TABLE 4. Adjusted odds ratios of frontal and temporal lobe atrophy progression in male participants distributed into quintiles of physical activity and total energy expenditure data.

	Odds Ratio, 95% CI				
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Frontal lobe (*n*)	76	76	76	76	77
Activity energy expenditure (kcal·d^{-1})	3.408, 1.205–9.643 (<143.2)	1.054, 0.321–3.462 (143.2 to <184.4)	1.623, 0.523–5.035 (184.4 to <226.2)	2.054, 0.691–6.904 (226.2 to <284.4)	1.00, referent (≥284.4)
No. of step per day	3.651, 1.304–10.219 (<5736.0)	1.216, 0.383–3.863 (5736.0 to <6955.0)	1.487, 0.471–4.689 (6955.0 to <8261.4)	2.403, 0.819–7.052 (8261.4 to <10,407.4)	1.00, referent (≥10,407.4)
Total energy expenditure (kcal·d^{-1})	4.816, 1.037–22.376 (<1771.4)	2.758, 0.652–11.672 (1771.4 to <1897.4)	4.639, 1.191–18.067 (1897.4 to <1983.4)	2.275, 0.553–9.358 (1983.4 to <2091.2)	1.00, referent (≥2091.2)
Temporal lobe (*n*)	76	76	76	76	77
Activity energy expenditure (kcal·d^{-1})	1.015, 0.473–2.178 (<143.2)	1.293, 0.617–2.708 (143.2 to <184.4)	0.800, 0.364–1.756 (184.4 to <226.2)	0.845, 0.390–1.833 (226.2 to <284.4)	1.00, referent (≥284.4)
No. of step per day	0.938, 0.435–2.024 (<5736.0)	1.100, 0.519–2.330 (5736.0 to <6955.0)	1.142, 0.538–2.425 (6955.0 to <8261.4)	1.123, 0.528–2.389 (8261.4 to <10,407.4)	1.00, referent (≥10,407.4)
Total energy expenditure (kcal·d^{-1})	1.045, 0.388–2.816 (<1771.4)	1.303, 0.554–3.065 (1771.4 to <1897.4)	1.229, 0.537–2.810 (1897.4 to <1983.4)	1.006, 0.439–2.307 (1983.4 to <2091.2)	1.00, referent (≥2091.2)

Odds ratios were controlled for age, BMI, education history, medical history (stroke, ischemic heart disease, hypertension, hyperlipidemia, and diabetes), current smoking, and alcohol intake in a multinomial logistic regression model.

were 12.363 (95% CI = 1.029–148.594), 12.743 (95% CI = 1.292–125.792), and 21.539 (95% CI = 2.381–194.839), respectively.

We also evaluated temporal lobe atrophy progression using the adjustment model, similar to the frontal lobe atrophy progression analysis. There were no significant differences between temporal lobe atrophy progression and physical activities or total energy expenditure (Tables 4 and 5) in any groups of participants.

DISCUSSION

Using longitudinal analyses, we showed that a high level of physical activity and total energy expenditure suppressed the frontal lobe atrophy progression that is induced by aging.

An inactive daily life appears to be a risk factor for frontal lobe atrophy progression. In male participants, those with the lowest activity energy expenditure (first quintile, <143.2 kcal) had a 3.408-fold risk of frontal lobe atrophy progression compared with those with the highest activity energy expenditure (fifth quintile, ≥284.4 kcal) (Table 4). Similarly, men with the fewest number of steps (first quintile, <5736.0 steps) had a 3.651-fold risk of frontal lobe atrophy progression compared with those with the most number of steps (fifth quintile, ≥10,407.4 steps) (Table 4). An activity energy expenditure of 143.2 kcal is equivalent to activity in 4 METs (e.g., raking the lawn and table tennis) for 33 min in 62.5-kg men (1). Thirty minutes of middle-intensity or greater activities per day, such as 5700 steps or more walking per day, may be necessary to reduce the risk of frontal lobe atrophy progression. In addition, daily physical activity decreases with aging (27). An increase in planned physical activities may be necessary to prevent frontal lobe atrophy progression in older people.

Not only the expenditure of energy with physical activity but also the energy metabolic rate of the whole body appears to be associated with frontal lobe atrophy. Low total energy expenditure tended to be a risk for frontal lobe atrophy in male and female participants (Tables 4 and 5). In a study of prosimians and anthropoid apes and humans, brain volume is correlated with basal metabolism (23). The amount of basal metabolism may determine frontal lobe atrophy progression. It is well known that basal metabolism decreases with aging (32). Age-related skeletal muscle loss (sarcopenia) may be a risk factor for frontal lobe atrophy progression due to decreasing basal metabolism. Physical activity may compensate for a reduction in basal metabolism in the elderly.

TABLE 5. Adjusted odds ratios of frontal and temporal lobe atrophy progression in female participants distributed into quintiles of physical activity and total energy expenditure data.

	Odds Ratio, 95% CI				
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Frontal lobe (*n*)	78	79	78	79	79
Activity energy expenditure (kcal·d^{-1})	1.442, 0.421–4.945 (<119.6)	1.422, 0.435–4.644 (119.6 to <148.4)	0.610, 0.148–2.520 (148.4 to <182.8)	1.233, 0.362–4.199 (182.8 to <226.4)	1.00, referent (≥226.4)
No. of step per day	1.559, 0.420–5.791 (<5825.2)	2.269, 0.627–8.209 (5825.2 to <7090.0)	0.826, 0.181–3.769 (7090.0 to <8374.0)	1.887, 0.505–7.053 (8374.0 to <9910.4)	1.00, referent (≥9910.4)
Total energy expenditure (kcal·d^{-1})	12.363, 1.029–148.594 (<1495.6)	12.743, 1.292–125.792 (1495.6 to <1570.2)	21.539, 2.381–194.839 (1570.2 to <1639.6)	4.261, 0.430–42.214 (1639.6 to <1722.0)	1.00, referent (≥1722.0)
Temporal lobe (*n*)	78	79	78	79	79
Activity energy expenditure (kcal·d^{-1})	0.978, 0.362–2.645 (<119.6)	1.023, 0.400–2.614 (119.6 to <148.4)	1.569, 0.591–4.162 (148.4 to <182.8)	1.547, 0.617–3.876 (182.8 to <226.4)	1.00, referent (≥226.4)
No. of step per day	0.879, 0.355–2.178 (<5825.2)	0.789, 0.311–2.005 (5825.2 to <7090.0)	0.825, 0.317–2.147 (7090.0 to <8374.0)	1.206, 0.489–2.974 (8374.0 to <9910.4)	1.00, referent (≥9910.4)
Total energy expenditure (kcal·d^{-1})	0.881, 0.260–2.984 (<1495.6)	1.127, 0.405–3.138 (1495.6 to <1570.2)	0.948, 0.337–2.668 (1570.2 to <1639.6)	1.285, 0.499–3.305 (1639.6 to <1722.0)	1.00, referent (≥1722.0)

Odds ratios were controlled for age, BMI, education history, medical history (stroke, ischemic heart disease, hypertension, hyperlipidemia, and diabetes), current smoking, and alcohol intake in a multinomial logistic regression model.

Although a low-activity energy expenditure and a low number of steps were risk factors for frontal lobe atrophy progression in male participants, they were not risk factors in female participants (Tables 4 and 5). Generally, there are many more men with brain atrophy than women (38). In this study, the ratios of frontal lobe atrophy progression were different between male and female participants (Table 2). Sex hormones may also affect the relationship between physical activity and frontal lobe atrophy. Androgens and estrogens are associated with brain volume (13,24), and the adaptability of the brain to physical activity may be higher in men than that in women.

In contrast to activity energy expenditure, total energy expenditure was associated with frontal lobe atrophy progression in both men and women. Basal metabolism is the maximal occupation ratio in total energy expenditure. The brain metabolic rate is included in the basal metabolism. In women, total energy expenditure including basal metabolism appears to be a better index of the risks for frontal lobe atrophy progression compared with physical activity parameters. However, because some of the odds ratios were exceedingly large in female participants, our logistic regression model may not have precisely estimated the risk of frontal lobe atrophy. There were 55 male participants with frontal lobe atrophy progression (Table 2), but only 35 female participants had frontal lobe atrophy progression (Table 2). These sex differences in the brain atrophy progression rate may have influenced estimation of the odds ratio. In women in particular, further investigations may be needed to determine the association of frontal lobe atrophy progression with total energy expenditure.

Brain atrophy is caused in part by obesity (19), metabolic syndrome, and its components (4,12). A high level of physical activity improves obesity and metabolic syndrome (29). Cross-sectional research suggests that prevention of obesity by physical activity causes the relationship between physical activity and brain volume (19). However, in this study, frontal lobe atrophy progression was associated with the physical activity level in logistic regression models that controlled for BMI. Physical activity or the total energy expenditure may be independent factors for preventing frontal lobe atrophy progression, regardless of obesity.

In this study, the activity energy expenditure, the number of steps, and the total energy expenditure were quantitative data collected by an accelerometer. The objectivity of our study is higher than that of past studies that estimated the physical activity level with a questionnaire (5,19).

A limitation of this study is the noninvasive approach using MRI. We could not elucidate the mechanism of frontal lobe atrophy progression induced by a low level of physical activity or total energy expenditure. In an animal study, the beta amyloid cumulative dose is active mass dependent in mouse brain (22). The death of neurons may be inhibited by physical activity. Some growth factors, such as nerve growth factor or brain-derived neurotrophic factor, contribute to neuronal survival or neurogenesis (31,39). The serum level of nerve growth factors fluctuates with physical exercise (16), and thus, exercise stimulus with physical activity may modify expression of nerve growth factors.

Exercise and physical activity have been reported to change the volume of every region of the brain, including the frontal lobe, the temporal lobe, the parietal lobe, and the hippocampus (3,5,8,19). Interestingly, our results showed associations between brain atrophy progression and physical activity or total energy expenditure only in the frontal lobe, but not in the temporal lobe. We hypothesize that the regional differences in brain atrophy progression were due to differences in the patterns of physical activities (including types, intensities, or frequencies). A previous study suggests that increased blood flow in the brain due to physical exercise promotes neurogenesis (30). Blood flow in the brain varies with exercise type and intensity (20,28). In this study, because the activity energy expenditure, the number of steps, and the total energy expenditure data were collected as the total amount per day with accelerometer sensors, the differences in the patterns of physical activities between participants were not determined. Further investigations that define these details may clearly uncover an association between physical activities and regional differences in brain atrophy progression.

In summary, using the longitudinal design of the NILS-LSA cohort, we evaluated the association between brain atrophy progression and daily physical activity and total energy expenditure in 774 community-living, middle-age, and elderly Japanese people with an 8-yr follow-up duration. Our data confirm that low levels of physical activity and total energy consumption are significant predictors of the risk for brain atrophy, and the effect of atrophy suppression is seen only in the frontal lobe. Promoting participation in physical activities may be beneficial in attenuating age-related frontal lobe atrophy and in preventing dementia.

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Aging Clinical and Experimental Research

SHORT COMMUNICATIONS

Slower adaptation to driving simulator and simulator sickness in older adults

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ABSTRACT. ***Background and aims:*** *Methods of assessing driving abilities in the elderly are urgently needed. Although the driving simulator (DS) appears to be a safe and cost-effective method of objectively evaluating driving performance, it may pose adaptation problems for elderly adults. In this study, we examined age-related adaptation deficits on the DS.* ***Methods:*** *Healthy young adults (n=15) and healthy elderly persons (n=17) completed some neuropsychological tests, and then performed a road-tracking task with the DS, which was repeated four times (Trials 1-4).* ***Results:*** *After simulated driving in DS, simulator sickness (SS) was observed in 18.8% of participants. The frequency of SS was 29.4% in elderly adults and 6.7% in young adults, and 17.6% of the elderly participants dropped out of the experiment. Performance on the Necker cube copying task was significantly correlated with the onset of SS. Driving performance also showed a significant interaction between group and trial, for both driving accuracy and vehicle speed. In addition, the performance of elderly adults significantly improved between trials 1 and 4, reaching a plateau in trial 4, whereas that of young adults did not change across trials.* ***Conclusion:*** *This study provides preliminary evidence of slower adaptation to a DS-based driving task by older adults, which was associated with cognitive aging. Age affected driving accuracy and velocity when a road-tracking task was simply repeated. It is concluded that the capacity of elderly people to adapt to DS environments should be taken into consideration when evaluating their performance on DS tasks.*
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INTRODUCTION

The proportion of licensed drivers over the age of 65 has increased with respect to two or three decades ago, and this number is expected to increase even further over the next few decades. It has been established that age-related decline, in both cognitive and perceptual and physical abilities, is associated with an increased risk of being involved in a traffic accident (1, 2). Identifying unsafe elderly drivers is therefore a critical issue in terms of individual and public safety (3, 4), and geriatric clinicians have been faced with the task of categorizing senior citizens into "safe" vs "unsafe" drivers (5). Valid methods for assessing the driving abilities of elderly people are urgently required.

While many consider road testing to be the gold standard by which to evaluate driving competence, road tests are costly and may be dangerous if the driver is incompetent. Although the driving simulator (DS) appears to be a safe and cost-effective method for objective evaluation of driving performance (6-9), DS applications are not without limitations, particularly when elderly adults are concerned. One important problem concerns the slower adaptation to simulation environments observed in elderly persons. When using a DS to evaluate the driving performance of elderly adults, it is necessary to discriminate between true driving abilities and age-related adaptation deficits specific to the simulator environment.

Simulator sickness (SS), or simulator adaptation syndrome, has been defined as a set of symptoms similar to those experienced after exposure to virtual interfaces, as well as to flight and driving simulators. Symptoms include headache, sweating, dry mouth, drowsiness, disorientation, vertigo, nausea, dizziness, and vomiting (10). One expla-

Key words: Driving simulator, elderly drivers, simulator sickness, learning effect, slow adaptation.

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nation is that symptoms are caused by a mismatch between visually perceived movements and the sense of movement perceived by the vestibular system, what is called the sensory conflict theory (10). Although SS is caused by several factors, aging is known to be one of them. Some studies have reported that older participants experience more SS in driving simulators than younger participants (10, 11). Cognitive variables may also play a certain role in SS; however, systematic studies have not investigated the relationship between SS and these variables, which is hindering the use of DS as an assessment tool for elderly persons with cognitive impairment.

In order to examine whether age-related adaptation deficits affect DS performance, we asked both elderly adults and young adults (controls) to drive a DS on four separate occasions, one immediately after the other, and compared the adaptation process between the two groups. In the present study, we focused on two specific markers of adaptation: the influence of simple repetition on task performance, and the occurrence frequency of SS. We also carried out a preliminary search to identify cognitive functions related to SS in elderly persons.

METHODS

Participants

We recruited 15 healthy young adults and 17 healthy elderly persons over 60 years of age. The participants were naïve with regard to this study, and were paid for their participation. They all had normal or corrected-to-normal vision, and reported no history of any psychotropic medication use, head injury with loss of consciousness, secondary neurological disorders, or drug intoxication.

None of the elderly participants showed any signs of general cognitive decline. Medical histories (including stabilograph assessment results and MRI scans) were obtained and carefully reviewed, to exclude any individuals with neuropsychiatric disease. Elderly participants with a diagnosis of dementia, and/or those with Mini-Mental State Examination (MMSE) (12) scores of 23 or less, and/or a Logical Memory delayed recall subtest score of 12 or lower on the Wechsler Memory Scale-Revised (WMS-R) (13) were excluded.

The ethics committee of the Nagoya University School of Medicine approved this study, and written informed consent was obtained from each subject prior to participation.

Tasks

Driving performance. Daily driving skills associated with traffic accidents were measured by a road-tracking task, which required participants to drive at a constant speed of 100 km/h while maintaining their vehicles at the center of a gently winding road. According to Park et al., SS emerges at a high rate in this type of DS situation, which includes high speed and multiple turns (14).

The standard deviation of the lateral position (SDLP; in cm), which indicates weaving, and the velocity (km/h) of the vehicle were used as performance measures. Recordings were made every 20 ms during the test, which lasted for 5 minutes. Details regarding the DS (manufactured by Toyota Central R&D Labs., Inc.) configuration and driving tasks used are available elsewhere (9, 15).

Evaluation of driving with the simulator was performed after neuropsychological testing was complete. Before starting the test, each driver was familiarized with the simulator by driving for a maximum of 5 minutes on a two-lane highway with no other traffic. The driving task was then repeated four times by each participant (trials 1-4).

Cognitive functions. Cognitive functions were assessed by structured performance tests selected to represent a broad range of cognitive domains, including those measured in previous studies related to complex driving tasks (16). To assess attention and executive function, the forward and backward digit span subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (17) and the paper-based Stroop Test (18) were completed. The Clock Drawing Test (CDT) (19) and Necker cube copying task (20) were completed to assess visuospatial function in elderly adults. An experienced psychologist examined all participants by the above test battery.

RESULTS

Participants were healthy young adults (n=15, 5 women and 10 men; age range, 29-43 years) and healthy elderly persons (n=17, 7 women and 10 men; age range, 60-79 years). SS was observed in 18.75% (6/32) of participants after simulated driving. The frequency of SS was 29.41% (5/17) in elderly adults and 6.67% (1/15) in young adults. This difference was not statistically significant (p=0.229, Fisher's exact test). Three elderly adults failed to complete the trials due to SS, and the data from one younger adult were excluded from following analyses, due to a mechanical problem. One-way Analysis of Variance (ANOVAs) were conducted for each neuropsychological task. The demographic characteristics of participants are listed in Table 1. The main effect of group was significant for the Stroop test ($F_{(1,26)}$=18.70, p=0.002), whereas no main effects were found for the WAIS-R digit span forward and backward tasks. Differences in cognitive functions between age groups are listed in Table 2.

In order to identify cognitive functions related to the onset of SS in elderly participants, the correlation between SS and each cognitive task score in the elderly group was analyzed. The results of Spearman's rank correlation method indicated that only the performance of the Necker cube copying test was significantly associated with the onset of SS ($\rho_{(15)}$= -0.68, p=0.002). SS was also associated with dropping out of the task (ρ(15)= -0.49,

Table 1 - *Demographic data of each age group: means ± standard deviations.*

	Elderly adults (n=14)	Young adults (n=14)
Female/male	5/9	5/9
Age (years)	66.6±4.7	35.2±5.0
Education (years)	15.1±3.0	16.0±0.0
Duration of holding a driving license (years)	43.7±7.2	15.1±5.4
Cognitive characteristics		
Mini-Mental State Examination	28.1±1.9	
WMS-R Logical Memory: immediate recall	21.2±5.9	
WMS-R Logical Memory: delayed recall	19.3±7.0	

WMS-R: Wechsler Memory Scale-Revised.

p=0.030). Table 3 lists the association between SS and each cognitive task score in the elderly group.

Figure 1 shows task performance trends from baseline to each time-point after repeating. To examine whether age-related adaptation deficits could be observed on the DS task, 2 (Group: young adults, elderly adults) × 4 (Trial: 1 to 4) factorial ANOVAs were carried out on driving performance measures. The results are summarized in Figure 1. For SDLP, the analysis revealed the main effects of group and trial ($F_{(1,26)}$=11.85, p=0.002; $F_{(3,78)}$=8.37, p=0.001). The interaction between group and trial was also significant ($F_{(3,78)}$=3.41, p=0.038). Following-up this interaction, we found a significant simple effect of group in all trials ($F_{(1,26)}$=11.09, p=0.003; $F_{(1,26)}$=13.87, p=0.001; $F_{(1,26)}$=8.50, p=0.007; $F_{(1,26)}$=5.41, p=0.028) and also a significant simple trial effect in elderly adults ($F_{(3,24)}$=8.03, p=0.001), but no such effect in young adults. Multiple comparisons with the Bonferroni adjustment were performed, and significant differences were found between trial 1 and 2 and trial 4 in the elderly group (p=0.001; p=0.001).

As regards velocity, analysis revealed the main effects of group and trial ($F_{(1,26)}$=15.95, p=0.001; $F_{(3,78)}$=15.07, p<0.001). The interaction between group and trial was also significant ($F_{(3,78)}$=11.72, p<0.001). Following up this interaction, a significant simple effect of group was found in all trials ($F_{(1,26)}$=21.86, p<0.001; $F_{(1,26)}$=12.85, p=0.001; $F_{(1,26)}$=9.62, p=0.005; $F_{(1,26)}$=7.70, p=0.010), together with a significant simple trial effect in elderly adults ($F_{(3,24)}$=12.67, p<0.001), but no such effect in young adults. Multiple comparisons with the Bonferroni adjustment were performed, and significant differences were found between trial 1 and 2 and trial 4 in the elderly group (p<0.001; p=0.044). These results showed that the performance of elderly adults improved from trial 1 to trial 4, whereas that of young adults did not change across trials. Moreover, by trial 4, the performance of the elderly group had reached a plateau.

Correlational analyses were conducted to examine the relationship between the road-tracking task trial and the neuropsychological task performance of each group. In the elderly group, there were significant negative correlations between SDLP values in the trial 3 and 4 and scores on the WAIS-R backward digit span subtest ($r_{(12)}$= -0.77, p=0.001; $r_{(12)}$= -0.60, p=0.023), and significant positive correlations between driving performance in trial 2, 3 and 4 and performance on the Stroop test ($r_{(12)}$=0.54, p=0.047; $r_{(12)}$=0.59, p=0.025; $r_{(12)}$=0.59, p=0.027). In the young group, there were significant positive correlations between SDLP values in trial 2 and scores on the WAIS-R forward digit span subtest ($r_{(12)}$=0.59, p=0.035), as well as significant negative correlations between SDLP values in trial 3 and performance on the Stroop test ($r_{(12)}$= -0.62, p=0.024). No sig-

Table 2 - *Neuropsychological scores of each age group: means ± standard deviations.*

	Elderly adults (n=14)	Young adults (n=14)	p (one-way ANOVA)
Clock Drawing Test	8.5±1.2		
Necker cube copying (correct/any distortion)	9/5		
WAIS-R: digit span forward	6.9±2.6	7.8±2.5	0.159
WAIS-R: digit span backward	7.4±2.5	6.7±2.0	0.667
Stroop Test (sec)	13.1±6.3	5.8±4.3	0.002

WAIS-R: Wechsler Adult Intelligence Scale-Revised.

Table 3 - *Association between occurrence of simulator sickness (SS) and cognitive functions in elderly group.*

	Simulator sickness			
	Onset SS (frequency of SS: 5/17)		SS in drop-outs (frequency of SS: 3/17)	
	Spearman's ρ	p	Spearman's ρ	p
Cognitive functions				
Clock Drawing Test	-0.34	0.142	-0.04	0.845
Necker cube copying	-0.68	0.002	-0.49	0.030
WAIS-R: digit span forward	-0.29	0.197	0.09	0.700
WAIS-R: digit span backward	-0.26	0.241	-0.17	0.445
Stroop Test	0.40	0.058	0.21	0.314

WAIS-R: Wechsler Adult Intelligence Scale-Revised.

nificant correlations were detected in the elderly group for velocity. In the young group, there were significant negative correlations between speed in trial 2 and scores on the WAIS-R forward digit span subtest ($r_{(12)}$= -0.62, p=0.022), as well as significant positive correlations between speed in trial 2 and performance on the Stroop test ($r_{(12)}$= -0.57, p=0.043).

DISCUSSION

Human behavior is dependent on dynamic interactions between people and their environment. The effects of normal aging on adaptation to the environment are controversial. Specifically, some studies have found no age-related adaptation deficits (21, 22), whereas others suggest that aging results in both slower adaptation and a reduced ability to adapt (23, 24). The present study demonstrates that aging affects both the occurrence of SS and the influence of simply repeating tasks on performance. Our results point toward the limitations of a DS to screen for unsafe elderly drivers. Protocols specifically designed to test the driving ability of senior citizens should be developed.

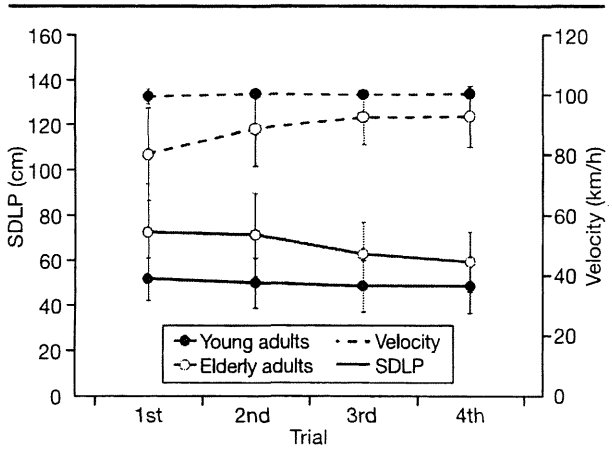

Fig. 1 - *Trends of task performances from baseline to each time point after task repetition.*

Our findings indicate that SS was typically observed in elderly adults. In addition, as 17.6% of our elderly drivers dropped out of the study because of SS, this result corroborates previous research (10, 11, 14). Brooks et al. speculated that one explanation of SS is the increased balance and dizziness problems experienced with aging (10). However, our older participants had no neuropsychiatric history and had normal stabilographic assessment results. This study demonstrates an association between SS onset and visuospatial function as measured by the Necker cube copying test, indicating that the increased SS in elderly people is caused by cognitive aging associated with visuospatial cognition. This finding suggests that people with compromised visuospatial cognition, such as patients with Alzheimer's disease, are more vulnerable to SS than normal elderly people.

Our study also demonstrates that the low driving accuracy of elderly persons is correlated with a decline in attention markers on later trials. Conversely, such a simple linear pattern was not found in younger adults. Rather, on the middle trials (2, 3), low driving accuracy and low velocity were correlated with high performance on attention tasks. These results suggest that variations in DS performance due to age-related adaptation deficits disappear across repeated tasks, and that DS performance directly reflects individual differences in attention and executive function. As the effects of aging on adaptive visuomotor mechanisms are a potential confounding factor (21-23, 25), the driving ability of elderly persons should be evaluated after they have reached a DS performance plateau. Repeating the driving task three times is an effective technique for adaptation to this type of DS. In addition, young adults had a different link between cognitive characteristics and adaptation to the DS in comparison with elderly adults.

This study has several limitations. The first is that the degree of SS was not quantified. However, drop-outs who experienced severe SS were all elderly, which supports the hypothesis that SS is an age-related adaptation deficit. A second limitation was the small sample size, which should be taken into consideration when interpreting the results. Lastly, no dementia patients participated in this study.

In conclusion, this study provides preliminary evidence concerning the slower adaptation to DS-based driving tasks associated with cognitive aging in older adults. Age affected driving accuracy and velocity when a simple road-tracking task was repeated. It is concluded that DS assessment of driving skills must be performed after a certain level of practice. The external validity of DS should also be further investigated. In order to standardize DS tasks as assessment tools, further research is needed on the effects of SS on simulator performance.

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REVIEW ARTICLE

Cognitive dysfunction: An emerging concept of a new diabetic complication in the elderly

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The incidence of type 2 diabetes mellitus (T2DM) has risen, and this trend is likely to continue. Recent advances suggest that T2DM is a risk factor for cognitive decline. We are now encountering novel complications of T2DM, namely cognitive dysfunction and dementia. Although the treatment strategy for diabetic patients with neurocognitive dysfunction has received a great deal of attention, the appropriate level of glycemic control for the prevention of the development and/or progression of cognitive decline in elderly diabetic patients remains to be elucidated. Another issue in diabetic treatment in patients with cognitive dysfunction is the selection of medicines. The best choice and combination of antidiabetic medications for the preservation of cognition should also be studied. Ample studies suggest that exercise helps to preserve cognitive function, although existing evidence does not necessarily indicate its effectiveness exclusively in diabetic patients. Exercise is a helpful non-pharmacological therapy. Considering the progressive aging of the worldwide population, more research to investigate the best way to manage this population is important. **Geriatr Gerontol Int 2013; 13: 28–34.**

Keywords: Alzheimer's disease type dementia, hypoglycemia, insulin resistance, neurocognitive assessment, vascular dementia.

Introduction

The incidence of type 2 diabetes mellitus(T2DM) has risen, and this trend is expected to continue.[1] Recent remarkable advances in pharmacological therapy in T2DM have resulted in a wide variety of treatments. Many large clinical trials have been carried out, and a variety of interventions are now available to prevent and treat the classic microvascular and macrovascular complications that occur with DM, so that people are living longer with the condition.[2] Recent studies suggested that T2DM is a risk factor for cognitive dysfunction and dementia in the elderly. With the increase in the number of elderly individuals with DM, the number of diabetic patients with cognitive dysfunction has been increasing. We are now encountering novel complications of T2DM that are not targeted by the current management strategies. As one of these new targets, cognitive impairment and dementia in patients with T2DM has generated a great deal of interest, and diabetic treatment in this population that takes brain protection into consideration should be provided.

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Cognitive impact of T2DM

Large epidemiological studies have shown the cognitive impacts of T2DM. In the Rotterdam Study,[3] T2DM patients showed an increased risk of developing dementia. The study also showed that patients treated with insulin were at a 4.3-fold higher relative risk for dementia. The Hisayama Study showed that the incidence of all-cause dementia, Alzheimer's disease (AD) and vascular dementia were significantly higher in patients with diabetes than in those with normal glucose tolerance[4] The same study showed that systemic insulin resistance was associated with the pathogenic process of AD, neuritic plaques formation.[5] The Religious Orders Study, which observed some 800 nuns and priests longitudinally for 9 years, showed that diabetic people had a 65% increased risk of developing AD.[6] The Honolulu Asia Aging Study, a cohort of Japanese Americans in Hawaii, showed that the diabetic population had a 1.8-fold higher risk of developing AD and a 2.3-fold risk of vascular dementia.[7,8]

Prospective trials also suggested that T2DM caused cognitive function to deteriorate in the elderly.

A diagnosis of diabetes increased the odds of cognitive decline 1.2-fold to 1.7-fold (95% CI 1.3–2.3) in several neurocognitive assessments.[9] A recent systematic review of large prospective trials reported that T2DM increased the risk of AD by a factor of 1.59 (range 1.15–2.7).[10] Another systematic review reported that T2DM has a risk of vascular dementia of 2.0–4.2.[9,11]

The advances in the research in this field strongly suggest that T2DM is a risk factor for cognitive dysfunction or dementia.[12,13]

Assessment of diabetes-associated cognitive dysfunction

To screen patients with cognitive impairment, several neuropsychological assessment tools might be applied. The Mini-Mental State Examination (MMSE) is an assessment scale for global cognition including orientation, memory, calculation, verbal ability and constructional disability.[14] A full score is 30, and a cut-off point of 23 out of 24 is usually used for the screening of dementia. The MMSE subset analysis identified impaired attention and calculation as specific characteristics of DM patients,[15] whereas patients with AD had lower scores in temporal orientation and recall.[16]

As a part of a large cohort study of older DM patients (Japanese Research of Cholesterol and Diabetes Mellitus, UMIN000000516 Japan CDM), we carried out MMSE on diabetic patients aged older than 65 years in a diabetic outpatient clinic (52 males, 61 females; mean age 74.7 ± 4.6 years). Of these patients, 75 were aged less than 75 years (younger-old mean age 69.9 ± 4.7 years) and 38 patients were aged older than 75 years (older-old mean age 80.7 ± 4.4). In the younger-old group, 76.0% of patients (57/75) had a MMSE score of more than 24 (mean score 25.3 ± 4.7), and in the older-old group, 52.6% (20/38) had a MMSE score of more than 24 (mean score 24.2 ± 4.6). This small assessment showed that many diabetic patients had lower cognitive scores indicative of dementia, especially in the older-old.

Diabetes affects a wide range of cognitive domains.[17] Among the domains affected by T2DM, cognitive speed might provide early detection of diabetes-related cognitive decline[18,19] The digit symbol substitution test (DSST) is a test of cognitive speed that can be carried out relatively easily. It consists of a number (e.g. nine) of digit-symbol pairs (followed by a list of digits). Under each digit, the patient is asked to write down the corresponding symbol as quickly as possible. The number of correct symbols written within the allowed time (e.g. 90 or 120 s) is measured.

In clinical settings, the diagnosis of dementia is generally made based on the Diagnostic and Statistical Manual of Mental Disorders III revised criteria in patients with or without DM.[20] The disturbance in memory impairment with at least one of the following is required for the diagnosis of dementia: abstract thinking, judgement, higher cortical function and personality changes interferes with work or social activities. The leading cause of dementia in diabetic patients is AD, as is those without DM. DM patients often have cerebrovascular disease, and clinical-pathological studies support the notion that vascular lesions aggravate the deleterious effects of AD pathology by reducing the threshold for cognitive impairment.[21]

Pathogenesis of diabetes-associated cognitive dysfunction

The precise mechanisms underlying T2DM-related cognitive dysfunction or the development of dementia, especially AD-type dementia, remain to be elucidated; however, several hypothetical mechanisms have been proposed (Fig. 1). To develop pharmacological and non-pharmacological strategies for treating the diabetic elderly with cognitive impairment, elucidating the pathogenesis of this complication might be essential.

High glucose concentration, a major pathological characteristic of diabetes, might have toxic effects on neurons in the brain through osmotic insults and oxidative stress, and the maintenance of chronic high glucose also leads to the enhanced formation of advanced glycation end-products (AGE).[22] AGE couple with free radicals and create oxidative damage, which in turn leads to neuronal injury,[23] and they also reactivate microglia, the resident innate immune cells in the brain. A wealth of evidence shows that activated microglia can become deleterious and damage neurons.[24]

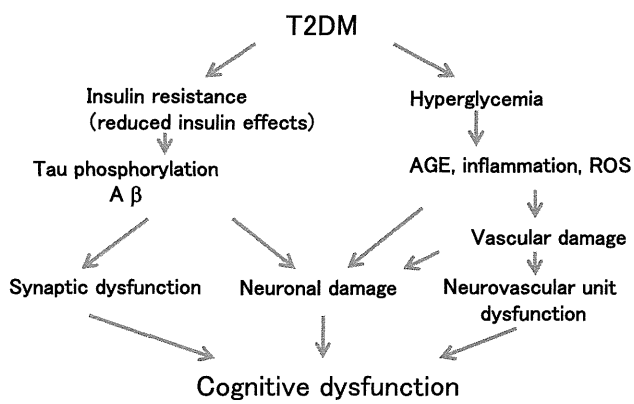

Figure 1 Pathogenesis of type 2 diabetes mellitus (T2DM)-associated cognitive dysfunction. Cognitive dysfunction in T2DM is induced by multiple pathways. Insulin resistance might be associated with Alzheimer's disease pathology, and hyperglycemia induces advanced glycation end-products (AGE) formation, inflammation and reactive oxygen species (ROS) production, which might lead to neuronal damage and neurovascular dysfunction.

T2DM, especially in conjunction with obesity, is characterized by insulin resistance and/or hyperinsulinemia. Insulin degrading enzyme (IDE) catabolizes insulin in the liver, kidneys and muscles.[25,26]

It is generally agreed that insulin located within the brain is mostly of pancreatic origin, having passed through the blood–brain barrier, although there is debate about the amount of insulin that is produced de novo within the central nervous system.[27] Major known actions of insulin in the brain include control of food intake (through insulin receptors located in the olfactory bulb and thalamus) and effects on cognitive functions, including memory.[28,29] Insulin also regulates acetylcholine transferase expression, which is an enzyme responsible for acetylcholine (ACh) synthesis. ACh is a critical neurotransmitter in cognitive function, and it might be relevant to neurocognitive disorders in diabetics.[30] Recent basic research showed that insulin signaling in the central nervous system prevents the pathological binding of amyloid beta (Aβ) oligomers.[31] Aβ oligomers are soluble molecules that attach with specificity to particular synapses, acting as pathogenic ligands.[32]

Insulin has multiple important functions in the brain, as aforementioned. These functions are disrupted in insulin-resistant states. The transport of insulin into the brain across the blood–brain barrier is reduced in insulin-resistance-associated hyperinsulinemia, and insulin levels in the brain are subsequently lowered.[33,34] Intranasal insulin showed some benefits in early AD patients.[35] With intranasal administration, insulin bypasses the periphery and the blood–brain barrier, reaching the brain and cerebrospinal fluid within minutes through extracellular bulk flow transport along olfactory and trigeminal perivascular channels, as well as through more traditional axonal transport pathways.[36,37]

Some basic research suggests that insulin signaling is involved in AD-related pathology through its effects on the Aβ metabolism and tau phosphorylation.[38] Insulin signaling activates PI3K/Akt pathway, which leads to inactivation of glycogen synthase kinase-3β (GSK-3β). GSK-3β regulates tau phosphorylation, one of the main pathological components in AD. Less insulin signaling might also induce increased activity of GSK-3β, which leads to the enhanced phosphorylation of tau protein and the formation of neurofibrillary tangles.[39] Decreased insulin signaling reduces the synthesis of several proteins, including IDE. IDE degrades Aβ as well as insulin, and reduced amounts of IDE might result in greater amyloid deposition. The results of pathological assessments in AD with or without DM, however, are highly controversial.[40,41] More research would be warranted to elucidate the relevance of insulin and insulin resistance in the underlying mechanism of T2DM-assocaiated cognitive dysfunction.

Diabetic patients often have ischemic brain lesions.[42] Even asymptomatic cerebral infarctions have affects on the cognition in elderly diabetic patients.[18,43] On cerebral magnetic resonance imaging, white matter hyperintensities and lacunae, both of which are frequently observed in the elderly, are generally viewed as evidence of small vessel disease in the brain (white matter lesions and lacunae). Small vessel diseases affect cognitive function in older diabetics.[18,44] DM also affects the function of microvascular endothelial cells. The deterioration of the endothelial cell function leads to the disruption of blood–brain barrier function, which might induce neuroinflammatory reactions and neurodegeneration.[45] The endothelial cells play a critical role in the control of hemodynamic coupling among neuronal, glial and vascular components; that is, "neurovascular units". Dysfunction of "neurovascular units" might have some impact on cognition in diabetic patients.[46]

Treatment of vascular risk factors including T2DM was reportedly associated with a lower conversion rate from mild cognitive impairment to AD[47] or slower cognitive decline in AD patients.[48] Comprehensive management in DM patients should be warranted.

Treatment and management of diabetic patients with cognitive impairment

T2DM is associated with cognitive dysfunction; however, it has not yet been made clear whether glycemic control leads to the preservation or improvement of cognitive function. Several prospective studies[19,49,50] have shown that higher glycated hemoglobin (HbA1c) levels at baseline are associated with cognitive decline. A recent prospective study by Christman *et al.*, however, showed that HbA1c levels at baseline had no effects on cognitive function.[51] A large cohort study, the Action to Control Cardiovascular Risk in Diabetes–Memory in Diabetes (ACCORD-MIND) trial, has found that HbA1c levels were cross-sectionally associated with worse performance on several cognitive functional tests.[52] However, the results of the interventional study were rather disappointing.[53] Although total brain volume in the intensive glycemic control group was significantly greater than in the standard treatment group after 40 months, there was no significant difference in cognitive assessment. The results of the study, however, should be interpreted cautiously because of the early drop-outs in the intervention group.

In the ACCORD-MIND study, the intensive control group achieved a HbA1c level of 6.6% compared with 7.5% in the standard treatment group. Several smaller studies involving less intensive glycemic treatment, however, indicated that modest cognitive decrements in patients with T2DM are partially reversible with the improvement of glycemic control,[54–59] although not invariably.[60] Postprandial hyperglycemia is associated

with atherosclerosis and diabetic complications,[61] and a control of postprandial hyperglycemia might prevent cognitive decline in older diabetic individuals.[59] These studies suggested that metabolic control might have beneficial effects in terms of cognitive function; however, the appropriate levels of blood glucose control remain unclear. In contrast, a recent report has suggested that a history of severe hypoglycemic episodes is associated with a greater risk of dementia.[62] The diabetic control in this population should be balanced between the merits of treatment and the risk of hypoglycemia.

Another issue related to the treatment that pertains to cognitive dysfunction is the selection and combination of antidiabetic medicines. The Rotterdam Study reported that insulin use increased the incidence of dementia.[3] However, many confounding factors must be considered when interpreting the results of that study. The patients who used insulin might have had worse diabetic control, a longer history and more complications, and these factors might have some impact on the incidence of dementia. Greater insulin resistance means that a greater amount of insulin is required to control the blood glucose level. The association of the use of an excessive amount of insulin with insulin resistance status might be undesirable, the appropriate prescription of insulin for maintaining a desirable blood glucose level has not yet been determined for individuals with insulin resistance. A small study reported that pioglitazone, an insulin sensitizer, has some beneficial effects on cognition in AD.[63] Comprehensive management in combination with insulin use would be necessary to achieve appropriate glycemic control, and efforts to reduce insulin resistance would be warranted.

Recently, a new class of diabetic pharmacological treatments known as incretin-related medicines has emerged. Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), whose activity is reduced in insulin resistance, have been implicated in central nervous system function, including cognition, synaptic plasticity and neurogenesis.[64] An animal study showed that GLP-1 prevented the neurodegenerative developments in AD model mice.[65] Further clinical investigation from the perspective of brain protection is warranted.

Many studies suggested that exercise has the potential to protect brain function. A systematic review of the Cochran database by Angevaren *et al.* reported the effects in elderly individuals without known cognitive impairment, and another systematic review of a prospective cohort study by Hamer *et al.* reported that exercise reduces the risk of incidence of dementia by 28% and of AD by 45%.[66,67]

Exercise also has effects on patients with mild cognitive impairment and dementia.[68] Although existing evidence does not indicate the effects of exercise on the protection of brain function exclusively in the diabetic population, exercise has multiple established effects on diabetic patients, including the improvement of insulin resistance. Studies to investigate the effects of exercise on diabetic cognitive dysfunction are warranted.

Cognitive dysfunction is associated with poor ability of self-care in elderly diabetics, and the use of both health and social services.[69] In addition, physical function is often more compromised in those with cognitive impairment. Individuals with DM with cognitive impairment might have difficulty carrying out the daily tasks of DM self-care effectively,[70] which might result in worse glycemic control than in individuals without cognitive impairment. A study reported that cognitively impaired DM patients were at increased risk of mortality and functional disability.[71] The relationship between cognition and self-management ability might be bidirectional. While it could be that poor self-management practices lead to poorer metabolic control and therefore brain dysfunction, cognitive deterioration would lead to changes in self-management ability.

A depressive mood is often comorbid with dementia,[72] especially in diabetics.[73] Depressed mood might also be associated with cognitive impairment and might interfere with effective self-management.[74–77]

People with dementia often experience behavioral and psychological symptoms of dementia (BPSD) during the course of their illness. The management of dementia is complicated by BPSD, such as psychosis, depression, agitation, aggression and disinhibition. BPSD also disrupts the daily diabetes care routine, with "denial" of having diabetes or memory loss (anosognosia) being the most disruptive.[78] Caregivers often report that caring for both diabetes and dementia is highly burdensome, that they feel overwhelmed by BPSD, and that they want more support from family and from the patients' healthcare providers.

To control BPSD, antipsychotic medication is sometimes prescribed. Antipsychotic drugs, especially second-generation drugs including olanzapine and quetiapine, have the potential to induce weight gain and elevate plasma glucose levels.[79] The use of these drugs in demented diabetic patients should be avoided.

Conclusion

Cognitive dysfunction might be a novel class of diabetic complication in the elderly. The management of diabetic patients with this complication is challenging and presents many unresolved problems. Considering the progressive aging of the worldwide population, it will be important to carry out investigations to improve our understanding of the association between T2DM and cognitive dysfunction, and to determine the best way to manage these populations.

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Disclosure statement

Nothing to declare.

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ORIGINAL ARTICLE: BEHAVIORAL AND SOCIAL SCIENCES

Day-care service use is a risk factor for long-term care placement in community-dwelling dependent elderly

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Aims: To identify predictors of long-term care placement and to examine the effect of day-care service use on long-term care placement over a 36-month follow-up period among community-dwelling dependent elderly.

Methods: This study was a prospective cohort analysis of 1739 community-dwelling elderly and 1442 caregivers registered in the Nagoya Longitudinal Study for Frail Elderly. Data included the clients' demographic characteristics, basic activities of daily living, comorbidities, and use of home care services, including the day-care, visiting nurse, and home-help services, as well as caregivers' demographic characteristics and care burden. Analysis of long-term care placement over 36 month was conducted using Kaplan–Meier curves and multivariate Cox proportional hazards models.

Results: Among the 1739 participants, 217 were institutionalized at long-term care facilities during the 36-month follow-up. Multivariate Cox regression models, adjusted for potential confounders, showed that day-care service use was significantly associated with an elevated risk for long-term care placement within the 36-month follow-up period. Participants using a day-care service two or more times/week had significantly higher relative hazard ratios than participants not using such a service.

Conclusion: The results highlight the need for effective measures to reduce the long-term care placement of day-care service users. Policy makers and practitioners must consider implementing multidimensional support programs to reduce the caregivers' willingness to consider long-term care placement. **Geriatr Gerontol Int 2012; 12: 322–329.**

Keywords: community, day-care service, elderly, long-term care placement, nursing home.

Introduction

Japan introduced a universal-coverage long-term care insurance (LTCI) program in April 2000.[1,2] This program brought a radical change from traditional, family-based care toward elderly care involving socialization and the integration of medical care and welfare

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services. There are two types of services covered by LTCI: community-based services and institutional services. Community-based services include various programs such as the home-help service, visiting bathing service, visiting rehabilitation, day care (rehabilitation), visiting nurse service, assistive device leasing, short stays (temporary stays at nursing facilities), in-home medical care, and care management services, care services provided by for-profit private homes, and allowance for the purchase of assistive devices and home renovation. In theory, the applicant can choose any certified providers and listed services.

In practice, a major role is played by a "care manager," a licensed professional who has passed an examination and undergone brief training, who draws up a care plan and a weekly schedule of service provision for individual seniors. It is essential that the care plan must be approved by the client or the client's family, and new care managers can be requested at any time if care plans prove inadequate. The maximum amount of reimbursement in the LTCI system is capped according to the care level.[3,4] Elderly beneficiaries pay a 10% co-payment for services received.

The aims of LTCI home care programs are to reduce the care burden of caregivers, maintain and improve the functional abilities and well-being of elderly people, and decrease the use of institutional care services and mortality. However, there is little evidence of how community-based services affect care recipients' outcomes, the subjective burden of caregivers or reduce the use of institutional care services.

The Nagoya Longitudinal Study for Frail Elderly (NLS-FE) compares outcomes of the use of different care services provided by the LTCI program; it was designed to provide a structured comparison of services and a comprehensive standardized assessment instrument.[5,6] Day-care service, which includes "day care" and "day rehabilitation," is provided in designated centers and is one of the major LTCI community-based services. Day-care service is a facility-based daytime program of nursing care, rehabilitation therapies, supervision and socialization that enables frail, older people, who are in poor overall health and have multiple comorbidities and varying physical or mental impairments, to remain active in the community. The individual visits the facility once or several times a week and then returns to his or her own home.

Although one of the aims of day-care service is to minimize or delay the possibility of institutionalization and maximize the potential for care recipients to maintain an independent life in the community, only a limited number of studies have examined the impact of day-care service on long-term care (LTC) placement among community-dwelling older adults. Moreover, most of these studies have targeted patients with dementia. Previous studies targeting dementia have demonstrated that day-care use is associated with nursing home placement in persons with Alzheimer's disease.[7,8] However, the effect of using day-care service on the LTC placement of community-dwelling, frail elderly with various chronic diseases remains unknown, although it has been reported that day-care services reduce caregiving time and provide respite to caregivers.[9,10]

In the present prospective cohort study using the NLS-FE cohort, we examined whether day-care service use among community-dwelling older people using various community-based services under LTCI in Japan influenced LTC placement during a 36-month follow-up period. Analysis of LTC placement over the 36-month was conducted using Kaplan–Meier curves and multivariate Cox proportional hazards models.

Methods

Subjects

The present study employed baseline data of the participants in the NLS-FE and data on the mortality of these patients during the 36-month follow-up. Details of participants and the NLS-FE have been published elsewhere.[5,6] The study population initially consisted of 1875 community-dwelling dependent elderly (632 men and 1243 women, age 65 years or older) who were eligible for LTCI, lived in Nagoya City and received various home care services from the Nagoya City Health Care Service Foundation for Older People, which has 17 visiting nursing stations associated with care-managing centers. These NLS-FE participants, who were enrolled between 1 December 2003 and 31 January 2004, were scheduled to undergo comprehensive in-home assessments by trained nurses at the baseline and at 6, 12, 24, and 36 months. At 3-month intervals, data were collected about any events participants experienced, including admission to the hospital, LTC admission and mortality. Per the procedures approved by the institutional review board of Nagoya University Graduate School of Medicine, participants provided written informed consent and, for those with substantial cognitive impairment, a surrogate (usually the closest relative or legal guardian) or family caregivers provided it.

Data collection

Data were collected from standardized interviews with patients or surrogates and caregivers conducted at clients' homes and from care-managing center records by trained nurses. The data included clients' demographic information, depressive symptoms as assessed by the short version of the Geriatric Depression Scale (GDS-15),[11] and a rating for the seven basic activities of daily living (ADL) (feeding, bathing, grooming, dressing, using the toilet, walking, and transferring) using

summary scores ranging from 0 (total disability) to 20 (no disability).[12] The interview with participants also included questions about using care services, including day-care service, which includes day care and day rehabilitation, visiting nurse service, and home-help service programs, as well as medical services. In addition, the weekly frequency with which clients used these services was obtained.

Information obtained from care-managing center records included data on the following physician-diagnosed chronic conditions: ischemic heart disease, congestive heart failure, cerebrovascular disease, diabetes mellitus, dementia, cancer, and other diseases comprising the Charlson comorbidity index,[13] which represents the sum of a weighted index that takes into account the number and seriousness of preexisting comorbid conditions.

Data were also obtained from caregivers concerning their own personal demographic characteristics and their subjective burden as assessed by the Japanese version of the Zarit Burden Interview (ZBI),[14] which is a 22-item self-report inventory that examines the burden associated with functional behavioral impairments in the home care situation.

For the analysis, 136 of the original 1875 participants were excluded because of missing data regarding service use or confounding/intermediary variables, leaving 1739 in the analysis. Of these 1739 participants, 412 could not complete the GDS-15 because of severe cognitive impairment or communication impairment. Also, among the 1739 older participants, 1442 participants had primary caregivers. Of these 1442 caregivers, 289 could not or refused to complete the ZBI.

We defined three types of care facilities providing LTCI as LTC facilities: nursing homes, care health facilities for the elderly, and group homes for elders with dementia. We assessed LTC placement over 36 months using event reports at 3-month intervals. LTC placement was confirmed by visiting nurses or care-managing center records. Placement time was defined as the number of months (3-month intervals) between the baseline interview and the event report of LTC placement. We censored participants living at home after 36 months of follow-up ($n = 773$), at death ($n = 401$), or at dropout ($n = 248$).

Statistic analysis

The Student's *t*-test and χ^2 test were used to compare differences at baseline between users and nonusers of day-care service. To create ideal model, we first evaluated the association between each covariate and LTC placement using univariate Cox proportional hazards model. LTC placement over 36 months was estimated for each group (day-care service use once or multiple times per week, and nonusers) using the Kaplan–Meier method. We then evaluated the impact of day-care service use and weekly frequency of service use on the overall model with a series of Cox proportional hazards models, which included gender, age, ADL status, presence or absence of dementia, and caregiver's sex, age and ZBI score. The risk of a variable was expressed as a hazard ratio (HR) with a corresponding 95%CI. All analyses were performed using the SPSS v. 11.(Chicago, IL, USA). $P \leq 0.05$ was considered significant.

Results

When the baseline characteristics were compared between day-care service users and nonusers, older age, a higher Charlson comorbidity index, and a lower GDS-15 score were observed in day-care service users than in nonusers (Table 1). Higher prevalence rates of cerebrovascular disease and dementia were also observed in day-care service users. The rates of nursing service use, home-help service use and living alone among day-care service users were lower than those of nonusers. Among caregivers' variables, the rate of male caregivers was significantly lower for day-care service users than nonusers. Higher ZBI score was detected in users' caregivers.

Among the 1739 participants, 217 participants were institutionalized at LTC facilities during the 36-month follow-up period. A higher rate of LTC placement was observed in day-care service users than in nonusers ($n = 143$, 18.5% vs. $n = 74$, 7.7%, $P < 0.001$) (Table 1). Among the 1327 participants who could complete the GDS-15, 150 participants were institutionalized at LTC facilities during the 36-month follow-up period. Of the 412 who could not perform the GDS-15, 67 were institutionalized at LTC facilities during the 36-month follow-up period. A higher LTC placement rate was observed in the participants who could not complete GDS-15 test than in those who could (16.3% vs. 11.3%, $P = 0.008$). There were no significant differences in LTC placement rate between participants living alone and those living with others (12.8% vs. 12.4%, $P = 0.802$). Furthermore, there was no significant difference in the LTC placement rate between participants living with caregivers who completed the ZBI and those who did not (13.0% vs. 11.1%, $P = 0.375$).

Cox hazard regression and Kaplan–Meier models

Table 2 shows the results of the unadjusted univariate Cox hazard regression analysis, which suggested that LTC placement within the 36-month follow-up period was associated with older age, a lower function of basic ADL, day-care service use, and the presence of dementia (Table 2). Among caregivers' variables, only higher care burden was associated with LTC placement. Figure 1A shows Kaplan–Meier curves exploring the

Table 1 Baseline characteristics of the 1739 care recipients and the 1442 caregivers

	Day-care service User	Nonuser	*P*-value
Care recipients ($n = 1739$)			
Men/women (% of men/total)	256/518 (33.1)	319/646 (33.1)	0.994
Age, years (mean, SD)†	81.4 (7.7)	80.2 (7.5)	0.002
Basic ADL, range: 0–20 (mean, SD)†	13.0 (5.9)	13.5 (6.7)	0.099
Charlson comorbidity index, range: 0–35 (mean, SD)†	2.2 (1.5)	1.8 (1.6)	<0.001
GDS-15 (range: 0–15), mean (SD)†‡	6.1 (3.6)	6.8 (3.7)	0.002
Chronic diseases (% of total)			
Ischemic heart disease	12.4	12.0	0.809
Congestive heart failure	8.7	8.4	0.845
Cerebrovascular disease	42.8	27.6	<0.001
Diabetes mellitus	12.4	11.7	0.659
Dementia	44.2	22.6	<0.001
Cancer	8.0	10.1	0.142
Visiting nurse service use (% of total)	38.1	54.0	<0.001
Home-help service use (% of total)	42.4	50.5	0.001
Regular medical checkups (% of total)	55.3	60.7	0.023
Living alone (% of total)	17.3	28.1	<0.001
Hospitalization during 36-month follow-up (% of total)	42.5	41.0	0.537
Long-term care placement during 36-month follow-up (% of total)	18.5	7.7	<0.001
Caregiver variables ($n = 1442$)			
Men/women (% of men/total)	137/553 (19.9)	217/535 (28.9)	<0.001
Age (years), mean (SD)†	63.4 (12.3)	64.3 (12.4)	0.177
Relationship to care recipient (% of total)			
Spouse	35.4	42.8	
Child	35.8	37.1	<0.001
Daughter-in-law	25.7	15.4	
Others	3.2	4.7	
ZBI score, range: 0–88 (mean, SD)†§	30.1 (16.8)	26.8 (17.0)	0.001

†Student's *t*-test, others were analyzed by χ^2 test (user vs.nonuser). ‡GDS-15, geriatric depression scale, $n = 1327$. §ZBI, the Zarit Burden Interview. $n = 1153$.

association between weekly frequency of day-care service use and time to LTC placement (3-month intervals). The risk of LTC placement was higher for participants who used day-care service more frequently than those who used it less frequently.

Table 3 shows the results of the series of Cox proportional hazards models that examine the HR of day-care service use to LTC placement during the 36-month follow-up period. The sequential adjustment had minor influences on the association between day-care service use and LTC placement during the 36-month follow-up period. The HR for the fully adjusted models was 2.34 (95%CI = 1.60–3.41).

In the Cox regression model adjusted for potential confounders, participants with more frequent use of day-care service had a significantly higher relative HR than participants with less frequent use of the service (Fig. 1B). Although there was no significant association between using day-care service once per week and the risk of LTC placement, participants using a day-care service two or more times per week had a significantly higher relative HR than participants not using the service.

Discussion

In the present study we demonstrated that day-care service use was associated with LTC placement during the 36-month study period among community-dwelling frail elderly using various community-based services under the LTCI program in Japan. Many previous studies have examined predictors of LTC placement in study samples, but these have been limited to people with dementia and there have been fewer evaluations of risk factors for LTC placement in community samples.[15–19] Few studies have comprehensively investigated how both caregiver and recipient characteristics influence LTC placement.[19] Previous observations

Table 2 Univariate Cox proportional hazards model to identify predictors of long-term care placement over 36 months

Variable	Univariate HR†	95% CI	*P*-value
Care recipients ($n = 1739$)			
Men (vs. women)	0.75	0.56–1.02	0.067
Age (continuous)	1.04	1.03–1.06	<0.001
Living with someone (vs. living alone)	1.02	0.74–1.39	0.920
Basic ADL (range: 0–20) (continuous)	0.97	0.95–0.99	0.001
Regular medical checkups per month (no regular checkup)	1.19	0.90–1.56	0.214
Formal care use (vs. nonuse)			
Visiting nurse	1.15	0.88–1.51	0.295
Day-care service	2.42	1.83–3.21	<0.001
Home helper	0.71	0.81–1.37	0.714
Charlson comorbidity index (continuous)	1.04	0.95–1.13	0.375
GDS-15 (continuous)†	1.01	0.96–1.05	0.762
Presence of chronic diseases (vs. absence)			
Ischemic heart disease	1.02	0.68–1.53	0.926
Congestive heart failure	1.16	0.73–1.84	0.523
Cerebrovascular disease	1.00	0.76–1.32	0.986
Diabetes mellitus	0.78	0.50–1.22	0.272
Dementia	3.00	2.29–3.92	<0.001
Cancer	0.84	0.49–1.44	0.520
Hospitalization during 36-month follow-up (vs. never admitted)	1.08	0.82–1.42	0.576
Caregiver variables ($n = 1442$)			
Men (vs. women)	0.95	0.67–1.33	0.752
Age (continuous)	1.01	1.00–1.02	0.059
Character of caregiver (vs. child)			
Spouse	0.90	0.64–1.28	0.555
Daughter-in-law	1.29	0.88–1.88	0.189
Others	1.21	0.60–2.43	0.596
ZBI score(continuous)‡	1.03	1.02–1.04	<0.001

†GDS-15, geriatric depression scale, $n = 1327$. ‡ZBI, the Zarit Burden Interview. $n = 1153$. HR, hazard ratio.

demonstrated that common risk factors of LTC placement of community-dwelling elderly were older age, presence of dementia, and caregiver's burden.[16,18,19]

Although one of the aims of day-care service is to minimize or delay the possibility of institutionalization and maximize the potential for care recipients to maintain an independent life in the community, only a limited number of studies have examined the impact of day-care service on LTC placement among community-dwelling older adults – and most of these have targeted demented patients. Previous studies targeting dementia have demonstrated that day-care use is associated with nursing home placement in persons with Alzheimer's disease.[7,8] We expanded the target group and demonstrated a striking association between day-care service use and the risk of LTC placement for community-dwelling dependent elderly patients with various chronic diseases, even after adjusting for the presence of dementia and caregiver's burden. We clearly showed, after adjusting for potential confounders, that the frequency of day-care service use had a negative impact on LTC admission with the 36-month follow-up period. The use of day-care service two or more times per week negatively affected LTC placement, but there was no significant association between institutionalization and the use of day-care service once a week. It is possible that participants with more comorbidities and a more depressive mood use day-care service more frequently; thus, participants using a day-care service two or more times per week were more likely to be placed in LTC facilities. However, even if comorbidity index score and GDS-15 score were included in the analysis, the association between LTC placement and the use of day-care service two or more times per week persisted (data not shown). This contrasts with our recent report that the risk of 21-month mortality among community-dwelling elderly was reduced significantly with frequent use of day-care service.[6] The complex decision to place older