rate among drivers under age 65 tended to decrease in the past decade, whereas that among older drivers remained at a high level.

Thus, the Japanese government has enforced a traffic safety campaign targeting older drivers and has paid special attention to older drivers suffering from dementia, who are considered a high-risk group. In 2002, Section 103 of the Road Traffic Act was amended. In the amended Act, dementia was included as a reason for license revocation, stating that if a driver is found to be 'demented', his/her driving license shall be revoked (Arai Y and Arai A, 2005; Arai Y, 2006). Such efforts can lead to raising the national profile of driving and dementia. However, there are several challenges related to implementation of the Act. It is not easy to identify drivers who suffer from dementia without guidelines and mandatory reports from physicians. In addition, without a clear consensus regarding the progressive decline of cognitive functions, it is difficult to decide when drivers should stop driving (Arai Y, 2006; Hirono, 2006). This has raised concern that many drivers may continue to drive after onset of dementia, as reported in previous studies (Odenheimer, 1993; Dobbs *et al.*, 2002; Adler and Kuskowski, 2003; Herrmann *et al.*, 2006).

The NPA reported that nationwide only 192 drivers had their driver's licenses revoked due to dementia over the last four years since the law was amended. Moreover, the most common reason for license revocation was 'concerns of family members' (133 cases), which was followed by 'police activity' (e.g., handling a traffic accident) (59 cases) ('Older drivers: introduction of cognitive assessments' (Japanese), *The Daily Police News*, 20 October 2006). Our previous study regarding family caregivers of current and former drivers who had dementia ($n = 21$) showed that a primary reason for driving cessation among former drivers was because 'family caregivers discovered the patient was driving dangerously' (48%), followed by 'patients and family caregivers were persuaded by physicians' (14%), 'traffic accidents' (14%), and 'other' (2%) (Arai A *et al.*, 2006). Cotrell and Wild (1999) demonstrated that either the patient or caregiver was responsible for decisions regarding driving status in most cases of those with Alzheimer's disease (AD) who stopped driving. Similarly, Perkinson *et al.* (2005) reported from focus-group interviews that most of the stakeholders with respect to driving by persons with AD believed that family members had primary responsibility for identifying and dealing with unsafe drivers. Thus, family members of dementia patients play a pivotal role in decision-making regarding patients' driving and in supporting the eventual goal of driving cessation.

However, the decision of driving cessation is often complicated for longtime drivers, and even more so for those with dementia and their family caregivers for a number of reasons: (1) rejection by drivers due to the symptoms of dementia such as memory impairment or unawareness of deficits; (2) rejection by drivers due to a strong need to drive, i.e., because it is a necessary form of transportation; and (3) conflicts between drivers and their family members due to different perceptions about driving such as opinions as to what driving means to the person who is driving. These reasons, including ones which are not necessarily related to dementia, can hinder driving cessation from occurring at the most appropriate time, jeopardizing personal and public safety.

Although much of the literature has focused on examining the medical and non-medical predictors of driving cessation in older adults with dementia (Wackerbarth and Johnson, 1999; Adler and Kuskowski, 2003; Carr *et al.*, 2005; Herrmann *et al.*, 2006), little is known about what kinds of difficulties exist between dementia patients and family members with respect to patients' driving cessation. As Carr *et al.* (2006) have suggested, research is needed regarding family or social barriers that may delay driving cessation in older adults with dementia.

The family or social barriers might be, in part, the result of disparities of perceptions regarding driving between dementia drivers and family members. Different perceptions about driving may cause family conflicts, posing possible barriers to achieving driving retirement at the most appropriate time. Furthermore, family caregiving can befall anyone; most individuals are susceptible to the possibility of suffering dementia or becoming family caregivers. It is thus important to explore perceptions among the general public, with the expectation that the findings would provide implications for drivers with dementia and their family caregivers. In addition, it can be useful information to allow the public to better understand and get involved in addressing issues of driving and dementia. We therefore aimed to explore the perceptions of driving in a sample of the general population and examine the differences of perceptions from age and driving status viewpoints.

Design and methods

In October 2007, we conducted a survey among the general public aged 40 and over in Japan. Participants were selected from a research panel organized by Social Survey Research Information (SSRI) Co., Ltd. The

panelists, who were recruited from the general population and were willing to participate in surveys, included 31 050 persons aged 40 or over. Each person eligible for this panel was competent in reading and answering a series of self-administered questionnaires distributed by the SSRI; therefore, the quality of this research panel was assured and responses were valid and reliable. All panelists lived independently in communities. If we found that more than one panelist resided in the same household, we limited participation to only one member from that household. Of the 1191 who agreed to participate in this study, 1010 were randomly selected to fit into predetermined categories by a quota sampling method (Moser and Kalton, 1989). This quota sampling method has been used in previous studies (Arai Y *et al.*, 2005; Arai Y *et al.*, 2008). The quota controls used in the present study were gender, age group, driving license status, and place of residence (urban: population $\geq$ 500 000, suburban: 100 000 to $<$ 500 000 or rural: $<$ 100 000) based on Japan's national statistics. Although there were similar distributions of most of the sociodemographic characteristics compared with Japanese population statistics, there was a slightly higher proportion of study participants who lived in a household with two or more generations, had higher education, or were or used to be administrative workers.

Each subject received a self-administered questionnaire that requested information about sociodemographic factors (e.g., education, annual household income, employment status, and living arrangement), driving status (drivers: those who had a driver's license and frequently drove, and those who had a driver's license and rarely drove; non-drivers: those who did not have a driver's license), and perceptions related to driving.

Perceptions about driving

We asked all participants including drivers and non-drivers to identify how they perceived 'driving' using the following question based on a previous study by Perkinson *et al.* (2005): 'Do you think that driving is a "right" which we all deserve'? We also asked only the frequent drivers (i.e., those who had a driver's license and frequently drove) about possible barriers to driving cessation using the following question: 'Assuming you have to stop driving, what would be the reasons, if any, for your reluctance to do so'?

The former question was answered by a four-point Likert scale (agree, agree somewhat, disagree somewhat, disagree), while the latter was a multiple choice question in which participants chose all the answers that applied from 15 items created by the authors (a psychiatrist and public health specialist: YA and AA).

Statistical analyses

Multiple logistic regression models were used to compare the older group (65+ years) and younger group (40–64 years), and the drivers and non-drivers, on their perceptions of driving, adjusting for potential confounding factors such as age group/driving status, gender, place of residence, education, annual household income, living arrangement, and employment status. The associations between the probability of each reason for feeling reluctance to stop driving and the age group were evaluated by calculating the crude odds ratios (ORs) and the ORs adjusted for potential confounding factors, including gender, place of residence, education, annual household income, living arrangement, and employment status using the logistic regression models. All calculations were performed using SAS version 9.1.3 for Windows (SAS Institute Inc., Cary, NC).

Results

Table 1 shows the characteristics of the respondents ($n = 1010$) by age group and driving status. Most of the older drivers were men; further, the older age group had fewer years of education and lower annual household incomes than the younger age group. The younger drivers were more likely to be employed and lived in households with two or more generations present. The younger participants also tended to live in urban areas. Most of the drivers in both age groups frequently drove.

Regarding how the participants perceived 'driving', the largest number of older drivers agreed that 'driving is a "right" which we all deserve' (Table 2). Perceptions of driving did not significantly differ between the age groups. However, we found that the drivers tended to regard 'driving' as a deserved right compared with the non-drivers after controlling for potential confounders.

As shown in Table 3, 'It would be difficult for me to go out' (65.8% of the total) was the most common reason given for reluctance to stop driving among the frequent drivers, followed by 'It would be difficult for my family members to go out' (43.0%), 'Loss of something I enjoy' (29.2%), and 'A driver's license is

Table 1 Characteristics of participants by age group and driving status

	Older (65+ years)		Younger (40–64 years)	
	Drivers ($n=192$)	Non-drivers ($n=258$)	Drivers ($n=451$)	Non-drivers ($n=109$)
Men, *n* (%)	136 (70.8)	89 (34.5)	251 (55.7)	29 (26.6)
Age, mean (SD)	72.9 (5.3)	75.5 (6.1)	48.0 (6.5)	52.9 (8.0)
Education, *n* (%)[a]				
<10 years	49 (25.9)	78 (30.4)	12 (2.7)	8 (7.4)
10–<13 years	74 (39.2)	134 (52.1)	148 (32.9)	55 (50.9)
13+ years	66 (34.9)	45 (17.5)	290 (64.4)	45 (41.7)
Annual household income (thousands of Yen), *n* (%)[b]				
–<4000	75 (42.4)	103 (43.3)	47 (11.0)	33 (31.7)
4000–<8000	69 (39.0)	103 (43.3)	185 (43.4)	46 (42.2)
8000+	33 (18.6)	32 (13.5)	194 (45.5)	25 (24.0)
Employed, *n* (%)	53 (27.6)	25 (9.7)	355 (78.7)	54 (49.5)
Living arrangement, *n* (%)[c]				
Alone	10 (5.4)	27 (11.1)	7 (1.6)	6 (5.7)
Couple	95 (50.8)	84 (34.4)	56 (12.8)	34 (32.4)
Two or more generations in household	82 (43.9)	133 (54.5)	374 (85.6)	65 (61.9)
Place of residence, *n* (%)[d]				
Urban	58 (30.7)	84 (34.6)	249 (55.6)	51 (49.5)
Suburban	56 (29.6)	71 (29.2)	103 (23.0)	27 (26.2)
Rural	75 (39.7)	88 (36.2)	96 (21.4)	25 (24.3)
Frequently driving, *n* (%)	145 (75.5)	na	372 (82.5)	na

Missing data: six data points (a), 65 data points (b), 37 data points (c), and 27 data points (d).

useful as an ID card' (27.2%). The reason 'Loss of a motivating factor in my life' was significantly more common among the older drivers than among the younger drivers, even after adjusting for potential confounders. Moreover, compared with the younger drivers, the older drivers appeared to be concerned about 'Loss of something I enjoy' ($p=0.05$) and 'Loss of a hobby' ($p=0.08$) after driving cessation, although these reasons were not significant.

Discussion

The present study clearly demonstrated the disparities in perceptions about driving in a sample of the Japanese general public.

Perceptions about driving varied according to the respondent's driving status. Irrespective of age group, drivers tended to believe that driving was a deserved right, whereas non-drivers were less likely to think so. Further research is needed regarding why the difference in perceptions existed. These different perceptions are nonetheless thought to be a cause of possible conflicts among family members or stakeholders; those drivers who perceive driving as a right may firmly refuse to give up driving or even rigidly adhere to continuing to drive. These results also indicate that drivers and non-drivers may have a different understanding of 'driving'. Therefore, it is necessary for the general population, irrespective of driving status, to promote a more precise recognition of current driving license regula-

Table 2 Perceptions of driving among the general public

	Older (65+ years)		Younger (40–64 years)		*p* value[b] (adjusted for potential confounding variables)	
	Drivers ($n=192$)	Non-drivers ($n=257$)[a]	Drivers ($n=449$)[a]	Non-drivers ($n=109$)	Older *vs.* younger	Drivers *vs.* non-drivers
'Driving is a "right" which we all deserve'					0.7462	0.0009
Agree/Agree somewhat, *n* (%)	147 (76.6)	146 (56.8)	311 (69.3)	72 (66.1)		
Disagree somewhat/Disagree, *n* (%)	45 (23.4)	111 (43.2)	138 (30.7)	37 (33.9)		

[a]One missing data point for the older non-drivers and two missing data points for the younger non-drivers.
[b]Calculated by multiple logistic regression model including age group/driving status, gender, place of residence, education, annual household income, living arrangement, and employment status.

Table 3 Possible reasons for reluctance to stop driving among frequent drivers (multiple answers)

Reason	Older drivers (65+ years, $n=144$)[a]	Younger drivers (40–64 years, $n=370$)[a]	Older *vs.* younger drivers	
	n (%)	*n* (%)	Crude OR	Adjusted OR[b]
I am not reluctant to stop driving	22 (15.3)	51 (13.8)	1.13	1.64
It would be difficult for me to go out	90 (62.5)	248 (67.0)	0.82	0.88
It would be difficult for my family members to go out	59 (41.0)	162 (43.8)	0.89	0.87
Loss of something I enjoy	56 (38.9)	94 (25.4)	1.87*	1.81
Loss of independent living	39 (27.1)	81 (21.9)	1.33	1.10
A driver's license is useful as an ID card.	38 (26.4)	102 (27.6)	0.94	1.16
Loss of a motivating factor in my life	28 (19.4)	30 (8.1)	2.74*	4.93*
Loss of a way to relax	21 (14.6)	43 (11.6)	1.30	1.85
Loss of a hobby	20 (13.9)	32 (8.7)	1.70	2.44
Loss of a sense of self	20 (13.9)	43 (11.6)	1.23	0.91
I want to keep my driver's license	18 (12.5)	38 (10.3)	1.25	0.77
Loss of my dignity	15 (10.4)	29 (7.8)	1.37	1.31
Loss of something I commit to regularly	14 (9.7)	22 (6.0)	1.70	2.02
Loss of an opportunity to be alone	8 (5.6)	22 (6.0)	0.93	2.06
I don't know how to return my license	0 (0.0)	0 (0.0)	—	—

[a]One missing data point for the older drivers and two missing data points for the younger drivers.
[b]Odds ratio (OR) was adjusted for gender, place of residence, education, annual household income, living arrangement, and employment status by multiple logistic regression model.
*$p < 0.05$.

tions to close the perception gap and for the sake of public safety.

Our study also showed that among the frequent drivers in both older and younger groups, most of the reasons for reluctance to stop driving were related to the possible loss of personal mobility (shown in Table 3). Our finding partly supports Freund's view (Freund and Szinovacz, 2002) in which decisions to stop driving were associated not only with competence but also with the availability of alternate transportation opportunities. In addition, a previous study regarding family caregivers of dementia patients by Mizuno *et al.* (2008) showed that family caregivers cited alternative transportation, and in particular the availability of family caregivers or other family members who could drive instead of the patient, as essential to facilitate the cessation of driving. It has also been reported that the availability of transportation services was a key factor in allowing older people to keep attending social activities and maintain autonomy (Roper and Mulley, 1996; Dickerson *et al.*, 2007; O'Neill, 2007). It is clear that alternate transportation is needed to facilitate the smooth transition to another form of transportation after driving retirement and prevent older people from experiencing restricted mobility. Although availability of a mass transit system varies between rural and urban areas in Japan, a bus or community bus (one that circles around the area) has been developed as a practical form of transportation to enhance the mobility of the residents and is expected to support those who have stopped driving as well as their family members.

We found a significant difference between the older and younger age groups with respect to the reasons for reluctance to stop driving. The older drivers were more likely to value the qualitative aspects of driving, for example, driving as 'a motivating factor in my life', 'something I enjoy', and consider a 'hobby'. It appears that driving is regarded not only as a mode of transportation but also as a meaningful activity for older drivers. This might be related to the findings of another study in which 93% of drivers diagnosed with dementia ($n=43$) thought that driving was important to their quality of life (Adler and Kuskowski, 2003). Both practical and qualitative aspects of driving can be important factors in maintaining independence among older people.

These noticeable reasons for reluctance to stop driving may be related to the negative consequences of driving cessation among older people or people with dementia cited in previous reports: increased depressive symptoms (Marottoli *et al.*, 1997; Fonda *et al.*, 2001; Ragland *et al.*, 2005), decreased out-of-home activity levels (Marottoli *et al.*, 2000), difficulties in accessing social and recreational services (Taylor and Tripodes, 2001), and increased risk for entry into a nursing home (Freeman *et al.*, 2006). We therefore suggest that more attention be devoted to not only the problem of decreased mobility but also alternatives to the qualitative aspects of driving. One possible

alternative would be to increase opportunities for participating in leisure, physical, and social activities and social services, which could help older people find something else to 'motivate them in their lives', 'enjoy', and have as a 'hobby' after driving retirement. Moreover, to seek appropriate alternatives for individuals, family members, and stakeholders should communicate with the older drivers early in the process of driving cessation to try to better understand what 'driving activity' means for them.

The limitations of this study should be noted. Although our study sample was selected from a research panel based on national statistics using a quota sampling method, a certain amount of selection bias was unavoidable. In addition, we categorized the respondents into two groups of driving status: drivers and non-drivers. However, we did not know if the non-drivers group included former drivers who had returned a driver's license and stopped driving. A self-administered questionnaire, as used in this study, can represent another information bias. Perceptions about driving were not sufficiently explored by the closed-ended format in the questionnaire; thus, the results should be carefully interpreted. We did not take into account in the analyses whether the licensed drivers had other drivers to provide transportation. Instead, we used living arrangement as a confounding factor related to the availability of alternate drivers that could be controlled in the analyses.

Despite these limitations, our findings provide useful insights into the possible family or social barriers to driving cessation in the case of drivers with dementia. As observed in the present study, the disparities in perceptions about driving may cause conflicts among stakeholders with respect to when dementia patients should have their licenses revoked. It is thus important to facilitate general public involvement in considering the public health issue of driving and dementia, closing the perception gap and developing strategies to better address the difficulties related to driving cessation as a whole society. Moreover, in addition to practicable transportation alternatives, the qualitative aspects of driving should also be paid more attention when preparing alternatives. In this way, the goal of more effectively meeting the needs of retiring drivers while also allowing them to maintain autonomy can be more easily achieved.

Conflict of interest

None known.

Key points

- The drivers among the general public that participated in this study tended to highly agree that 'driving is a "right" which we all deserve', compared with the non-drivers.
- The most common reason given for reluctance to stop driving among frequent drivers was the loss of personal mobility; further, older drivers were more likely than younger drivers to value the qualitative aspects of driving.
- Disparities in the general public's perceptions about driving may present possible family or social barriers to driving cessation in the case of drivers with dementia.
- It is suggested that not only mobility but also the qualitative aspects of driving be paid more attention when developing alternatives to driving.

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ORIGINAL ARTICLE

Plasma sex hormone levels and mortality in disabled older men and women

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Aim: To investigate the relationship between circulating sex hormone levels and subsequent mortality in disabled elderly.

Methods: This prospective observational study was comprised of 214 elderly subjects aged 70–96 years (117 men and 97 women; mean ± standard deviation age, 83 ± 7 years), receiving services at long-term care facilities in Nagano, Japan. All-cause mortality by baseline plasma sex hormone levels was measured.

Results: After excluding deaths during the first 6 months, 27 deaths in men and 28 deaths in women occurred during a mean follow up of 32 months and 45 months (up to 52 months), respectively. Mortality rates differed significantly between high and low testosterone tertiles in men, but did not differ significantly between middle and low tertiles. Compared with subjects in the middle and high tertiles, men with testosterone levels in the low tertile (<300 ng/dL) were more likely to die, independent of age, nutritional status, functional status and chronic disease (hazard ratio [HR] = 3.27, 95% confidence interval [CI] = 1.24–12.91). In contrast, the low dehydroepiandrosterone sulfate (DHEA-S) tertile was associated with higher mortality risk in women (multivariate adjusted HR = 4.42, 95% CI = 1.51–12.90). Exclusion of deaths during the first year and cancer deaths had minimal effects on these results. DHEA-S level in men and testosterone and estradiol levels in women were not related to mortality.

Conclusion: Low testosterone in men and low DHEA-S in women receiving care at facilities are associated with increased mortality risk, independent of other risk factors and pre-existing health conditions. **Geriatr Gerontol Int 2010; 10: ••–••.**

Keywords: dehydroepiandrosterone, disabled elderly, mortality risk, testosterone.

Introduction

Japan has the longest life expectancy at birth in the world for both men and women, although women live 8 years longer than men on average.[1,2] One explanation for this phenomenon is that estradiol production during the premenopausal years partially protects women from cardiovascular disease (CVD). In contrast, there has been a suspicion that testosterone itself is harmful; however, recent studies support the hypothesis that testosterone may be beneficial to survival in aging men.[3–8]

It is well established that endogenous androgens decline with advancing age in men.[9] Because testosterone has important physiological effects on muscle, bone, brain, erythropoietin and the vascular system, decreased testosterone levels could contribute to age-associated symptoms and diseases in older men, such as decreased muscle mass and strength,[10] impaired physical performance,[11,12] osteoporosis[13] and fractures,[12,14]

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depressed mood,[15] cognitive impairment,[16,17] anemia[18,19]and frailty.[20] In our previous study in which older persons receiving day-care services or admitted to a facility were investigated, higher plasma testosterone levels were associated with better activities of daily living (ADL), cognitive function and vitality in men.[21] On the other hand, several epidemiological studies have demonstrated that a decline in testosterone level was associated with mortality risk in community-dwelling middle-aged or older men.[3-8] In cause-specific analyses, some studies have shown that a low testosterone level was associated with an increased risk of death due to CVD.[4,5] However, the above-mentioned studies were performed in community samples of Caucasian men, and this issue remains to be clarified in frail or disabled older men.

The majority of dehydroepiandrosterone (DHEA), an endogenous steroid precursor to testosterone and estrogen, exists as the sulfated form (DHEA-S) in the circulation, and DHEA and DHEA-S are the most abundant adrenal sex steroid hormones, with concentrations reported to be more than 100-fold higher than those of testosterone and estradiol,[22] suggesting an important physiological role of DHEA(-S). Their circulating levels also peak in young adults and decline with age in both men and women. Although the role of androgens in older women's health is not fully understood, postmenopausal women with intact ovaries continue to produce androgens, DHEA and testosterone, while their production of estradiol is minimal.[23] In our previous study,[21] in older women, higher DHEA and DHEA-S levels were related to better ADL, while estradiol and testosterone levels showed no relations. Other reports have shown a correlation between DHEA level and cognitive function,[24] depression,[25] osteoporosis[26] and frailty in older women.[27] Several studies that examined the association between DHEA-S and mortality in women have shown mixed results,[28-32] and mostly found no relation; however, both low and high levels of DHEA-S at baseline[28] and some trajectory patterns such as a steep decline or extreme variability[32] have been reported to correlate with increased mortality.

These lines of evidence suggest that endogenous androgens, including testosterone and DHEA(-S), may play a role in physical and mental function as well as longevity in older individuals. We hypothesized that low plasma androgen levels could be a mortality risk factor even in elderly with disability who are receiving facility services.

Methods

Study population

In this longitudinal observational study, 218 consecutive persons aged 70 years or older (121 men aged 70–96 years and 97 women aged 70–95 years; mean ± standard deviation [SD] age, 83 ± 6 and 83 ± 5 years, respectively) who attended health service facilities for the elderly (facilities that provide nursing care and rehabilitation services to elderly people with disability, *Mahoroba-no-Sato*) located in Nagano Prefecture, Japan were enrolled. The participants were in a chronic stable condition and receiving services under Long-term Care Insurance, which is provided by the Japanese Government, either under admission or as day care. The principal exclusion criteria were malnutrition (serum albumin <3.5 mg/dL or body mass index [BMI] <16 kg/m^2), extremely low ADL status (Barthel Index[33] <50), malignancy, acute inflammation (fever, white blood cell count >10 000/μL, or other signs of infection within 4 weeks before enrollment), severe anemia (blood hemoglobin <10.0 g/dL) and overt endocrine disease because these conditions may affect both plasma sex hormone levels and mortality. Deaths that occurred during the first 6 months of follow up (four men and no women) were also excluded to minimize the influence of comorbidity on both sex hormone levels and mortality; therefore, the remaining 214 persons were analyzed in this study. The institutional review board of *Mahoroba-no-Sato* approved the study protocol, and all participants and/or their family members gave written informed consent.

Hormone measurements

Blood samples were obtained from the participants in the morning after an overnight fast, and plasma hormone levels in addition to blood cell counts and blood chemical parameters were determined by a commercial laboratory (Health Sciences Research Institute, Yokohama, Japan). Testosterone and estradiol were assayed using chemiluminescence immunoassays with minimum detection limits of 7 ng/dL (0.2 nmol/L) and 4 pg/mL (14.7 pmol/L), respectively. DHEA-S was assayed using a sensitive radioimmunoassay with a minimum detection limit of 2.0 μg/dL (0.05 μmol/L). The intra-assay coefficients of variation for these measurements were less than 5%.

Functional and anthropometric measurements

Trained nurses and physical therapists visited the participants at the health facilities and performed comprehensive geriatric assessments. Basic ADL was assessed by Barthel Index,[33] cognitive function by Hasegawa Dementia Scale – Revised (HDS-R, 30-point scale),[34] mood by the Geriatric Depression Scale (GDS, 15 items),[35] and ADL-related vitality by Vitality Index (10-point scale).[36] BMI was calculated

as weight in kilograms divided by the square of height in meters.

Comorbidity

Diseases were ascertained by experienced physicians according to pre-established criteria that combine information from self-reported physician diagnoses, medical records, current medication, clinical examinations and blood tests. Diseases included in the current analysis were hypertension, heart disease (including any of angina pectoris, myocardial infarction, congestive heart failure and arrhythmia), stroke, diabetes mellitus, osteoarthropathy (arthritis, rheumatism, osteoporosis and history of fractures), lung disease (including bronchial asthma and chronic obstructive pulmonary disease) and other chronic diseases (chronic kidney disease, gastrointestinal disease, Parkinson's disease and psychological disorders). We also obtained data on anti-androgenic treatment and intake of glucocorticoids, opiates and hormone supplements that could affect plasma hormone levels, but no subject was taking any of these.

Follow up

The subjects were followed up in 2002–2009, for a period of up to 52 months (mean ± SD, 32 ± 13 [34] months in men and 45 ± 11 [49] months in women). Time and causes of death of deceased persons were ascertained using medical records and death certificates. All deaths were registered with International Classification of Diseases, 10th version (ICD-10) codes,[37] based on the information from death certificates. We categorized deaths into the following four specific causes: (i) diseases of the circulatory system (I00–I99) including heart disease and cerebrovascular disease; (ii) diseases of the respiratory system (J00-J99); (iii) neoplasms (C00-D48); and (iv) other causes. Subjects who were alive were confirmed by checking appointment records of the facilities. Survival of 16 subjects whose records were not available was ascertained by the phone interview of each subject. Causes of death were determined for all the subjects without any missing cases.

Statistical analysis

Differences between testosterone tertiles in men and between DHEA-S tertiles in women were analyzed using ANOVA for continuous variables and χ^2-test for categorical variables. Survival was analyzed using Kaplan–Meier plots and log–rank tests. Hazard ratios (HR) for mortality were analyzed using Cox proportional hazards regression. Significance tests were two-sided, with an α-level of 0.05. Data were analyzed using SPSS statistical software.

Results

Characteristics of study subjects

Over the follow-up period, 27 men and 28 women died, yielding a mortality rate of 86.5/1000 person-years at risk in men; and 69.9/1000 person-years at risk in women. Of those, 13 deaths were due to diseases of the circulatory system (eight to ischemic and other heart disease and five to cerebrovascular disease), 10 to diseases of the respiratory system and four to cancer in men; while 14 deaths were due to diseases of the circulatory system (nine to ischemic and other forms of heart disease and four to cerebrovascular disease), eight to diseases of the respiratory system, five to cancer and two to other causes in women. Men who died were significantly older, had lower serum albumin and cholesterol, lower ADL and cognitive status, higher prevalence of heart disease, and lower testosterone level than survivors; whereas in women, subjects who died were older, had lower hemoglobin, higher prevalence of heart disease and lower plasma DHEA-S level than survivors (data not shown).

Table 1 shows the baseline characteristics of the male subjects by tertile of plasma testosterone. A significant difference was observed in serum albumin and hemoglobin levels, ADL and cognitive status among tertiles of testosterone in men. Table 2 shows the baseline characteristics of the female subjects by tertile of plasma DHEA-S. A significant difference was found in age and ADL status among DHEA-S tertiles in women, while other variables did not differ between the tertile groups.

Mortality and plasma sex hormone levels in men

As shown in Figure 1(a), Kaplan–Meier survival analysis by tertile of plasma testosterone level revealed that testosterone level was associated with mortality in men. After adjusting for age, Cox proportional hazards models showed that there was an inverse relation between testosterone level and mortality. Mortality rate differed significantly between the high and low testosterone tertiles, but not significantly between the middle and low tertiles: tertile 3 (high), reference; tertile 2 (middle), HR = 2.51 (95% confidence interval [CI] = 0.66–9.50); and tertile 1 (low), HR = 6.63 (95% CI = 1.92–23.21). Accordingly, we investigated the increased mortality in tertile 1 versus tertiles 2–3 (Table 3). Compared with subjects within tertiles 2–3,

Table 1 Association between potential confounding variables and testosterone tertiles in men

Characteristic	Testosterone tertiles T1 <10.4 nmol/L (<300 ng/dL), $n = 39$	T2 10.4–16.3 nmol/L (300–470 ng/dL), $n = 40$	T3 >16.3 nmol/L (>470 ng/dL), $n = 38$	*P*-value
Age, years	83 ± 7	83 ± 6	81 ± 6	0.11
Nutritional parameters				
Body mass index, kg/m^2	21.3 ± 3.4	22.8 ± 3.8	21.7 ± 3.0	0.21
Hemoglobin, g/dL	12.7 ± 1.9	13.8 ± 1.3	14.0 ± 1.7	<0.01
Albumin, g/dL	4.0 ± 0.3	4.1 ± 0.2	4.2 ± 0.3	<0.01
Total cholesterol, mg/dL	173 ± 38	195 ± 36	176 ± 28	0.05
Prevalent diseases, *n* (%)				
Hypertension	17 (44)	16 (40)	12 (32)	0.53
Heart disease	10 (26)	5 (13)	7 (18)	0.32
Stroke	12 (31)	15 (38)	8 (21)	0.34
Diabetes mellitus	8 (21)	5 (13)	8 (21)	0.31
Osteoarthropathy	8 (21)	9 (23)	7 (18)	0.94
Lung disease	2 (5)	3 (8)	3 (8)	0.52
Other chronic diseases	17 (44)	19 (48)	18 (47)	0.95
Functional parameters				
Barthel Index	79 ± 12	82 ± 11	87 ± 13	0.04
HDS-R	18 ± 7	19 ± 6	22 ± 5	0.02
Vitality Index	9.2 ± 1.1	9.3 ± 0.9	9.5 ± 0.9	0.46
GDS	5.0 ± 3.1	5.6 ± 3.7	5.6 ± 2.9	0.66
Sex hormone levels				
Testosterone, nmol/L	7.6 ± 2.5	13.3 ± 1.6	20.9 ± 3.9	<0.01
(ng/dL)	(219 ± 73)	(382 ± 43)	(602 ± 112)	
DHEA-S, μmol/L	1.7 ± 1.1	1.8 ± 1.6	1.7 ± 1.2	0.94
(μg/dL)	(64 ± 42)	(69 ± 57)	(63 ± 45)	

Values are shown as mean (standard deviation). Differences between the groups were analyzed using ANOVA for continuous variables and χ^2-test for categorical variables. DHEA-S, dehydroepiandrosterone sulfate; GDS, Geriatric Depression Scale; HDS-R, Hasegawa Dementia Scale – Revised.

a testosterone level within tertile 1 was associated with approximately fourfold higher mortality risk. Adjustment for age, nutritional parameters (BMI, albumin, hemoglobin, total cholesterol) and functional parameters (Barthel Index, HDS-R, Vitality Index, GDS), and prevalent diseases showed no major influence on the result. In order to examine how follow-up time and cancer impacted on the results, assuming that the subjects may have had subclinical cancer or a fatal illness at baseline, we performed further analyses excluding deaths that occurred in the first 12 months ($n = 9$) and deaths from cancer ($n = 4$). However, the significant associations remained after these exclusions (Table 3). On the other hand, DHEA-S level was not associated with mortality when DHEA-S was entered as tertiles (data not shown).

Although the statistical power was not strong enough, we studied the risk for cause-specific mortality by tertiles of testosterone level in men. Neither deaths from diseases of the circulatory system nor those from non-circulatory causes showed a significant association with testosterone tertiles (tertile 1 vs tertile 2–3, HR = 3.18, 95% CI = 1.87–11.6, $P = 0.17$; HR = 3.46, 95% CI = 0.29–7.29, $P = 0.64$, respectively).

Mortality and plasma sex hormone levels in women

As shown in Figure 1(b), a low DHEA-S level was associated with higher mortality by Kaplan–Meier survival analysis. Age-adjusted Cox proportional hazards models revealed that the association was not significant when each tertile of DHEA-S was entered as a continuous variable; however, a significant association was observed when tertile 1 was compared with tertiles 2–3 (Table 3). The association remained significant after excluding deaths that occurred in the first 12 months ($n = 2$) and deaths from cancer ($n = 5$). Moreover, further adjustment had no major influence on the result. In women, testosterone and estradiol levels were not associated with mortality when they were entered as tertiles (data not shown).

In cause-specific mortality analysis, compared with tertiles 2–3, the low tertile of DHEA-S level was associated with higher risk of death from diseases of the

Table 2 Association between potential confounding variables and DHEA-S tertiles in women

Characteristic	DHEA-S tertiles T1 <1.17 μmol/L (<43 μg/dL), *n* = 33	T2 1.17–1.49 μmol/L (43–55 μg/dL), *n* = 32	T3 >1.49 μnmol/L (>55 μg/dL), *n* = 32	*P*-value
Age, years	83 ± 6	82 ± 6	80 ± 6	0.08
Nutritional parameters				
Body mass index, kg/m^2	22.3 ± 2.7	22.5 ± 3.2	23.7 ± 2.7	0.31
Hemoglobin, g/dL	12.6 ± 1.4	12.6 ± 1.2	13.1 ± 1.1	0.16
Albumin, g/dL	4.1 ± 0.3	4.2 ± 0.3	4.3 ± 0.2	0.18
Total cholesterol, mg/dL	205 ± 30	204 ± 35	205 ± 35	0.99
Prevalent diseases, *n* (%)				
Hypertension	10 (30)	14 (44)	15 (47)	0.47
Heart disease	4 (12)	7 (22)	8 (25)	0.46
Stroke	5 (15)	4 (13)	6 (19)	0.79
Diabetes mellitus	5 (15)	4 (13)	5 (16)	0.90
Osteoarthropathy	8 (24)	11 (34)	13 (40)	0.47
Lung disease	3 (9)	2 (6)	2 (6)	0.56
Other chronic diseases	17 (52)	19 (59)	18 (56)	0.90
Functional parameters				
Barthel Index	90 ± 7	93 ± 8	95 ± 8	0.04
HDS-R	23 ± 6	22 ± 7	25 ± 5	0.39
Vitality Index	9.2 ± 1.4	9.1 ± 2.2	8.8 ± 2.9	0.35
GDS	6.8 ± 2.6	5.9 ± 3.4	6.9 ± 3.3	0.16
Sex hormone levels				
DHEA-S, μmol/L	0.8 ± 0.2	1.3 ± 0.1	2.0 ± 0.3	<0.01
(μg/dL)	30 ± 7	49 ± 4	73 ± 12	
Testosterone, nmol/L	1.2 ± 0.6	1.2 ± 0.6	1.3 ± 0.5	0.81
(ng/dL)	35 ± 17	36 ± 17	37 ± 13	
Estradiol, pmol/L	56 ± 32	57 ± 37	67 ± 46	0.41
(pg/mL)	15.3 ± 8.6	15.5 ± 10.2	18.3 ± 12.5	

Values are shown as mean (standard deviation). Differences between the groups were analyzed using ANOVA for continuous variables and χ^2-test for categorical variables. DHEA-S, dehydroepiandrosterone sulfate; GDS, Geriatric Depression Scale; HDS-R, Hasegawa Dementia Scale – Revised.

circulatory system (HR = 13.1, 95% CI = 2.39–72.3, $P < 0.01$), while there was no association with deaths from non-circulatory causes (HR = 0.93, 95% CI = 0.86–1.02, $P = 0.14$).

Discussion

In this small prospective study of Japanese elderly who were receiving care in facilities, a low testosterone level was associated with mortality in men independent of multiple risk factors and pre-existing health conditions. In addition, a low DHEA-S level in older women was related to increased mortality. In contrast, DHEA-S level in men and testosterone and estradiol levels in women were not related to mortality.

Recent prospective cohort studies in Western countries have yielded inconsistent findings about the use of a low total testosterone level as a predictor of all-cause and cardiovascular mortality in middle-aged to older men.[4,5,38,39] In the two studies that found no significant prediction of mortality,[38,39] the populations were younger (mean or median ages were in the early 50s), testosterone levels were higher and mortality rates were lower (11.6 and 15.4/1000 person-years, respectively) compared to those in studies that found positive results. In the present study, although the sample size was small, the subjects were frail and older than those in any previously reported studies, with a relatively small age range and higher mortality rate. Therefore, the relation between testosterone level and mortality might have been easier to detect in our study than in other studies with healthy middle-aged and older men.

There could be several mechanisms by which endogenous testosterone affects mortality in men. Although the number of subjects was too small to perform cause-specific analysis in the present study, other studies have reported that a low testosterone level predicted increased risk of death due to CVD.[4,5] Further, in addition to the relation to muscle strength, physical performance and ADL,[10–12,21] some but not all reports have

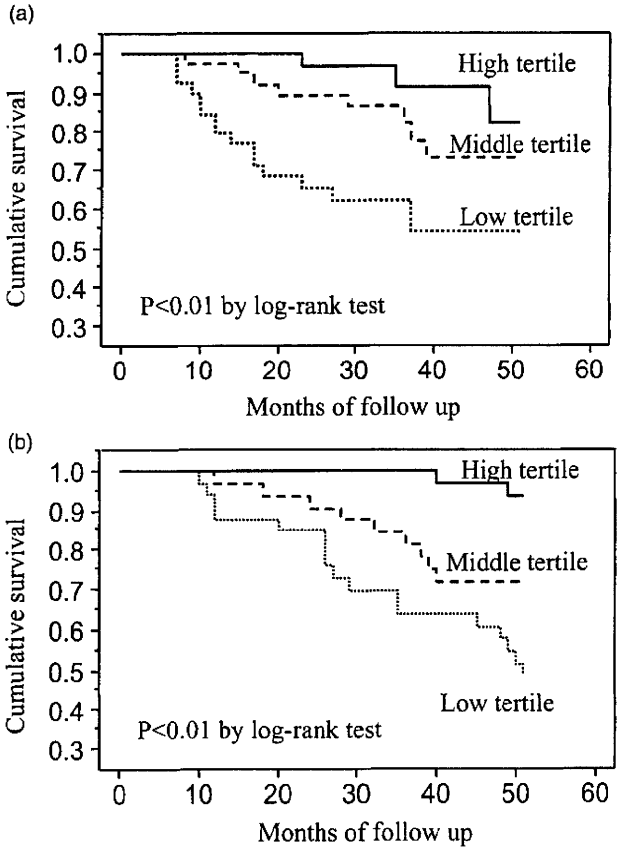

Figure 1 (a) Survival curves by tertile group of plasma testosterone level in men. (b) Survival curves by tertile group of plasma dehydroepiandrosterone sulfate level in women.

demonstrated an association between low testosterone level in older men and risk of a fall or fracture and frailty.[12-14,20] It is noteworthy that in the 10 men who died of respiratory infection, four had a history of a fall and fracture, which resulted in worse disability. Accordingly, a low testosterone level may contribute to frailty, which influences men's susceptibility to illness and falls and the capability to recover from disease or fractures, and thereby affects mortality.

Other than aging, systemic illness can result in decreased testosterone levels; therefore, low testosterone levels in older men could be attributable to acute and chronic diseases,[40] and the possible reverse causality should be considered. To evaluate this possibility, we excluded the first 12 months of observation and still found that in 12–52 months of observation, men in the low testosterone tertile had a greater risk of mortality from all causes than those in higher tertiles. We carefully excluded subjects with critical diseases and conditions at baseline, although our subjects were old with multiple chronic diseases, and it is difficult to exclude the possibility that men with subclinical critical conditions might have been included. Moreover, at baseline, there was a significant difference in functional status (ADL and cognition) and nutritional parameters (serum albumin and hemoglobin levels) between testosterone tertiles, as reported previously;[21] thus, our results need to be confirmed in a cohort with no difference in these factors between testosterone groups to exclude the influence of these biases on mortality. Also, it needs to be explored whether low testosterone in older men plays a pathogenic role, such as affecting the immune system, developing physical frailty and depression, or simply serves as a marker for biological vulnerability and poor prognosis. Long-term studies also need to test whether testosterone treatment should yield clinically significant improvements in mortality in appropriately selected older men, with consistent symptoms and signs and unequivocally low serum testosterone levels.

Low DHEA-S has been associated with increased all-cause and cardiovascular mortality in older men;[26,27,41] however, no association was found in the present study. Because DHEA(-S) is an inactive prohormone and we and others have found an association between testosterone and mortality,[3-8] it is suggested that testosterone could be a stronger predictor of mortality in older men.

On the other hand, a low DHEA-S level in older women was associated with a poor prognosis after adjusting for multiple factors related to mortality. Other previous reports showed an inconsistent relationship between DHEA-S level and mortality in older women,[29-31] possibly due to differences in the cohorts including age, DHEA-S level, heterogeneity of health status and mortality rate, and the method of statistical analysis used to demonstrate the relationship, regression models with linear/non-linear assumption.

Previous studies support a potential physiological role of DHEA-S, which could contribute to reduced mortality, an anti-inflammatory action and immune regulatory activity.[42] However, there are still many unanswered questions regarding DHEA's role in aging, and there is insufficient evidence to support DHEA replacement for increasing longevity in older women. It also needs to be explored whether the DHEA-S level contributes to mortality or is merely a biomarker of the underlying health condition of older women.

Our study has some limitations. First, the sample size was too small to reach a clear conclusion with strong statistical power, thus limiting the precision of the estimates, which is reflected in the broad range of HR for mortality. Second, the results are based on single measurements of sex hormones, which do not allow assessment of changes in levels over time; therefore, they may overestimate or underestimate the association between hormone levels and mortality. Third, we did not measure estradiol levels in men, although it would have been helpful to see whether the effects of testosterone on mortality are mediated by testosterone itself or by aromatization to estradiol in older men. Finally, active forms of testosterone such as bioavailable and

Table 3 Hazard ratios for low tertile 1 vs tertiles 2–3 of plasma sex hormone levels for all-cause mortality in men and women

	Unadjusted	Model 1	Model 2
Men (n = 117)			
HR of low testosterone for mortality	3.83 (1.74–8.40)**	3.71 (1.54–8.04)**	3.27 (1.24–12.91)*
Excluding first-year deaths (n = 108)	3.81 (1.53–6.93)**	3.49 (1.14–7.39)**	3.08 (1.11–13.62)*
Excluding deaths from cancer (n = 113)	4.18 (1.77–9.86)**	4.03 (1.70–9.58)**	5.02 (1.51–15.41)*
Women (N = 97)			
HR of low DHEA-S for mortality	3.77 (1.77–8.07)**	3.86 (1.79–8.32)**	4.42 (1.51–12.90)*
Excluding first-year deaths (n = 95)	3.38 (1.55–7.37)**	3.43 (1.56–9.54)**	3.58 (1.12–11.46)*
Excluding deaths from cancer (n = 92)	3.82 (1.69–8.60)**	3.55 (1.54–8.19)**	3.92 (1.28–11.98)*

*P < 0.05; **P < 0.01 vs reference group (tertile 2–3). Values are expressed as HR (95% CI). Model 1, adjusted for age; Model 2, adjusted for age, nutritional parameters, functional parameters and prevalent disease. DHEA-S, dehydroepiandrosterone sulfate; HR, hazards ratio.

calculated free testosterone were not measured, because a direct assay of bioavailable testosterone or an assay of sex hormone binding globulin, which is necessary for free testosterone calculation, is not available in Japan. However, because most of the above-mentioned previous reports have shown an association of total testosterone with mortality, the fundamental findings might not have differed if active forms of testosterone had been analyzed.

In conclusion, a low testosterone level in men and a low DHEA-S level in women are associated with increased mortality risk, independent of multiple risk factors and several pre-existing health conditions in disabled elderly. To our knowledge, the present study is the first that showed testosterone as a predictor of mortality in Asian men. Also, this is the first study that investigated frail or disabled older persons receiving care at facilities. Our results imply the clinical importance of measuring plasma androgen levels even in disabled elderly to estimate their prognosis.

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ORIGINAL ARTICLE

Relationship between interleukin-6 and cerebral deep white matter and periventricular hyperintensity in elderly women

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Aim: We evaluated the relationships between serum levels of high-sensitivity C-reactive protein (hsCRP) and interleukin (IL)-6 with the severity of leukoaraiosis.

Methods: One hundred and thirty-seven elderly women who attended the Center for Comprehensive Care on Memory Disorders at Kyorin University Hospital were enrolled in this study. Leukoaraiosis was assessed by periventricular hyperintensity (PVH) score and deep white matter hyperintensity (DWMH) score.

Results: Serum log IL-6 level correlated with PVH and DWMH scores, but hsCRP did not. By multinomial logistic analysis, IL-6 was significantly related to DWMH score, independent of age and systolic blood pressure.

Conclusion: IL-6 is presumably an important marker of leukoaraiosis, as is the case with silent cerebral infarction. **Geriatr Gerontol Int 2011; 11: ••–••.**

Keywords: interleukin-6, leukoaraiosis, white matter hyperintensity.

Introduction

Leukoaraiosis, an isointense lesion on T_1-weighted images and hyperintense lesion on T_2-weighted images of magnetic resonance imaging (MRI), is considered to be a type of ischemic change in the brain on the basis of decreased blood flow in the area of leukoaraiosis.[1] In addition, leukoaraiosis is likely to have a relationship with vascular risk factors such as hypertension and diabetes.[2] On the other hand, the severity of leukoaraiosis also has a relationship with symptoms of the geriatric syndromes such as dementia, gait disturbance and functional disability.[3–5] Hence, leukoaraiosis is regarded as a significant brain lesion linking vascular risk factors and the occurrence of geriatric syndromes. Previous research on leukoaraiosis showed that women tended to have more white matter lesions than men,[6] and progression of deep white matter hyperintensity (DWMH) lesion was grater in women than men.[7] Furthermore, Gouw *et al.* showed that leukoaraiosis tended to develop greater in women than men and lacunes were vice versa.[8] Recently, many studies have focused on the relationships between brain ischemia and inflammation. Above all, Hoshi *et al.* demonstrated that serum high-sensitivity C-reactive protein (hsCRP) and interleukin (IL)-6 levels correlated with silent brain infarction.[9] They suggested an involvement of inflammation in cerebral infarction. However, few studies have examined the relationships between inflammatory markers and other cerebral ischemic changes such as leukoaraiosis.Therefore, we investigated whether serum levels of hsCRP and IL-6 have a relationship with leukoaraiosis in elderly women.

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Methods

Patients

One hundred and thirty-seven women who attended the Center for Comprehensive Care on Memory Disorders at Kyorin University Hospital were included in this study. This study was approved by the Ethics Committee of Kyorin University School of Medicine. Accordingly, written informed consent was obtained from all patients.

MRI

Magnetic resonance imaging (MRI) was performed on 1.5-T scanners (Toshiba Medical Systems, Tochigi, Japan). T_1-weighted images (repetition time [TR] = 496 msec, echo time [TE] = 12 msec), T_2-weighted images (TR = 4280 msec, TE = 105 msec) and fluid attenuated inversion recovery-weighted images (TR = 8000 msec, TE = 105 msec, 5 mm slice thickness) were obtained in the axial planes.

Periventricular hyperintensity and DWMH Score

Leukoaraiosis was classified as periventricular hyperintensity (PVH) adjacent to the lateral ventricle, and DWMH located in the deep white matter apart from the lateral ventricles. PVH was evaluated in six regions in three slices. Each region was rated as five grades (0–4) according to the systematic quantification method developed by Junque *et al.*[3] The sum of all grades in the six regions was defined as the PVH score (range 0–40).[4] DWMH was evaluated in the frontal, temporal, parietal and occipital lobes and in the basal ganglia in both hemispheres. Each lesion was rated as three grades according to the diameter, as described by de Groot *et al.*[5] The sum of all grades in five regions in both hemispheres was defined as the DWMH score.[4]

Laboratory tests

Blood samples were obtained in the morning after an overnight fast. Serum levels of hsCRP and IL-6 were measured using nephelometry and enzyme-linked immunosorbent assay, respectively. The intra-assay coefficients of variation for the measurements of hsCRP and IL-6 were 1.3% and 2.9%, respectively.

Statistical analysis

Because the distribution of hsCRP and IL-6 levels appeared to be left-skewed, they were normalized by logarithmic transformation. We used Spearman's ρ to investigate correlations between parameters and PVH score or DWMH score. Also, to test independently the effect of the inflammatory markers associated with the severity of leukoaraiosis, multinomial logistic regression analysis was performed with the grade of PVH (tertiles of PVH score) or DWMH (tertiles of DWMH score) as the dependent variable; and hsCRP or IL-6, together with age and systolic blood pressure (SBP) as independent variables. $P < 0.05$ was considered statistically significant. All data were analyzed using SPSS ver. 17.0.

Results

The characteristics of the study subjects are shown in Table 1. They were non-obese normolipidemic elderly persons, however, SBP was elevated. The distribution of PVH score and DWMH score of these subjects were 1–24 and 0–209, respectively. In Spearman's correlation coefficient, IL-6 correlated with PVH score ($\rho = 0.340$, $P \leq 0.05$) and DWMH score ($\rho = 0.299$, $P \leq 0.05$) (Fig. 1), whereas hsCRP showed no relation to PVH score or DWMH score (Table 2). PVH score and DWMH score also correlated with age and SBP. When log IL-6 and log hsCRP were grouped by tertile (see legend to Fig. 2), it was found that the average PVH score and DWMH score were higher in the highest tertile of IL-6 level than in the lowest tertile according to the Kruskal–Wallis test (Fig. 2a,b). On the other hand, this increment was not found in hsCRP (Fig. 2c,d).

Because leukoaraiosis can be observed on MRI even in normal elderly persons,[10] and hypertension is known to be a risk factor for leukoaraiosis,[11] we performed multinomial logistic regression analysis using PVH or DWMH severity (tertiles of PVH and DWMH score) as the dependent variable, and age, SBP and inflammatory

Table 1 Clinical characteristics of study subjects (women, $n = 137$)

Age (years)	76 ± 7
BMI (kg/m^2)	20.8 ± 3.3
SBP (mmHg)	142 ± 26
DBP (mmHg)	80 ± 14
PVH score (points)	8.2 ± 4.0
DWMH score (points)	61.4 ± 51.0
Total cholesterol (mmol/L)	5.38 ± 0.91
HDL cholesterol (mmol/L)	1.50 ± 0.36
LDL cholesterol (mmol/L)	3.23 ± 0.65
Triglyceride (mmol/L)	1.08 ± 0.46
Log IL-6 (ng/L)	0.35 ± 0.46
Log hsCRP (μg/L)	2.58 ± 0.58

All parameters are expressed as mean ± standard deviation. IL-6 and CRP are shown as log transformed. BMI, body mass index; DBP, diastolic blood pressure; DWMH, deep white matter hyperintensity; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; LDL, low-density lipoprotein; PVH, periventricular hyperintensity; SBP, systolic blood pressure.

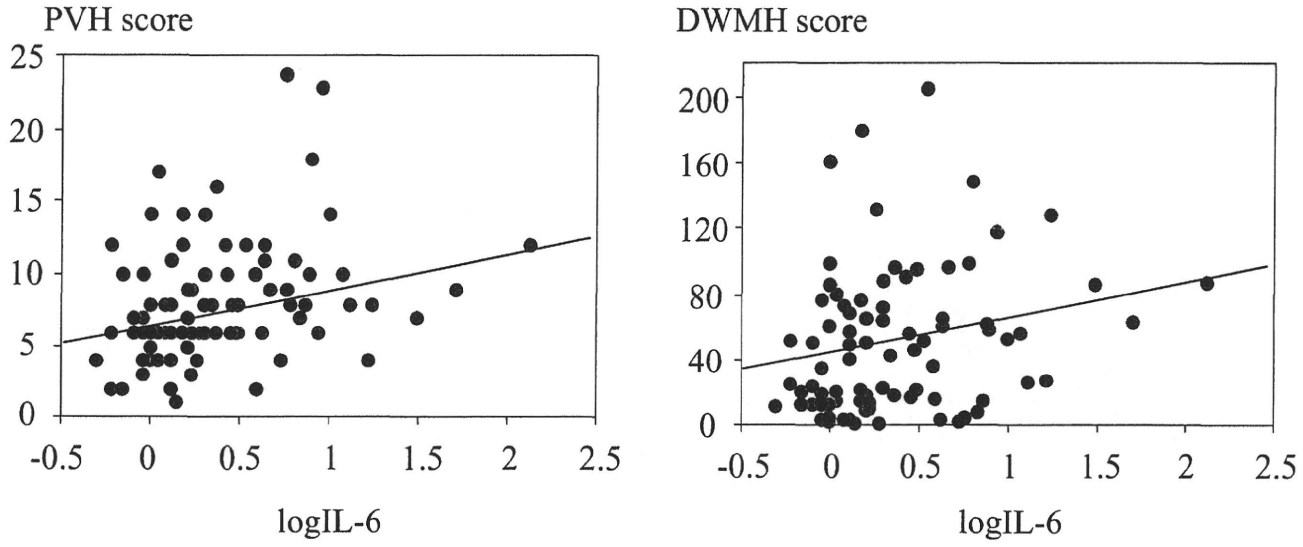

Figure 1 Relations between periventricular hyperintensity (PVH) score and log interleukin (IL)-6 (left panel; $\rho = 0.340$, $P \leq 0.05$, $n = 137$), and deep white matter hyperintensity (DWMH) score and log IL-6 (right panel; $\rho = 0.299$, $P \leq 0.05$, $n = 137$).

Table 2 Spearman's correlation coefficient between leukoaraiosis and parameters

	PVH score		DWMH score	
	ρ	*P*	ρ	*P*
Age	0.411	<0.001	0.271	0.002
BMI	−0.156	0.085	−0.124	0.179
SBP	0.215	0.014	0.232	0.009
Total cholesterol	−0.128	0.192	−0.149	0.134
HDL cholesterol	−0.053	0.595	−0.205	0.041
LDL cholesterol	−0.093	0.349	−0.025	0.802
Triglyceride	−0.014	0.885	0.080	0.421
Smoke	0.337	0.005	0.443	0.000
Log IL-6	0.340	0.002	0.299	0.006
Log hsCRP	−0.018	0.867	0.019	0.855

BMI, body mass index; DBP, diastolic blood pressure; DWMH, deep white matter hyperintensity; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; LDL, low-density lipoprotein; PVH, periventricular hyperintensity; SBP, systolic blood pressure.

markers as independent variables. As shown in Table 3, it was confirmed that the level of IL-6 was significantly associated with the progression of PVH grade (from lowest to middle and middle to highest) and DWMH score (from middle to highest). However, this trend was not found in hsCRP.

Discussion

In this study, we showed relationships between IL-6 and PVH score and IL-6 and DWMH score. It is assumed that IL-6 has an association with cerebral ischemic changes such as leukoaraiosis as well as silent brain infarction.[9] Additionally, PVH and DWMH were correlated with IL-6, but not with hsCRP. With respect to this point, Schmidt *et al.* suggested that CRP is a marker of active carotid atherosclerosis, but not of a small vessel disease-related brain lesion.[12] On the other hand, it is envisaged that elevated hsCRP levels generally reflect large vessel atherosclerosis. Because leukoaraiosis is regarded as one of the brain changes caused by small vessel disease, our results support the idea of Schmidt *et al.*

Interleukin-6 is one of the principal acute-phase reactants, playing a significant role in the activation of the coagulation–fibrinolysis system. On the other hand, leukoaraiosis has been associated with a hypercoagulable condition. Endothelium-derived adhesion molecules have been reported to be elevated in patients with great leukoaraiosis or lacunar infarcts. Leukocyte-mediated injury of the small vessels and ensuing upregulation of endothelial adhesion molecules are implicated in the pathogenesis of leukoaraiosis.[13]

The Rotterdam Scan Study showed that higher hsCRP levels were associated with presence and progression of leukoaraiosis after adjustment for cardiovascular risk factors and carotid atherosclerosis.[14] The subjects in the Rotterdam Scan Study were a population-based cohort ($n = 1033$), while the subjects in the present study were outpatients in the memory clinic ($n = 137$). In this respect, the difference in characteristics and numbers of the subjects may have given rise to the different results in terms of hsCRP in the present study and the Rotterdam Scan Study.

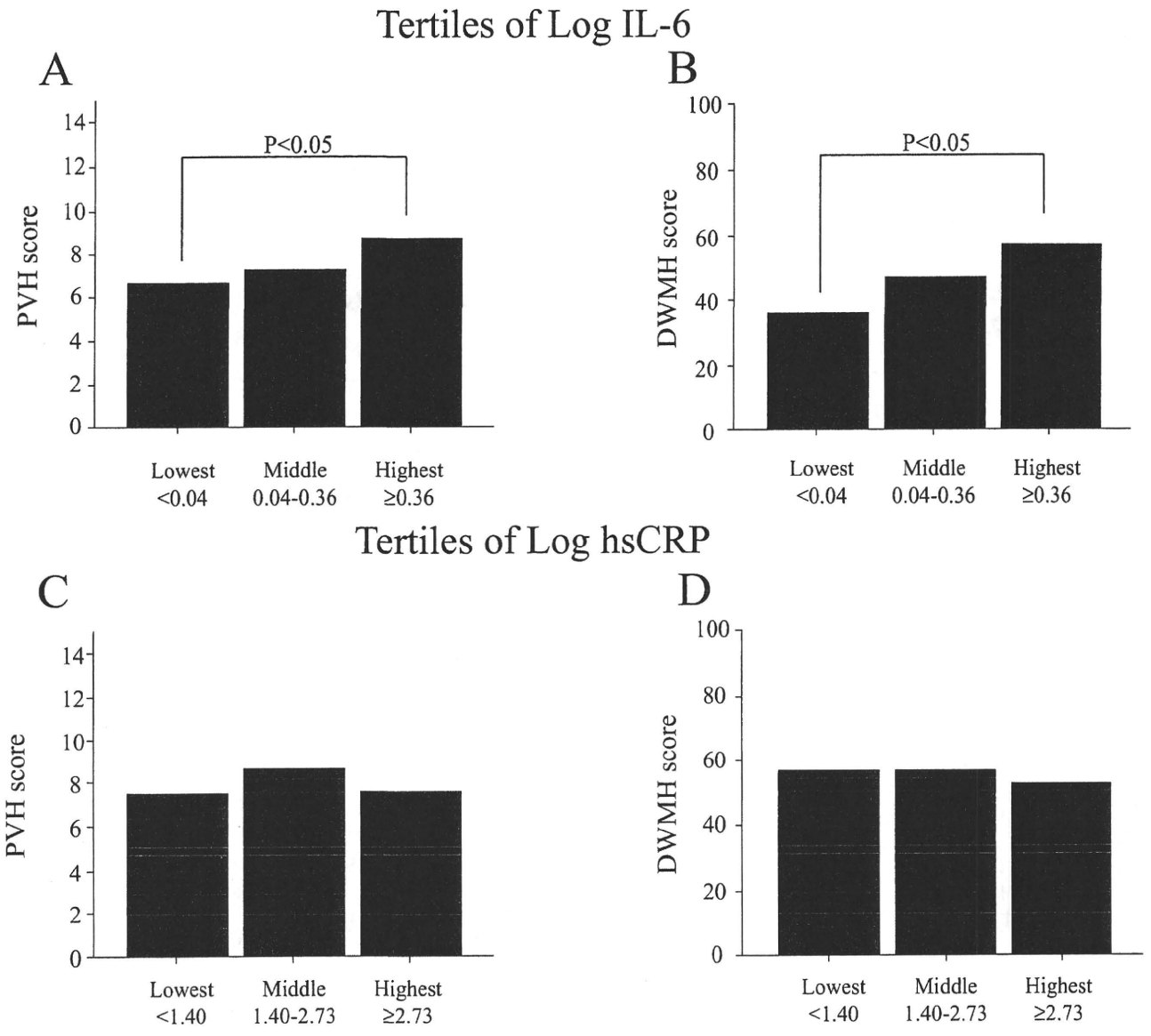

Figure 2 Average of periventricular hyperintensity (PVH) score and deep white matter hyperintensity (DWMH) score by tertile of interleukin (IL)-6 (a,b) and tertile of high-sensitivity C-reactive protein (hsCRP) (c,d). Log IL-6 tertile; lowest, <0.04 pg/mL, $n = 55$, 73.4 ± 7 1 years old (y/o); middle, 0.04–0.36 pg/mL, $n = 38$, 76.9 ± 6.8 y/o; highest, ≥0.36 pg/mL, $n = 44$, 79.5 ± 5.3 y/o. Log hsCRP; lowest, <1.40 ng/mL, $n = 44$, 73.9 ± 7.0 y/o; middle, 1.40–2.73 ng/mL, $n = 46$, 77.6 ± 7.1 y/o; highest, ≥2 73 ng/mL, $n = 41$, 77.8 ± 6.3 y/o.

In the Framingham Heart Study, no association was found between hsCRP and leukoaraiosis on MRI.[15] In the Cardiovascular Health Study, hsCRP level was modestly associated with semi-quantified leukoaraiosis volume, but the effect attenuated after excluding prevalent cerebrovascular and coronary disease cases.[13] In addition, Wright *et al.* was not able to find an association between hsCRP and leukoaraiosis volume.[16] Together, the relationships between leukoaraiosis and hsCRP varied depending upon different reports. This may come from the difference in study subjects and analytical methods. Further investigation is necessary to hold more definite opinion about which inflammatory biomarker represents the presence and development of leukoaraiosis.

Several lines of evidence suggest a relationship between IL-6 and symptoms of the geriatric syndromes, unique features of common health problems associated with poor morbidity in elderly people, such as dementia,[17] functional disability[18] and frailty.[19] On the other hand, the severity of leukoaraiosis also has a relationship with symptoms of geriatric syndromes such as dementia, falls, gait disturbance and functional disability.[3-5] Therefore, IL-6 may be an important biomarker linking the severity of leukoaraiosis to the geriatric syndromes. Because the present study is

Table 3 Associations between inflammation markers and the severity of leukoaraiosis according to tertiles (PVH score or DWMH score) adjusting for age and systolic blood pressure (logistic regression analysis)

	Log hsCRP, μg/L Odds ratio (95% CI)	Log IL-6, ng/L Odds ratio (95% CI)
PVH grade (tertiles)		
Lowest to middle	1.84 (0.78–4.31)	5.80 (1.43–23.60)
Middle to highest	0.39 (0.12–1.32)	4.39 (1.02–18.85)
DWMH grade (tertiles)		
Lowest to middle	0.81 (0.333–1.99)	3.18 (0.78–12.95)
Middle to highest	1.25 (0.48–3.29)	7.85 (1.69–36.38)

Grade of leukoaraiosis according to tertiles of PVH score or DWMH score. CI, confidence interval; DWMH, deep white matter hyperintensity; IL-6, interleukin-6; hsCRP, high-sensitivity C-reactive protein; PVH, periventricular hyperintensity.

cross-sectional, a longitudinal study would corroborate the associations of IL-6 with leukoaraiosis, and IL-6 with the geriatric syndromes.

In conclusion, we demonstrated that IL-6 level is significantly associated with the severity of PVH and DWMH lesions. The results of the present study, together with the previous studies, suggest that IL-6 is an important marker of the progression of cerebral ischemic disease, linking to the presence of geriatric syndromes.

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COMMISSION REPORT

Survey on geriatricians' experiences of adverse drug reactions caused by potentially inappropriate medications: Commission report of the Japan Geriatrics Society

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Aim: The Japan Geriatrics Society (JGS) developed the guidelines for medical treatment and its safety in the elderly and the list of potentially inappropriate medication use, a Japanese version of the Beers list, in 2005. The JGS working group in collaboration with the Japan Broadcasting Corporation conducted the survey to geriatricians to investigate their experiences of adverse drug reactions (ADR) caused by potentially inappropriate medications.

Methods: In September 2008, the survey mails were sent to all the JGS certified geriatricians ($n = 1492$). The questionnaire consisted of 1 year of experiences of ADR of any type, past experiences of ADR by the use of antipsychotic benzamides, hypnotic benzodiazepines, digoxin (≥0.15 mg/day), vitamin D_3 (alfacalcidol ≥1.0 μg/day) and additional drugs, and their attitudes to reduce the dose/number of drugs for the prevention of ADR.

Results: A total of 425 geriatricians responded (response rate 29%). Seventy-two percent experienced ADR within 1 year. Past experiences of ADR were reported by 79% for antipsychotic benzamides, 86% for hypnotic benzodiazepines, 70% for digoxin and 37% for vitamin D_3. Free responses included frequent ADR by non-steroidal anti-inflammatory, antihypertensive, antiplatelet, anti-arrhythmic, antidiabetic and antidepressant drugs. Reduction of drugs for ADR prevention was attempted by 93%.

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