participant. Detailed information was provided in previous reports (Niu et al., 2005; Yang et al., 2010). A GDS score of  $\geq 14$  or the use of an antidepressant was used to indicate depressive symptoms (Burke et al., 1992). A MMSE score of  $< 24$  was used to indicate cognitive impairment (Folstein et al., 1975).

## 2.6. Statistical analysis

Descriptive data are presented as means (95% confidence interval [CI]) or percentages. The values of the medical-care expenditures, number of days of hospital stay or visits were used as the dependent variable and the CRP levels as the independent variable. The differences between the variables among the CRP levels were examined by analysis of covariance (ANCOVA) for continuous variables or by the multiple logistic regression analysis for variables of proportion after adjustment for age and sex. Since medical-care expenditures were not normally distributed, the category of high medical-care expenditures ( $> 75$ th percentile of medical-care expenditures: inpatient expenditures  $> \$494$ /month;

outpatient expenditure  $> \$522$ /month; total expenditures  $> \$1103$ /month) was used to examine the relationship of CRP levels with medical-care expenditures. Multiple logistic regression analysis was used to examine the relation of CRP levels with high medical-care expenditures after adjustment for age, sex, BMI, smoking and drinking habits/history, PA, use of statin drugs, use of aspirin and use of non-steroidal anti-inflammatory drugs (NSAIDs, not including aspirin), hypertension, diabetes, depressive symptoms, educational attainment, impaired cognitive function, history of CVD, renal disease, liver disease, cancer, and arthritis. Moreover, because the medical-care expenditures of individuals in their last months of life are higher than those in non-dying persons (Felder et al., 2000), we also examined the relationship between CRP and medical-care expenditures by excluding expenditures related to death and those during the last month of the follow-up period. ANCOVA was used to examine the relationship between CRP and the number of days of hospital stay or visits after adjustment for the above confounding factors. All *p* values for linear trends across the CRP categories were calculated using the median of each CRP category. The interactions were assessed by testing the interaction term added to the adjusted model as a covariate. A significant difference was defined as  $p < 0.05$ . All statistical analyses were performed using a Statistical Analysis System 9.1 edition for Windows (SAS Institute Inc., Cary, NC, USA).

## 3. Results

Age- and sex-adjusted baseline characteristics according to the levels of CRP are presented in Table 1. Mean BMI was significantly higher in correlation with higher CRP levels (*p* for trend  $< 0.0001$ ). Although not statistically significant, the mean HDL-C value was highest in the lowest CRP category (*p* for trend = 0.06). The prevalence of hypertension, diabetes, ex-smoker status, current

**Table 1**  
Age- and sex-adjusted baseline characteristics according to CRP categories (*n* = 925).

	Cutoff of CRP (mg/L)			<i>p</i> for trend
	$< 1$	1–3	$> 3$	
No. of participants	645	193	87	
Age (y)	76.2(75.9–76.6)	75.7(75.1–76.4)	76.5(75.5–77.5)	0.58
Sex (male, %)	42.6	46.6	39.1	0.72
BMI (kg/m <sup>2</sup> )	23.3(23.1–23.6)	24.7(24.3–25.2)	25.5(24.8–26.2)	$< 0.0001$
Hypertension (%)	64.5	71.5	85.1	$< 0.0001$
Hypercholesterolemia (%)	45.9	52.3	50.6	0.28
HDL-C (mg/dL)	55.9(54.8–56.9)	51.9(50.0–53.8)	52.9(50.1–55.8)	0.06
Diabetes (%)	7.9	10.9	18.4	$< 0.01$
Smoker				
Current smoker (%)	10.5	18.7	10.3	0.41
Ex-smoker (%)	29.0	29.5	36.8	0.049
Drinker				
Current drinker (%)	11.6	11.9	19.5	0.04
Ex-drinker (%)	46.2	42.5	41.4	0.19
Self-reported illness				
Renal (%)	6.1	8.3	10.3	0.10
CVD (%)	14.1	18.1	20.7	0.07
Liver (%)	6.2	11.4	4.6	0.96
Cancer (%)	6.5	7.3	8.1	0.55
Arthritis (%)	17.2	16.5	21.8	0.38
Use of NSAIDs (%)	15.5	16.6	13.8	0.72
Use of statin drugs (%)	17.8	14.5	18.4	0.86
Use of aspirin drugs (%)	9.2	11.9	16.1	0.04
Moderate PA (levels 3 and 4) (%) <sup>*</sup>	29.9	24.9	33.3	0.73
High PA (levels 5 and 6) (%) <sup>*</sup>	31.5	28.0	23.0	0.09
Cognitive impaired (MMSE $< 24$ ) (%)	11.2	13.0	11.5	0.88
Depressive symptoms (GDS $\geq 14$ or use of antidepressant) (%)	20.5	24.9	16.1	0.53
Educational attainment				
$\leq 9$ y	24.2	21.2	26.4	0.83
9–12 y	43.6	43.0	47.1	0.61

Note: Variables are presented as adjusted least squares mean (95% CI) or %; *p* values for trend are based on median values in each category.

<sup>\*</sup> Detailed information was provided in previous reports (see reference, Niu et al., 2005; Yang et al., 2010).

**Table 2**  
Adjusted high medical costs in relation to CRP categories (n = 925).

	Cutoff of CRP (mg/L)			p for trend
	<1	1–3	≥3	
No. of participants	645	193	87	–
No. of high-inpatient medical expenditures (>\$494/month)	89	31	20	
Odds ratio (95% CI)				
Model 1 <sup>†</sup>	1	1.20(0.76–1.85)	1.87(1.06–3.18)	0.02
Model 2 <sup>**</sup>	1	1.19(0.75–1.85)	1.92(1.07–3.32)	0.02
Model 3 <sup>***</sup>	1	1.03(0.63–1.67)	2.05(1.08–3.80)	0.03
No. of hospital stay (days/month) <sup>***,†</sup>	1.64(1.12–2.15)	1.76(1.22–2.29)	1.95(1.36–2.54)	0.11
No. of high-outpatient medical expenditures (>\$522/month)	164	44	21	–
Odds ratio (95% CI)				
Model 1 <sup>†</sup>	1	0.87(0.59–1.26)	0.93(0.54–1.55)	0.68
Model 2 <sup>**</sup>	1	0.87(0.59–1.27)	0.93(0.54–1.54)	0.87
Model 3 <sup>***</sup>	1	0.72(0.47–1.09)	0.68(0.38–1.20)	0.13
No. of hospital visits (days/month) <sup>***,†</sup>	7.93(6.56–9.29)	7.39(5.97–8.81)	7.75(6.19–9.3)	0.72
No. of high-total medical expenditures (>\$1103/month)	91	28	22	–
Odds ratio (95% CI)				
Model 1 <sup>†</sup>	1	1.03(0.64–1.61)	2.06(1.19–3.46)	0.01
Model 2 <sup>**</sup>	1	1.01(0.63–1.59)	2.14(1.23–3.64)	<0.01
Model 3 <sup>***</sup>	1	0.87(0.53–1.41)	2.23(1.21–4.04)	0.02

p values for trend are based on median values in each category.

<sup>†</sup> Crude model.

<sup>\*\*</sup> Adjusted for age, sex.

<sup>\*\*\*</sup> Adjusted for model 2 + BMI, smoking and drinking habits/history, PA, use of statin drugs, use of aspirin and use of NSAIDs (not including aspirin), hypertension, diabetes, depressive symptoms, impaired cognitive function, educational attainment, history of CVD, renal disease, liver disease, cancer, or arthritis.

<sup>†</sup> Variables are presented as least squares mean (95% CI).

drinking, and use of aspirin was significantly higher in the higher CRP level groups ( $p$  for trend  $\leq 0.049$ ). Although not statistically significant, the proportion of patients with a history of renal disease and CVD appeared to be the highest in the high CRP category ( $p$  for trend = 0.10 and 0.07, respectively), and high PA showed a higher proportion in the lowest CRP categories ( $p$  for trend = 0.09). Otherwise, no significant differences were observed among CRP categories ( $p$  for trend  $\geq 0.19$ ).

Because all subjects were >70 years of age and there was no baseline data that could be used for medical-care expenditures, the accumulated total medical-care expenditures for the initial 6 months in relation to CRP levels were compared. After adjustment for potential confounding factors (see Table 2, model 3), no significant relationship between CRP levels and high medical-care expenditures was observed for any type of expenditures, including inpatient, outpatient, and total expenditures ( $p$  for trend  $> 0.45$ ).

Table 2 shows the adjusted results of the relationship between CRP levels and high medical-care expenditures. In final models, increasing CRP levels showed a significant positive relationship with high total medical expenditures ( $p$  for trend = 0.02). Similar results were obtained with regard to high inpatient medical expenditures ( $p$  for trend = 0.03). In contrast, a relationship between the levels of CRP and high outpatient medical expenditures was not found in any model ( $p$  for trend  $\geq 0.13$ ). The results of the tests for interaction between the CRP categories and other confounders in the final models were also not statistically significant. Although not statistically significant, increasing CRP levels tended to relate positively to average number of days of hospital stay in multiple models ( $p$  for trend = 0.11). No relationship was found between the levels of CRP and average number of hospital visits in the final model ( $p$  for trend = 0.72). Excluding CRP levels, several variables were also significantly related with medical expenditures in the final model. Females or individuals with a high or moderate level of PA were less likely to be included in the high total medical expenditures (Odds rate [ORs] = 0.35, 95% CI: 0.19–0.64, in female; ORs = 0.55, 95% CI: 0.34–0.87, in high PA; ORs = 0.46, 95% CI: 0.28–0.74, in moderate PA) or high inpatient medical expenditures category (ORs = 0.32, 95% CI: 0.17–0.58, in female; ORs = 0.47, 95% CI: 0.29–0.77, in high PA; ORs = 0.59, 95%

CI: 0.36–0.93, in moderate PA), compared to males or those with a low level of PA. In contrast, the ORs for the high total medical expenditures category were significantly higher among individuals with a history of arthritis (ORs = 2.07, 95% CI: 1.04–3.94) or use of NSAIDs (ORs = 2.08, 95% CI: 1.26–3.40), compared to those without these conditions. For the high inpatient medical expenditures, the ORs were significantly higher among individuals with a history of CVD (ORs = 1.77, 95% CI: 1.06–2.9) or use of NSAIDs (ORs = 2.09, 95% CI: 1.26–3.43), compared to those without these conditions. The ORs for the high outpatient medical expenditures were significantly higher among individuals with several disease statuses or use of medication: hypertension, 1.48 (95% CI: 1.02–2.17); diabetes, 2.76 (95% CI: 1.68–4.51); history of cancer, 2.26 (95% CI: 1.44–3.54); history of liver disease, 2.50 (95% CI: 1.40–4.42); use of statin drugs, 1.76 (95% CI: 1.17–2.64); use of aspirin drugs, 1.97 (95% CI: 1.18–3.25); use of NSAIDs, 2.07 (95% CI: 1.36–3.14), compared to those without these conditions. No significant relationships were observed between other covariates and medical expenditures.

Furthermore, exclusion of deaths ( $n = 75$ ) and last-month expenditures during the follow up period did not essentially change the adjusted high inpatient, outpatient, and total medical expenditures ( $p$  for trend 0.04, 0.16, and 0.07, respectively) (data not shown).

#### 4. Discussion

In this longitudinal study, we examined the relationship between serum CRP levels and medical-care expenditures during 6 year-follow up period among the community-dwelling elderly population. The relationship between CRP and medical-care expenditures was also examined by excluding death-related costs and expenditures of the last month of the follow-up period. Higher CRP level was associated with higher medical care expenditures characterized by higher inpatient medical expenditures. The results of the present analysis suggested that elevated baseline CRP levels are an independent predictor of prospective hospitalizations, total medical expenditure, and an increase in the number of days spent in the hospital among community-dwelling elderly.

Comparative evaluation of various inflammatory markers favor CRP from the clinical chemistry perspective (Pearson et al., 2003). Although the detection of elevated levels of CRP is not specific to a particular disease, it is a useful indicator of inflammatory processes (Morley and Kushner, 1982). Moreover, systemic low-level inflammation has been related with onset, development, and worsening of many diseases among the elderly (Wilson et al., 2006; Sabatine et al., 2007). Several studies have indicated that elevated levels of CRP are related to the severity of various diseases including CVD (Pearson et al., 2003), late-life disability (Kuo et al., 2006), sleep apnea syndrome (Chung et al., 2007), community-acquired pneumonia (Almirall et al., 2004), and cancer (Elahi et al., 2004). CRP levels could therefore be an independent indicator of medical-care expenditures based on the association between elevated CRP and the severity of certain diseases, deterioration or the need for emergency care in the elderly population. The results of the present study confirm that CRP levels are a useful predictor of medical-care expenditures. In contrast, no significant relationship was found between CRP levels and high outpatient expenditures. All the subjects in this study population were >70 years of age, and 86.8% persons received outpatient services (only 1.5% for inpatient services) during the first month of the survey. Moreover, 94.1% of the subjects received outpatient services (4.9% for inpatient services) during the first 3 months of this survey. These data indicated that almost all subjects received outpatient services at the baseline, suggesting that outpatient expenditures only reflect chronic disease status, and are not indicative of disease progression or a decline in health status associated with total medical-care expenditures.

Considering the results of this study, CRP screening and reduction of CRP by interventions may reduce medical costs in the elderly populations. In fact, a previous study estimated the potential cost-effectiveness of CRP screening in middle-aged patients without overt hyperlipidemia (Blake et al., 2003). The results of this study indicated that a strategy involving CRP screening to target statin therapy for the primary prevention of CVD could be relatively cost-effective. Whether reducing serum CRP levels through targeted therapy will lead to reduced medical-care expenditures in elderly subjects remains an important research question. Preliminary randomized control trials showed a significant effect of antibiotics on CRP (Stone et al., 2002; Wiesli et al., 2002). A treatment-induced reduction of CRP (including the treatment of causative conditions such as high BMI) from  $\geq 3$  mg/L to  $< 1$  mg/L would result in about 55% reduction in high inpatient medical expenditures according to our study.

The present study included an examination of the relationship between CRP and medical-care expenditures excluding death-related expenses and expenditures of the last month of the follow-up period. Exclusion of death and last-month of follow-up expenditures did not essentially change the relationship between CRP and medical-care expenditures. These results suggest that the significant association between CRP and medical-care expenditures was independent of all-cause mortality.

Excluding CRP levels, use of NSAIDs was independently and significantly related with higher outpatient, inpatient, and total medical expenditures. This finding is consistent with several previous reports showing that patients taking NSAID incur greater gastrointestinal disease costs, which may partly explain our result (Moore et al., 2000; Solomon et al., 2003). Furthermore, consistent with our previous reports, PA was significantly related with higher inpatient, and total medical expenditures, but not outpatient medical expenditures (Yang et al., 2010). This finding shows that PA may have a beneficial effect on serious diseases needing emergency care. Alternatively, the injury during PA is related with increased medical costs, and may partly explain why PA was not significantly related with outpatient medical expenditures.

Interestingly, we found that several disease statuses, such as hypertension, diabetes, history of liver disease and cancer were significantly related with higher outpatient medical expenditures, but not inpatient and total medical expenditures. These findings suggest that a daily outpatient service for several disease statuses may be beneficial for cost-effectiveness as it would prevent worsening of the disease.

This study had several limitations. First, because evaluations were carried out in a public facility and participants were sufficiently active and healthy to participate in the survey, it is possible that the current results do not apply to subjects at higher risk. Second, although this prospective study reliably established a temporal relationship between serum CRP levels and medical-care expenditures, a randomized trial should be undertaken to confirm whether reducing inflammatory status by use of a cost-effective drug would reduce medical expenditures in an elderly population. Third, the usefulness of the data was limited by the lack of diagnostic information for each instance of medical-care expenditure. Because elevated baseline CRP levels were only associated with future high inpatient expenditures, but not with outpatient expenditures, CRP may be a powerful predictor of severe diseases requiring hospitalization. Further study is necessary to clarify the details of these diseases.

## 5. Conclusions

The present study suggests that elevated baseline CRP levels are an independent predictor of prospective medical-care expenditure increases among Japanese community-dwelling elderly. Further study is required to clarify whether reducing CRP in the elderly by use of a drug is a cost-effective measure.

## Conflict of interest statement

All the authors have no conflicts of interest exists to disclose.

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## 介護予防サービス利用者における日常生活の過ごし方と 要介護認定等の推移との関連

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## Activities in Daily Life and Changes in Care Level among Users of Preventive Care Service under Long-Term Care Insurance

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**Abstract Objectives:** The aim of this study was to investigate the association between social roles (engaged in working outside or house work) or hobbies and changes in care level among users of Preventive Care Service under Long-Term Care Insurance.

**Methods:** A total of 8,734 Preventive Care Service users were analyzed. The assessment was conducted between February 2007 and December 2008. The improvement, maintenance, and aggravation in care level were defined by changes in care level from the beginning to the end. To assess their activities in daily life, the participants were asked, "Which is the major activity in your daily life? Please select one from the following: working outside, house work, hobbies, watching television, others, or none." We used the multiple logistic regression model to calculate the odds ratio (OR) and 95% confidence interval (CI) of the maintenance or improvement in care level according to the category of activity.

**Results:** As compared with subjects who answered none, the multivariate adjusted ORs (95% CI) of the maintenance or improvement in care level were 2.0 (1.4-2.9) for those who answered working outside, 1.5 (1.2-1.8) for those who answered house work, and 1.5 (1.2-1.9) for those who answered hobbies. However, those who answered watching television or others did not show a significant association with the maintenance or improvement in care level.

**Conclusions:** In this study, compared with subjects who answered none, those who answered that they were engaged in working outside, house work, or hobbies were associated with having significantly higher ORs of the maintenance or improvement in care level.

**Key words:** social role (社会的役割), hobby (趣味), changes in care level (要介護認定等の推移), Preventive Care Service under Long-Term Care Insurance (介護予防事業)

## 緒 言

介護保険制度は、平成 18 年度より「予防重視型システム」へと転換し、要支援者を対象に新予防給付、認定非該当者を対象に地域支援事業〔一般高齢者施策・特定高齢者施策（現一次予防事業・二次予防事業）〕が開始された。介護予防サービス利用者において、どのような特性を有する者で生活機能が改善するのかを調査することは、介護予防効果の期待できる対象者を絞り込むとともに、到達可能な目標を提示するうえで重要となる。そのため、著者らは厚生労働省継続的評価分析支援事業において、全国で介護予防サービスを利用する高齢者を対象に、介護予防サービス利用開始時の個人特性（年齢、性別、疾患既往歴、基本チェックリスト、うつ状態、認知機能、家族構成、ソーシャルサポート）と 1 年後の要介護認定等の推移との関連について検討した (1)。その結果、要介護認定等の維持・改善と関連する要因は、若年であること、脳血管疾患、認知症、骨折・転倒の既往がないこと、高齢による衰弱がないこと、基本チェックリスト得点が低いこと、改訂長谷川式簡易知能評価スケール (HDS-R) の得点が高いこと、認知的活動の頻度が多いことであった。また、日常生活の過ごし方で「特になし」と回答した者に比べ、「役割」のある者では、要介護認定等の維持・改善のオッズ比が有意に高いことも示された。しかし、その当時の解析は役割の有無のみを検討したものであり、日常生活の過ごし方の内容〔自宅外の仕事（役割）、家の仕事（役割）、趣味〕と要介護認定等の推移との関連までは検討していなかった。介護予防は高齢者個々の生活行為や参加を向上させ、家庭や社会における役割の遂行を促すことで、一人ひとりの生きがいや自己実現のための取り組みを支援するものとされていることから、役割を持つことが高齢者の生活機能や要介護度の推移にどのような影響を及ぼすかを解明することは、介護予防サービスのあり方を考えるうえで重要な意味を有するものと考えられる。

高齢者が自宅の内外で役割を持つこと、趣味を持つことの重要性は先行研究でも報告されている。自宅内・外の役割、趣味のある者は、要介護状態を引き起こす身体機能低下 (2)、生活機能低下 (3, 4)、認知症の発症や認知機能低下 (4-9) のリスクが低いことが報告されている。しかし、これらの先行研究は健康レベルや心身機能レベルの比較的良好な地域住民を対象としており、介護予防サービス利用者のような生活機能の低下した者を対象とした研究はこれまで行われていない。

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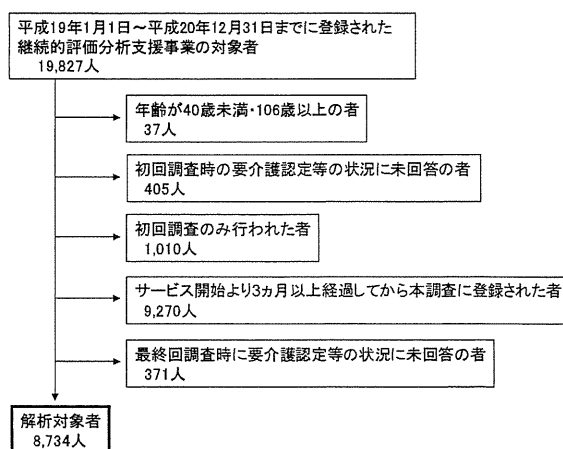


図 1 対象者の流れ図

本研究の目的は、介護予防サービス利用者〔特定高齢者（現二次予防事業対象者）、要支援者〕を対象として、日常生活の過ごし方の種類に着目し、自宅外の仕事での役割、家の仕事での役割、趣味が要介護認定等の維持・改善へ及ぼす影響について明らかにすることである。

## 方 法

### 1. 対象者

継続的評価分析支援事業には、各都道府県を通じて、参加する地域包括支援センターが概ね 2・3ヵ所程度募集され、沖縄県を除く 46 都道府県、83 センターからの参加が得られた。対象者は、予防給付または地域支援事業特定高齢者施策のために介護予防ケアプランを作成された者全員（特定高齢者・要支援者）とし、平成 19 年 1 月 1 日から平成 20 年 12 月 31 日までの調査期間中に随時登録された。登録された者から、年齢が 40 歳未満・106 歳以上の者、初回調査時の要介護認定等の状況に未回答の者、初回調査のみ行われた者、サービス開始より 3ヵ月以上経過してから本調査に登録された者（生活機能や心身機能の推移を介護予防サービス利用開始時から調査するため）、最終回調査時に要介護認定等の状況に未回答の者を除外し、最終的に 8,734 人（男性 2,139 人、女性 6,595 人）を解析対象者とした (図 1)。

### 2. 調査項目

調査は対象者の生活機能、心身機能の推移を把握するため、介護予防サービスの利用開始時、介護予防ケアプランの更新毎（概ね 3ヵ月毎）、介護予防サービスからの離脱時に、同一の調査票を用いて行った。調査票は、利用者本人、地域包括支援センター、サービス事業所の担当者が所定の項目をそれぞれ記入した。

調査項目は、基本情報（調査対象者の性別、生年月日）、要介護認定等の状況（特定高齢者・要支援 1・2 の区分、

障害高齢者の日常生活自立度, 認知症高齢者の日常生活自立度), 介護予防サービスの内容, 認知機能 (HDS-R), 食事・栄養の状態, 家族構成 (同居者の続柄, 人数), 疾患既往歴, 過去 3 ヶ月間の入院歴とその原因疾患, 基本チェックリスト, 生活の質, ソーシャルサポート, 睡眠の状態, 認知的活動 (Cognitive activity score), うつ状態 [Geriatric Depression Scale 短縮版 (GDS15)], ふだんの過ごし方, 口腔機能の状態, 活動 (移動・歩行), 各プログラムの内容 (運動器の機能向上プログラム, 栄養改善プログラム, 口腔機能の向上プログラム, アクティビティプログラム) であった。調査内容の詳細を以下に示す。

日常生活の過ごし方は, 「日中, おもな過ごし方はどれですか」という質問から「自宅外の仕事 (役割)」, 「家の仕事 (役割)」, 「趣味」, 「主にテレビ」, 「その他」, 「特になし」のうち 1 つを選択するよう求めた。

うつ状態は, GDS15 を用いた (10)。GDS15 は 15 項目の質問に対して, 「はい・いいえ」のいずれかで回答し, 各項目でうつ症状を表す回答に 1 点を加え, 全項目の合計点で評価した [うつ状態あり (GDS15 が 11 点以上)・なし (10 点以下) に分類]。

認知機能は, HDS-R を用いて, 全項目の合計点を評価した [認知機能低下あり (HDS-R が 20 点以下)・低下なし (21 点以上) に分類] (11)。

認知的活動は, Wilson らによる Cognitive activity score を用いた (12)。「テレビを見る」, 「ラジオを聞く」, 「新聞を読む」, 「雑誌を読む」, 「本を読む」, 「ゲームをする」の 6 つの活動について, それぞれ「ほとんど毎日 (5 点)」, 「週に数回 (4 点)」, 「月に数回 (3 点)」, 「年に数回 (2 点)」, 「年に 1 回以下 (1 点)」の 5 段階から, 全項目の合計点を評価した [下位 (Cognitive activity score が 14 点以下)・中位 (15-18 点)・上位 (19 点以上) に分類]。

### 3. 統計解析

日常生活の過ごし方が要介護認定等の推移に及ぼす影響について, 交絡要因を調整した多重ロジスティック回帰分析を実施した。

目的変数は要介護認定等の維持及び改善とした。それは, 介護予防の目的が要介護状態の発生をできる限り防ぐこと, 要介護状態にあつてはその悪化をできる限り防ぐことと定義されているためであった。要介護認定等の維持・改善, 悪化は, ベースライン時と最終回調査時 (サービス離脱時含む) との比較から評価した (表 1)。

説明変数は日常生活の過ごし方とし, 「特になし」群を基準として, 「自宅外の仕事 (役割)」群, 「家の仕事 (役割)」群, 「趣味」群, 「主にテレビ」群, 「その他」群別に, 要介護認定等の維持・改善に関するオッズ比 [95% 信頼区間 (CI)] を算出した。

多重ロジスティック回帰分析の調整項目は, 年齢 (連続変数), 性別 (男性・女性), 同居者 (なし・あり), 疾患既往歴 [脳血管疾患, 関節疾患, 認知症, 骨折・転倒, 高齢による衰弱 (あり・なし)], 基本チェックリスト得

表 1 要介護認定等の悪化・維持・改善の定義

ベースライン時の要介護認定等の状況			
	特定高齢者	要支援 1	要支援 2
最終回調査時の状況			
一般高齢者	改善	改善	改善
特定高齢者	維持		
要支援 1	悪化	維持	維持
要支援 2		悪化	
要介護 1~5			悪化

点 (連続変数), うつ状態 [あり (GDS15 が 11 点以上)・なし (10 点以下)], 認知機能 [低下あり (HDS-R が 20 点以下)・低下なし (21 点以上)], 認知的活動 [下位 (Cognitive activity score が 14 点以下)・中位 (15-18 点)・上位 (19 点以上)], 地域包括支援センター 83 ヶ所 (各地域包括支援センターによって要介護認定等の維持・改善率に差があったため, 要介護認定等の維持・改善率が高い地域包括支援センターの順に 10 分類) とした。

加えて, 日常生活の過ごし方と要介護認定等の推移との関連は, ベースライン時の要介護認定等の状況やサービス利用期間により異なる可能性がある。そのため, ベースライン時の要介護認定等の状況では, 特定高齢者・要支援者に層別化して解析を行った。同様に, サービス利用期間では, 1 年以内・1 年以上の利用期間別に層別化して解析を行った。サービス利用期間は, ベースライン調査時を起点として, 調査期間内の最終回調査時 (サービス離脱時含む) までとした。全対象者におけるサービス利用期間の平均日数土標準偏差は 299±192 日であった。一方, 特定高齢者では 213±163 日, 要支援者では 325±194 日であった。なお, サービス利用期間別の解析では, サービス利用期間によってベースライン時の特定高齢者, 要支援者の割合が異なることから, 調整項目にベースライン時の要介護認定等の状況を加えた。

統計解析は SAS version 9.2 statistical software package (Cary, NC, USA) を使用した。すべての解析は両側検定で行い, P<0.05 を統計学的に有意差ありとした。

### 4. 倫理上の配慮

本研究は介護保険給付というセンシティブな個人情報を取り扱うため, 対象者個人の利益と利権を侵害することのないように最大限の配慮を払う必要がある。研究対象者には, 調査の意義・目的・方法, 個人情報の保護, 調査成果の公表, 調査への同意 (同意撤回) について説明し, 同意を得た。また, 地域包括支援センターで収集されたデータは, 同センターで連結不可能匿名化したうえで研究者に提供された。

データ提供を受ける東北大学大学院医学系研究科公衆衛生学分野では, 情報処理に関わる実務担当者を制限し,

表 2 日常生活の過ごし方別基本特性

変数	日常生活の過ごし方					
	特になし	自宅外の仕事	家の仕事	趣味	主にテレビ	その他
全対象者 (8,734 人)	946	460	2,804	1,151	2,697	676
特定高齢者 (2,011 人)	95	272	879	316	354	95
要支援者 (6,723 人)	851	188	1,925	835	2,343	581
年齢 (平均±標準偏差)	82.4±7.0	78.7±7.0	79.7±6.6	81.4±7.0	80.6±7.4	81.2±6.8
性別 (%)						
男性	28.9	29.1	13.7	26.3	31.8	28.0
女性	71.1	70.9	86.3	73.7	68.2	72.0
同居者なし (%)	29.4	27.4	34.5	31.6	31.6	32.1
疾患既往歴						
脳血管疾患あり (%)	17.4	13.3	12.3	14.7	20.5	18.9
関節疾患あり (%)	20.3	23.9	27.3	24.4	22.5	24.6
認知症あり (%)	7.1	3.3	3.7	3.8	5.6	6.4
骨折・転倒あり (%)	15.9	11.1	16.1	17.2	18.1	18.8
高齢による衰弱あり (%)	8.4	4.8	8.1	8.2	8.8	5.3
基本チェックリスト (平均±標準偏差)	13.2±4.0	8.3±3.7	9.1±3.9	9.9±4.0	11.6±3.9	11.4±4.0
うつ状態あり (%) <sup>a</sup>	21.8	3.5	5.4	4.8	11.8	9.2
認知機能低下あり (%) <sup>b</sup>	34.5	14.6	11.7	13.1	25.2	25.3
認知的活動 (%) <sup>c</sup>						
下位	59.3	34.7	33.9	22.6	47.6	41.3
中位	22.5	31.9	29.2	26.6	29.5	27.4
上位	18.2	33.4	37.0	50.9	22.9	31.3

<sup>a</sup> うつ状態あり：Geriatric Depression Scale 短縮版が 11 点以上

<sup>b</sup> 認知機能低下あり：改訂長谷川式簡易知能評価スケールが 20 点以下

<sup>c</sup> 認知的活動下位：Cognitive activity score が 14 点以下，中位：15-18 点，上位：19 点以上

情報を厳格な管理の下に扱い、提供された情報を目的外利用しないことを取り決めた。

なお、本研究課題は東北大学医学部倫理審査委員会で承認されている（承認番号：2007-430）。

## 結 果

### 1. 対象者の基本特性

対象者のうち、特定高齢者は 2,011 人 (23.0%)、要支援者は 6,723 人 (77.0%) であった。日常生活の過ごし方で「自宅外の仕事 (役割)」と回答した者は 460 人 (5.3%)、「家の仕事 (役割)」は 2,804 人 (32.1%)、「趣味」は 1,151 人 (13.2%)、「主にテレビ」は 2,697 人 (30.9%)、「その他」は 676 人 (7.7%)、「特になし」は 946 人 (10.8%) であった。

表 2 は、ベースライン時における日常生活の過ごし方別に基本特性を示した。「特になし」群に比べ、「自宅外の仕事 (役割)」群、「家の仕事 (役割)」群、「趣味」群は、年齢が低く、脳血管疾患、認知症の既往者が少なく、基本チェックリスト得点が低く、うつ状態の者、認知機能の低下した者、認知的活動が下位群の者が少なかった。一方、「家の仕事 (役割)」群は、男性が少なく、同居者のいない者が多かった。また、「自宅外の仕事 (役割)」群は、同居者のいない者が少なかった。

表 3 要介護認定等の推移

全対象者	ベースライン時の 要介護認定等の状況			
	特定高齢者	要支援 1	要支援 2	
対象者数	8,734	2,011	3,064	3,659
最終回調査時の状況				
維持・改善 (%)	79.6	93.9	70.2	79.7
悪化 (%)	20.4	6.1	29.8	20.3

### 2. 要介護認定等の推移

全対象者では、最終回調査時に維持・改善していた者は 79.6% (改善 12.0%・維持 67.6%)、悪化していた者は 20.4% であった。ベースライン時の要介護認定等の状況別では、特定高齢者の維持・改善は 93.9% (改善 27.7%・維持 66.2%) であり、要支援者に比べ高かった [75.4% (改善 7.3%・維持 68.0%)]。また、悪化していた者は、特定高齢者で 6.1%、要支援 1 で 29.8%、要支援 2 で 20.3% であった (表 3)。

### 3. 日常生活の過ごし方と要介護認定等の維持・改善に関するオッズ比

要介護認定等の維持・改善に関する多変量調整オッズ比は、「特になし」群に比べ、「自宅外の仕事 (役割)」群で 2 倍 [2.0 (95%CI; 1.4-2.9)]、「家の仕事 (役割)」群、



表 4 日常生活の過ごし方と要介護認定等の維持・改善に関するオッズ比

	日常生活の過ごし方					
	特になし	自宅外の仕事	家の仕事	趣味	主にテレビ	その他
全対象者 (8,734 人)	946	460	2,804	1,151	2,697	676
維持・改善者 (6,955 人)	665	413	2,372	961	2,036	508
年齢・性別調整オッズ比 (95% 信頼区間)	1.0 (基準)	3.3 (2.3-4.5)	2.1 (1.7-2.4)	2.1 (1.7-2.5)	1.2 (1.0-1.4)	1.2 (1.0-1.5)
P 値	—	<0.01	<0.01	<0.01	0.02	0.08
多変量調整オッズ比 (95% 信頼区間)	1.0 (基準)	2.0 (1.4-2.9)	1.5 (1.2-1.8)	1.5 (1.2-1.9)	1.1 (1.0-1.4)	1.1 (0.9-1.4)
P 値	—	<0.01	<0.01	<0.01	0.14	0.34

多変量調整で用いた変数は、年齢、性別、同居者、疾患既往歴 (脳血管疾患、関節疾患、認知症、骨折・転倒、高齢による衰弱)、基本チェックリスト、うつ状態、認知機能、認知的活動、地域包括支援センター (要介護認定等の維持・改善率が高い地域包括支援センターの順に 10 分類) とした。

表 5 ベースライン時の要介護認定等の状況、サービス利用期間で層別化した、日常生活の過ごし方と要介護認定等の維持・改善に関する多変量調整オッズ比

対象者数	維持・改善者数 (%)	日常生活の過ごし方											
		特になし		自宅外の仕事		家の仕事		趣味		主にテレビ		その他	
		OR (95% CI)	P 値	OR (95% CI)	P 値	OR (95% CI)	P 値	OR (95% CI)	P 値	OR (95% CI)	P 値		
ベースライン時の要介護認定等の状況													
特定高齢者 2,011	1,889 (93.9)	1.0 (基準)	—	2.2 (0.8-5.8)	0.12	1.6 (0.7-3.4)	0.24	2.8 (1.1-7.0)	0.03	1.4 (0.7-3.0)	0.37	1.6 (0.6-4.7)	0.38
要支援者 6,723	5,066 (75.4)	1.0 (基準)	—	1.3 (0.9-1.9)	0.23	1.3 (1.1-1.6)	<0.01	1.3 (1.1-1.7)	0.02	1.1 (0.9-1.4)	0.20	1.1 (0.9-1.4)	0.47
サービス利用期間													
1 年以内 5,602	4,475 (79.9)	1.0 (基準)	—	1.8 (1.1-3.0)	0.02	1.6 (1.2-2.0)	<0.01	1.4 (1.0-1.9)	0.02	1.1 (0.9-1.3)	0.53	1.0 (0.7-1.3)	0.92
1 年以上 3,132	2,480 (79.2)	1.0 (基準)	—	2.2 (1.3-3.9)	<0.01	1.3 (0.9-1.8)	0.12	1.7 (1.1-2.5)	0.01	1.2 (0.9-1.7)	0.23	1.5 (0.9-2.3)	0.09

OR : オッズ比, CI : 信頼区間

多変量調整で用いた変数は、年齢、性別、同居者、疾患既往歴 (脳血管疾患、関節疾患、認知症、骨折・転倒、高齢による衰弱)、基本チェックリスト、うつ状態、認知機能、認知的活動、地域包括支援センター (要介護認定等の維持・改善率が高い地域包括支援センターの順に 10 分類) とした。サービス利用期間別の解析では、調整項目にベースライン時の要介護認定等の状況を加えた。

「趣味」群で 1.5 倍 [「家の仕事 (役割)」群 1.5 (95%CI; 1.2-1.8), 「趣味」群 1.5 (95%CI; 1.2-1.9)] 有意に高いことが示された (表 4)。

#### 4. 要介護認定等の状況、サービス利用期間で層別化した、日常生活の過ごし方と要介護認定等の維持・改善に関する多変量調整オッズ比

ベースライン時の要介護認定等の状況で層別化解析した結果、特定高齢者の層では、「特になし」群に比べ、「趣味」群で 2.8 倍、維持・改善のオッズ比が有意に高いことが示された。一方、「特になし」群に比べ、「自宅外の仕事 (役割)」群では 2.2 倍、「家の仕事 (役割)」群では 1.6 倍、維持・改善のオッズ比は高いことが示されたが、統計学的有意性は認められなかった。一方、要支援者の層では、「特になし」群に比べ、「自宅外の仕事 (役割)」群、「家の仕事 (役割)」群、「趣味」群で、維持・改善のオッズ比はいずれも 1.3 であり、「自宅外の仕事 (役割)」群では統計学的有意性は認められなかったものの、「家の仕事 (役割)」群、「趣味」群では、有意に維持・改善す

ることが示された。

サービス利用期間で層別化解析した結果、1 年以内の層では、「特になし」群に比べ、「自宅外の仕事 (役割)」群で 1.8 倍、「家の仕事 (役割)」群で 1.6 倍、「趣味」群で 1.4 倍、維持・改善のオッズ比が有意に高いことが示された。1 年以上の層では、維持・改善のオッズ比は、「特になし」群に比べ、「家の仕事 (役割)」群では 1.3 であり、統計学的有意性は認められなかったものの、「自宅外の仕事 (役割)」群では 2.2 倍、「趣味」群では 1.7 倍高く、有意に維持・改善することが示された (表 5)。

#### 考 察

本研究は継続的評価分析支援事業に参加した特定高齢者、要支援者における日常生活の過ごし方と要介護認定等の推移との関連について検討し、日常生活の過ごし方で「特になし」と回答した者に比べ、「自宅外の仕事 (役割)」、「家の仕事 (役割)」、「趣味」と回答した者の維持・改善のオッズ比は有意に高いことが明らかになっ

た。また、上記の関連は、ベースライン時の要介護認定等の状況（特定高齢者・要支援者）及びサービス利用期間（1年以内・1年以上）による影響を受けないことが明らかになった。

高齢者における社会的役割や趣味は、生きがいや主観的健康感を高め(13)、身体活動量やうつ状態を改善させることが知られている(14, 15)。また、身体活動量の低下やうつ状態は生活機能を低下させることが報告されていることから(16-18)、本研究結果は役割や趣味を持つことが身体活動量やうつ状態を改善させ、その結果として要介護認定等を維持・改善させた可能性がある。

一方、日常生活の過ごし方において、「特になし」と回答した者に比べ、「主にテレビ」と回答した者は、要介護認定等の維持・改善のオッズ比が有意なレベルまで高くならなかった。先行研究では、テレビを見ることやラジオを聞くことは、要介護状態を引き起こす認知機能の低下や認知症発症リスクの低下には貢献しないことが報告されており(8, 19)、むしろ、ふだんテレビを見て過ごすことが多い者では、認知機能低下リスクが高くなるとの報告もある(20)。

## 1. 本研究の長所・限界

本研究の長所として以下のことが挙げられる。第1に、これまでの先行研究では、地域在住の健常高齢者を対象としており、生活機能の低下した特定高齢者・要支援者を対象とした研究は行われていなかった。本研究結果は、生活機能の低下した高齢者でも社会的役割や趣味を持つことの重要性を示すものであった。また、本研究の対象者は全国46都道府県、83ヵ所の地域包括支援センターから集められた特定高齢者・要支援者8,734名であり、代表性、サンプル数ともに優れている。

第2に、社会経済的要因、疾患既往歴、身体・精神的要因、認知的活動の状況を含む、多くの交絡要因は、社会的役割や趣味と要介護認定リスクとの関連を過大評価させる可能性がある。国内における先行研究では、趣味のない者に比べ、ある者で、認知症を伴う要介護認定リスクが低いことが報告されている(6)。しかし、この研究は、年齢調整による男女別の解析のみを行っており、趣味が交絡要因と独立して認知症発症リスクを低下させているのか分からなかった。本研究は、年齢・性別調整による結果に加え、多変量調整による結果を示し、多変量調整のオッズ比は、いずれの群でも年齢・性別調整によるオッズ比より低い点推定値を示した(表4)。これは、上記の交絡要因が日常生活の過ごし方と要介護認定等の推移との関連を減弱させたものと考えられる。したがって、先行研究の結果は過大評価されている可能性がある(6)。本研究結果は、多変量調整による解析を行うことで、交絡要因の影響を制御したうえで日常生活の過ごし方と要介護認定等の推移との関連を検討することができた。

本研究では、以下の限界が挙げられる。本研究結果は

ベースライン時の要介護認定等の状況及びサービス利用期間による影響を受けなかった。しかし、特定高齢者の層における「自宅外の仕事(役割)」群、「家の仕事(役割)」群、要支援者の層における「自宅外の仕事(役割)」群、サービス利用期間が1年以上の層における「家の仕事(役割)」群では、統計学的有意性は認められなかった(表5)。この原因は、対象者を層別化して解析したことにより、対象者数が減り、統計学的な検出力が低下したことが考えられる。

加えて、本研究の調査期間は2年間(平成19年1月1日から平成20年12月31日まで)であったことから、介護予防サービス利用者における社会的役割や趣味が要介護認定等の推移に与える長期的な影響は分からなかった。長期的な影響を調査することは、高齢者の健康寿命の延長を目指すうえで重要となるため、さらなる調査が必要と考える。

本研究では、自宅内外の役割や趣味だけでなく、主にテレビを見みて過ごすことが要介護認定等の推移へ及ぼす影響を明らかにするため、「特になし」群を基準として調査を行った。しかし、「特になし」と回答した者は、年齢が高く、基本チェックリスト得点が高く、うつ状態の者、認知機能の低下した者、認知的活動が下位群の者が多かったことから(表2)、より虚弱な者を含む群を基準としていた。そのため、自宅内外の役割や趣味が要介護認定等の推移へ及ぼす影響は過大評価されていた可能性がある。しかし、「主にテレビ」群を基準とした時、表4の結果と同様、要介護認定等の維持・改善のオッズ比は「自宅外の仕事(役割)」群、「家の仕事(役割)」群、「趣味」群で有意に高かった。

## 2. 今後の展望

これまで地域住民を対象とした先行研究では、社会的役割や趣味を持つ者は、要介護状態を引き起こす身体機能低下(2)、生活機能低下(3, 4)、認知症の発症や認知機能低下(4-9)のリスクが低いことが報告されてきた。本研究結果は生活機能の低下している対象者においても同様に、日常生活の過ごし方で「自宅外の仕事(役割)」、「家の仕事(役割)」、「趣味」を有する者で、要介護認定等の維持・改善のオッズ比が有意に高いことが明らかになった。介護予防事業では、閉じこもり予防・支援マニュアルが作成され、「閉じこもらない生活」、「活発な生活」の重要性が強調されている(21)。本研究結果は、その重要性を支持するものである。一方、どうすれば高齢者に社会的役割や趣味を持たせられるのか、新たに社会的役割や趣味を持つことによって、要介護認定の予後にどのような影響を及ぼすのかについては明らかになっていない。今後、これらを解明するために、高齢者の社会参加を促す取り組みや趣味の提供が、要介護状態への移行を予防するのにかつて、介入研究で明らかにしていく必要があると考える。

### 3. 結語

本研究結果から、介護予防サービス利用者を対象として、自宅外の仕事での役割、家の仕事での役割、趣味を有する者は、要介護認定等の推移が維持・改善することが明らかになり、自宅内外の役割や趣味を持つことの重要性が示された。

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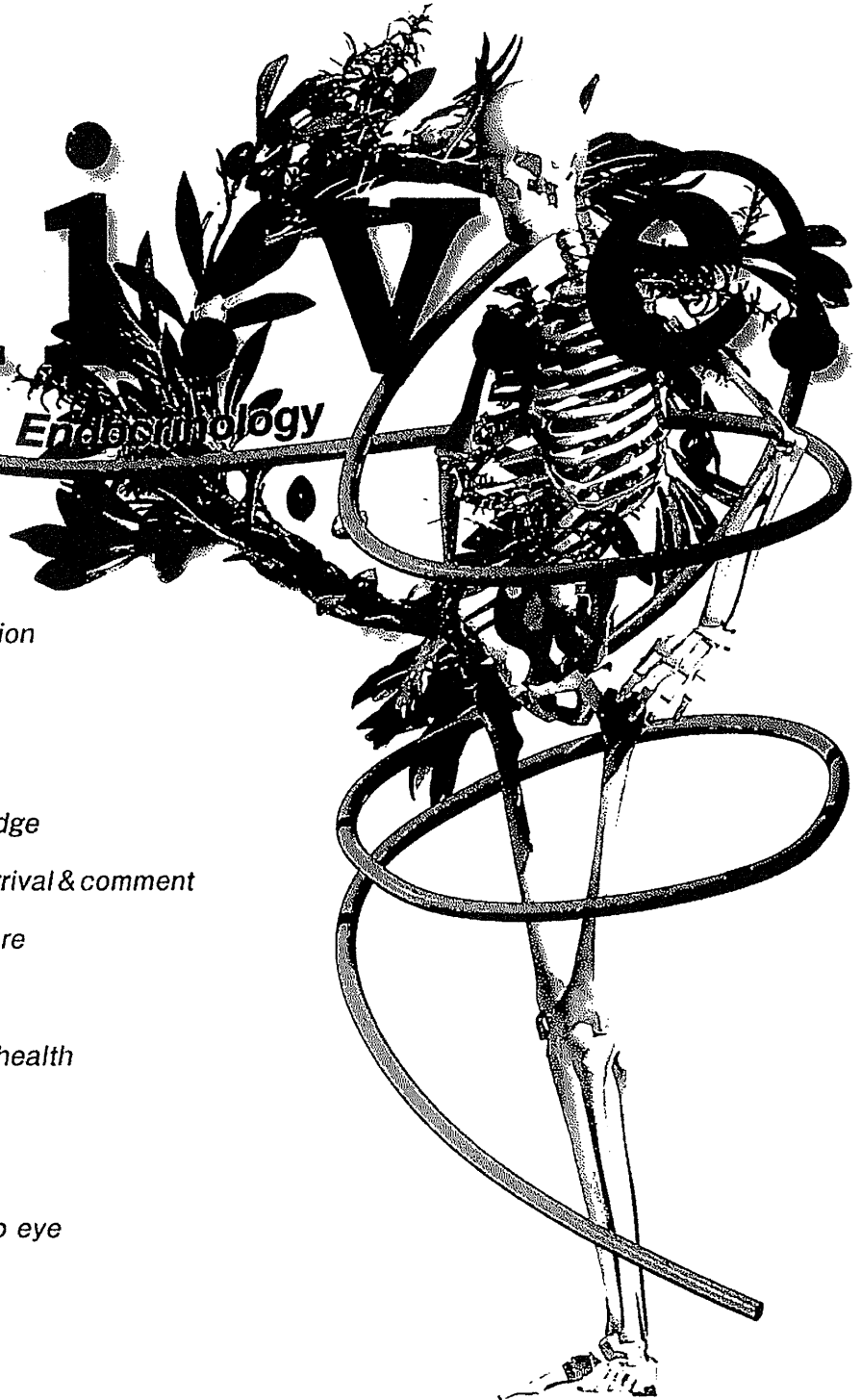
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### 文 献

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—骨代謝と生活習慣病の連関—

O.l.i.v.e.  
Osteo Lipid Vascular & Endocrinology



座談会/Round table discussion

**糖尿病と骨粗鬆症**

山岸昌一(司会)

梶 博史/斎藤 充/吉澤達也

骨粗鬆症講座/Basic knowledge

新着論文 要訳と解説/New arrival & comment

研究者インタビュー/Learn more

症例の実際/Case study

骨の健康のために/For bone health

O.l.i.v.e. plus

コラム/Column

アピール・ツー・アイ/Appeal to eye