lation-based longitudinal study, with a mean follow-up of 6.2 years, confirmed a reduced incidence rate of dementia for people who exercised 3 or more times a week (13.0 per 1000 person-years), compared with those who exercised fewer than 3 times per week (19.7 per 1000 person-years). People who exercised 3 or more times a week had a relative hazard of 0.68 (CI 0.48-0.96) for developing dementia compared with those who exercised fewer than 3 times per week (12). Moreover, Scarmeas et al. (7) demonstrated that engagement in leisure activities may reduce the risk of incident dementia. These findings support the hypothesis that physical and leisure activities reduce the likelihood for cognitive decline in community-dwelling older adults.

Some studies have failed to observe the benefits of physical activity (or exercise) in preserving cognitive function (14-18), suggesting that the effects of physical activity on cognitive functions might change according to the type of activity; but most of the studies examined the effects of composite physical activity (17), and the effect of individual activities is not well known. Furthermore, these previous studies did not examine brain atrophy; the relationship between these activities and brain atrophy (especially the MTA) was not clear.

To address these issues, we recruited community-dwelling older adults who had memory problems and conducted magnetic resonance imaging (MRI). The purpose of this study was to determine what kind of daily activity was associated with MTA atrophy as assessed by the voxel-based morphometry method.

## METHODS

### *Subjects*

The subjects were recruited from two volunteer databases (n=1543) that included elderly (aged 65 and over), who were selected by random sampling or who attended a health check in Obu, Japan. In the first eligibility assessment of this study, 528 potential subjects who had a Clinical Dementia Rating of 0.5 or memory complaints were enrolled. One hundred sixty-five subjects responded to the second eligibility assessment, and 125 out of 165 subjects completed all assessments. People who needed assistance for basic activities of daily living or who had neurological or psychiatric illness, cardiovascular disease, head trauma, drug abuse issues, alcoholism, severe pain, and contraindication of MRI were excluded. Finally, 122 subjects remained and met the definition of MCI using Petersen criteria (19).

All subjects received an MRI, a questionnaire on daily activity, and neuropsychological tests; Mini-mental State Examination (20) and Wechsler Memory Scale-Revised (WMS-R) Logical Memory (21) were assessed by speech therapists. Depressive symptoms were assessed by the Geriatric Depression Scale (22). The details of the study were explained to all subjects in advance, and written consent was obtained from each subject. In addition, this study was conducted in accordance with the Helsinki Declaration, and was approved by the ethics committee of the National Center for Geriatrics and Gerontology.

### *MRI procedure and voxel-based MRI analysis*

We determined the atrophy of MTA including the entorhinal cortex (MTA-ERC) using the voxel-based specific regional analysis for Alzheimer's disease (VSRAD) (23-25), which yields a Z-score as the end point for the assessment of medial temporal lobe volume. MRI was performed using a 1.5-T system (Magnetom Avanto, Siemens, Germany). Three-dimensional volumetric acquisition of a T1-weighted gradient echo sequence was then used to produce a gapless series of thin sagittal sections using a magnetization preparation rapid-acquisition gradient-echo sequence (repetition time, 1700 ms; echo time, 4.0 ms; flip angle 15°, acquisition matrix 256 × 256, 1.3-mm slice thickness). According to the VSRAD procedure proposed by Matsuda and Hirata et al. (23, 25), the acquired MRI images were reformatted to gapless 2-mm thin-slice transaxial images.

In the voxel-based MRI analyses, the first anatomical standardization used affine transformation. The normalized MRI images were then segmented into gray matter, white matter, cerebrospinal fluid and other components using a modified version of the clustering algorithm, the maximum likelihood "mixture model" algorithm. The segmentation procedure involved a calculation for each voxel using a Bayesian probability of belonging to each tissue class based on *a priori* MRI information with a non-uniformity correction. The segmented gray matter images were then subjected to an affine and non-linear anatomical standardization using an *a priori* gray matter template. The anatomically standardized gray matter images were smoothed with an isotropic Gaussian kernel 12 mm full-width at half-maximum to exploit the partial volume effects, so as to create a spectrum of gray matter intensities. Gray matter intensities are equivalent to the weighted average of gray matter voxels located in the volume fixed by the smoothing kernel. Each gray matter image of the patients was compared with the mean and SD of gray matter images of the healthy volunteers using voxel-by-voxel Z-score analysis after voxel normalization to global mean intensities: Z-score = (control mean-individual value) / (control SD). The Z score thus reflected the degree of atrophy in bilateral MTA-ERC. Higher Z scores indicate clearer MTA-ERC atrophy.

### *Daily activities assessment*

Daily activities were assessed using a questionnaire of 20 items that originated from brainstorming. The members who participated in brainstorming were 4 male physical therapists (the years of experience as a physical

therapist were 18 years, 9 years, 4 years, and 1 year, respectively) and 2 female office workers (a married woman and a single woman). They discussed and chose the questionnaire items based on what was necessary for older adults to live independently in the community. In the present study, we used the 20 activity items (e.g., instrumental activities of daily living, social activities) that remained after discussion. We excluded items for basic activities of daily living (such as taking a bath, going to the toilet, and changing clothes) from the present questionnaire because all of our subjects were living independently in a community. The details of the questionnaire can be found in the *Appendix*. The subjects were asked whether they did each activity during the past one month, and they answered "yes (did)" or "no (did not)".

### *Statistical analysis*

Subjects were divided into two groups: older adults without or with slight atrophy (Z score <2; non-atrophy group) and those with moderate or severe atrophy (Z score ≥2; atrophy group) in the MTA-ERC based on the results of the VSRAD. At first, we conducted an unpaired t-test or chi-square test to compare the characteristics of the subjects and the proportions of each daily activity in the two groups. If there were significant differences in the proportions of daily activity, we assigned 0 (did not) or 1 point (did) to these items in accordance with subject's response. Then, we summed the number of points by each subject. Second, multiple logistic regression analysis was performed to examine the independent associations between MTA-ERC atrophy and daily activity adjusted for demographic variables. We used moderate or severe MTA-ERC atrophy (Z score ≥2) as the dependent variable. The independent variables included age, sex, education status, MMSE score, state of achievement of each daily activity, and the summed score of daily activities (0 to 4). Statistical analysis was done using SPSS 12.0 for Windows, and all statistics were processed at a significance level of $p<0.05$.

## RESULTS

The characteristics of the atrophy group (Z score ≥2; n=37) and the non-atrophy group (Z score <2; n=85) are listed in Table 1. There were significant differences in age (74.3±6.9 *vs* 79.5±6.2, $p<0.01$), sex (men/women=35/50 *vs* 26/11, $p<0.01$), education (10.9±2.7 *vs* 9.5±2.0, $p<0.01$), and MMSE score (26.7±2.2 *vs* 25.4±3.1, $p<0.05$) between the two groups. However, there were no significant differences in other characteristics.

In regard to 4 activity items (cleaning, intellectual activity, culture lesson, using a personal computer), the atrophy group had a significantly lower proportion of the people who had answered "yes (did)" than the non-atrophy group ($p<0.05$). Other items did not show significant differences between groups (Table 2). Therefore, the summed score included the number of those activity items where group differences were found and ranged from 0 to 4. The mean values of the summed score of the atrophy and non-atrophy groups were 1.5±1.1 and 2.4±1.0, respectively.

In multiple logistic regression analysis, no association was observed between MTA-ERC atrophy and the proportions of each daily activity, whereas the summed score showed a significant relationship with MTA-ERC atrophy even after adjustment for age, sex, education, and MMSE (odds ratio 0.576, 95% CI 0.358-0.924, $p=0.022$; Table 3).

## DISCUSSION

Atrophy of the medial temporal lobe, especially the hippocampus and entorhinal cortex, is an MRI-based measure validated to predict conversion and understand progression to AD (1, 4, 5). In recent studies, the VSRAD was used to automatically and quantitatively assess MTA-

Table 1 - *Characteristics of the subjects.*

| Variables | | Z score <2 (n=85) | Z score ≥2 (n=37) | p-value |
|---|---|---|---|---|
| Age | year | 74.3±6.9 | 79.5±6.2 | <0.001** |
| Men | n (%) | 35 (58.8) | 26 (29.7) | 0.003** |
| Education | year | 10.9±2.7 | 9.5±2.0 | 0.003** |
| MMSE | score | 26.7±2.2 | 25.4±3.1 | 0.028* |
| GDS | score | 3.6±3.2 | 4.1±2.9 | 0.477 |
| Atrophy of MTA-ERC | z-score | 0.9±0.5 | 2.7±0.7 | <0.001** |
| Diagnosis | | | | |
| CVD | n (%) | 3 (3.5) | 3 (8.1) | 0.258 |
| Hypertension | n (%) | 28 (32.9) | 17 (45.9) | 0.171 |
| Diabetes mellitus | n (%) | 10 (11.8) | 1 (2.7) | 0.088 |

Values are mean±SD or n (%). **p<0.01; *p<0.05. MMSE: Mini-mental State Examination; GDS: Geriatric Depression Scale; MTA-ERC: Medial temporal area including the entorhinal cortex; CVD: Cerebrovascular disease.

Table 2 - *The relationship between atrophy of the medial temporal area and individual daily activities in atrophy and non-atrophy groups.*

| No | Item | | Z score <2 (n=85) | | Z score ≥2 (n=37) | | p-value |
|---|---|---|---|---|---|---|---|
| 1 | Reading | n (%) | 83 | (97.6) | 36 | (97.3) | 0.665 |
| 2 | Going to a neighborhood | n (%) | 84 | (98.8) | 37 | (100.0) | 0.697 |
| 3 | Cleaning | n (%) | 83 | (97.6) | 29 | (78.4) | 0.001** |
| 4 | Talking by telephone | n (%) | 82 | (96.5) | 33 | (89.2) | 0.124 |
| 5 | Taking out garbage | n (%) | 74 | (87.1) | 31 | (83.8) | 0.631 |
| 6 | Talking with somebody | n (%) | 80 | (94.1) | 35 | (94.6) | 0.641 |
| 7 | Caring for a grandchild | n (%) | 59 | (69.4) | 22 | (59.5) | 0.285 |
| 8 | Gardening | n (%) | 70 | (82.4) | 28 | (75.7) | 0.394 |
| 9 | Going out by bus or train | n (%) | 73 | (85.9) | 30 | (81.1) | 0.501 |
| 10 | Sports or hobbies | n (%) | 61 | (71.8) | 20 | (54.1) | 0.057 |
| 11 | Intellectual activities | n (%) | 54 | (63.5) | 15 | (40.5) | 0.019* |
| 12 | Attending a meeting | n (%) | 44 | (51.8) | 22 | (59.5) | 0.433 |
| 13 | Working as a coordinator | n (%) | 28 | (32.9) | 7 | (18.9) | 0.115 |
| 14 | Culture lessons | n (%) | 45 | (52.9) | 9 | (24.3) | 0.003** |
| 15 | Going to unknown place | n (%) | 46 | (54.1) | 16 | (43.2) | 0.269 |
| 16 | Carrying a heavy load | n (%) | 62 | (72.9) | 26 | (70.3) | 0.762 |
| 17 | Managing money | n (%) | 85 | (100.0) | 35 | (94.6) | 0.090 |
| 18 | Visiting friends | n (%) | 69 | (81.2) | 28 | (75.7) | 0.489 |
| 19 | Operating a video | n (%) | 33 | (38.8) | 9 | (24.3) | 0.111 |
| 20 | Using a personal computer | n (%) | 23 | (27.1) | 4 | (10.8) | 0.047* |

Values are the number (%) answered "yes (did)". **p<0.01; *p<0.05.

ERC atrophy and has been introduced for the diagnosis of Alzheimer-type dementia with MRI. Hirata et al. (23) found a high accuracy (87.8%) for discriminating patients with very early AD at the mild cognitive impairment (MCI) stage from control subjects by VSRAD. It is assumed that VSRAD data are effective for assessing initial brain atrophy in an AD progression process. To determine the relationship between MTA-ERC atrophy and daily activities, we conducted MRI scanning and an interview on detailed daily activities in older adults who had memory problems, but not dementia.

In the group comparison, there were significant differences in age. A previous study found a correlation between increasing age and decreasing brain volume (26), and found that brain atrophy may accelerate with increasing age (27). Our results are consistent with previous studies, and suggest that MTA-ERC atrophy was affected by advancing age. On the other hand, there were no significant differences in vascular risk factors, such as hypertension, diabetes mellitus, and cerebrovascular disease. White-matter changes appear to be more frequent in individuals with vascular risk factor, and apathy is a prominent syndrome related to cerebral white-matter changes (28). We consider that this result reflects the equivalence of subcortical vascular damage in both groups.

Older adults who carried out cleaning activity, intellectual activity, a culture lesson, and personal computer

Table 3 - *Relationship between atrophy of the medial temporal area and daily activities.*

| Variables | | OR | 95% CI | p-value |
|---|---|---|---|---|
| Cleaning | (yes/no) | 0.143 | (0.020-1.013) | 0.052 |
| Intellectual activities | (yes/no) | 0.510 | (0.204-1.279) | 0.151 |
| Culture lessons | (yes/no) | 0.484 | (0.174-1.343) | 0.163 |
| Using a personal computer | (yes/no) | 0.407 | (0.103-1.608) | 0.200 |
| Summed scores of activities | (0-4) | 0.576 | (0.358-0.924) | 0.022* |

Dependent variable, the presence of medial temporal area atrophy (Z score ≥2). *p<0.05 (adjustment for age, sex, education, MMSE score). OR: odds ratio; CI: confidence interval; MMSE: Mini-Mental State Examination.

use were significantly less likely to have moderate to severe MTA-ERC atrophy than the older adults who did not carry out those activities. These are activities that were cognitively stimulating or required planning rather than simply physical activity itself. The risk of dementia is reduced by daily activities, particularly leisure activities (e.g., reading, playing board games, playing musical instruments, and dancing) (17) or other activities (knitting, doing odd jobs, gardening, and traveling) (15). However, these daily activities have not been examined in association with brain atrophy, although the analysis of MTA-ERC atrophy may lead to an understanding of why older adults who maintained daily activities demonstrated a decreased risk for decline in cognitive function and dementia compared with inactive older adults. Moreover, there was one report that MCI patients were significantly impaired in 14 out of 18 activities, particularly memory activities such as finding things at home, keeping appointments, and remembering information from conversations or from the television, or complex reasoning activities, such as checking bank accounts, writing letters or notes, preparing meals, traveling, or shopping (29). MCI is the prodromal stage of AD, and memory decline and brain atrophy particularly in MTA were characterized in this stage. Our findings indicated that some daily activities involving cognitive stimulation or household-related planning were associated with MTA-ERC atrophy. Limitations on daily activities, such as cleaning, intellectual activity, culture lesson, and using a personal computer, may be characteristic of older adults with a higher rate of MTA atrophy. To discover the risk of AD early, it will be useful to assess the level of cognitively stimulating activities. However, cleaning activity can be further examined because our results indicated that the non-atrophy group contained significantly more women. This activity is usually considered to be female-associated work. Furthermore, education modifies the relationship of AD pathology to cognitive function (30), and the higher degree of education may lead to engagement in more complex activities (e.g., using a personal computer). The non-atrophy group had a higher education level compared with the atrophy group in our study. Thus, it is possible that group differences in activity level may be associated with sex or education.

In multiple logistic regression analysis adjusted for age, sex, education, and MMSE score, no statistically significant associations were observed between MTA-ERC atrophy and the proportion of execution of each daily activity, whereas the summed score of significant activity items was significantly associated with MTA-ERC atrophy. We assessed only whether subjects did or did not do each activity during the past one month. There is a possibility that the simple assessment of the activities was unable to reflect the true activity status of the subjects. It might be one reason we did not observe an association between MTA-ERC atrophy and individual activities. On the other hand, the summed score of daily activities may reflect activity status and was associated with MTA-ERC atrophy in the older adults. These results are almost consistent with a previous study that examined the association between the risk of AD and composite cognitive activity (16-18). Perhaps it will be difficult to inhibit brain atrophy only by specific activity. As for the association with MTA-ERC atrophy, composite cognitive activity is a stronger measure than a specific cognitive activity.

Environmental enrichment is known to profoundly affect the central nervous system at the functional, anatomical, and molecular levels, and during the critical period and adulthood, which was confirmed in an experimental study using animals (31). In other animal studies, there were several reports that learning caused synaptogenesis in cerebellar cortex (32) and exercise enhanced hippocampal neurogenesis in the hippocampus (33). In humans, one study reported that aerobic exercise training increased brain volume (34). These findings have suggested that physically or cognitively stimulating activities cause neurogenesis of the cerebral nerve and enhancement of the neural network, further supporting the findings in this study.

There were no significant associations between individual physical activities (such as sports, going out, and gardening) and MTA-ERC atrophy in the present study. We cannot conclude that physical activity and MTA-ERC atrophy were unrelated because it is difficult to extract only physical activities from the questionnaire, which addressed daily activities. Little is known about the relationship between brain volume and physical activity in older adults. Aerobic exercise training has been shown to increase brain volume (34), and the regions of increased brain volume were anterior cingulate cortex, supplementary motor cortex, right inferior frontal gyrus, left superior gyrus, and anterior white matter. In the present study, there was no relationship between MTA-ERC atrophy and a habit of sports activities. Although sports involve aerobic exercise, the type of sport varies in the level of endurance and movement required and overall length performed. Thus, the relationship between sports activities and MTA requires in-depth study for comprehensive examination. Further research is needed to identify what regions are associated with physical activities and what physical activity in daily life is associated with MTA-ERC atrophy in older adults.

There are several limitations in this study. First, because the relationship between MTA-ERC atrophy and daily activities was examined using a cross-sectional design, it was difficult to prove any causal relationship. Second, frequency and duration of participation was not assessed for each daily activity. The relationship between MTA-ERC atrophy and the frequency of participation in daily activities

was not clear. Previous studies examining the association between physical or leisure activity and the risk of dementia showed the reduction in risk is related to the frequency of participation (12, 17). Therefore, daily activity must be assessed in detail. Third, our results showed significant differences in age, sex, and educational level between the atrophy and non-atrophy groups. These factors would have a strong influence on brain atrophy or daily activities. In particular, epidemiologic evidence suggests a correlation between increasing age and decreasing brain volume (26), and brain atrophy may accelerate with increasing age (27). Even though we adjusted age in multivariate analysis, we might not have completely removed the influence of age. Finally, we did not get the information on the other factors that affect lifestyle (e.g. family member, place of living, income, cultural difference). This information may be more useful to understand the association between brain atrophy and daily activities. Additional analysis adjusted for potential confounding factors would be required in the future.

## CONCLUSIONS

In conclusion, the older adults who carried out cleaning, intellectual activity, a culture lesson, and personal computer use were a significantly lower proportion of the people who had moderate to severe MTA-ERC atrophy compared with the older adults who did not carry out these activities. The summed score of the daily activities was independently associated with MTA-ERC atrophy, suggesting that MTA-ERC atrophy is associated with cognitively stimulating activities or household-related activities requiring planning rather than physical activities in older adults. To determine the effect of intellectual activities on MTA-ERC volume, a longitudinal or an interventional study is necessary.

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## APPENDIX 1: Daily activities assessment

*Remember the past one month, and please answer whether you did or did not do the following activities. (Please check yes or no.)*

| | | Yes | No |
|---|---|---|---|
| 1 | Did you read a book or a newspaper? | | |
| 2 | Did you go to a neighborhood by yourself? | | |
| 3 | Did you clean your house? | | |
| 4 | Did you talk by telephone? | | |
| 5 | Did you take out garbage? | | |
| 6 | Did you talk with somebody every day? | | |
| 7 | Did you take care of a grandchild or a pet? | | |
| 8 | Did you work on a garden or farm? | | |
| 9 | Did you go out by bus or train by yourself? | | |
| 10 | Did you do some sports or hobbies? | | |
| 11 | Did you do any intellectual activities (such as a game or learning)? | | |
| 12 | Did you attend a community meeting? | | |
| 13 | Did you work as a coordinator like a group leader? | | |
| 14 | Did you take any culture lessons? | | |
| 15 | Did you go to an unknown place with a map? | | |
| 16 | Did you carry a heavy load when shopping? | | |
| 17 | Did you manage money by yourself? | | |
| 18 | Did you visit your friends? | | |
| 19 | Did you operate a video or a DVD player? | | |
| 20 | Did you use a personal computer? | | |

## REFERENCES


1. Jack CR, Petersen RC, Xu YC et al. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. Neurology 1999; 52: 1397-403.
2. de Leon MJ, DeSanti S, Zinkowski R et al. MRI and CSF studies in the early diagnosis of Alzheimer's disease. J Intern Med 2004; 256: 205-23.
3. Ries ML, Carlsson CM, Rowley HA et al. Magnetic resonance imaging characterization of brain structure and function in mild cognitive impairment: a review. J Am Geriatr Soc 2008; 56: 920-34.
4. Jack CR, Petersen RC, Xu Y et al. Rates of hippocampal atrophy correlate with change in clinical status in aging and AD. Neurology 2000; 55: 484-9.
5. Killiany RJ, Hyman BT, Gomez-Isla T et al. MRI measures of entorhinal cortex vs hippocampus in preclinical AD. Neurology 2002; 58: 1188-96.
6. Fratiglioni L, Wang HX, Ericsson K, Maytan M, Winblad B. Influence of social network on occurrence of dementia: a community-based longitudinal study. Lancet 2000; 355: 1315-9.
7. Scarmeas N, Levy G, Tang MX, Manly J, Stern Y. Influence of leisure activity on the incidence of Alzheimer's disease. Neurology 2001; 57: 2236-42.
8. Yaffe K, Barnes D, Nevitt M, Lui LY, Covinsky K. A prospective study of physical activity and cognitive decline in elderly women: women who walk. Arch Intern Med 2001; 161: 1703-8.
9. Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. Arch Neurol 2001; 58: 498-504.
10. Wang HX, Karp A, Winblad B, Fratiglioni L. Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: a longitudinal study from the Kungsholmen project. Am J Epidemiol 2002; 155: 1081-7.
11. Fratiglioni L, Paillard-Borg S, Winblad B. An active and socially integrated lifestyle in late life might protect against dementia. Lancet Neurol 2004; 3: 343-53.
12. Larson EB, Wang L, Bowen JD et al. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Ann Intern Med 2006; 144: 73-81.
13. Abbott RD, White LR, Ross GW, Masaki KH, Curb JD, Petrovitch H. Walking and dementia in physically capable elderly men. JAMA 2004; 292: 1447-53.
14. Hill RD, Storandt M, Malley M. The impact of long-term exercise training on psychological function in older adults. J Gerontol 1993; 48: 12-7.
15. Fabrigoule C, Letenneur L, Dartigues JF, Zarrouk M, Commenges D, Barberger-Gateau P. Social and leisure activities and risk of dementia: a prospective longitudinal study. J Am Geriatr Soc 1995; 43: 485-90.
16. Wilson RS, Bennett DA, Bienias JL et al. Cognitive activity and incident AD in a population-based sample of older persons. Neurology 2002; 59: 1910-4.
17. Verghese J, Lipton RB, Katz MJ et al. Leisure activities and the risk of dementia in the elderly. N Engl J Med 2003; 348: 2508-16.
18. Verghese J, LeValley A, Derby C et al. Leisure activities and the risk of amnestic mild cognitive impairment in the elderly. Neurology 2006; 66: 821-7.
19. Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med 2004; 256: 183-94.
20. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189-98.
21. Wechsler D. Wechsler Memory Scale-Revised Manual. San Antonio, Texas: The Psychological Corporation, 1987.
22. Yesavage JA. Geriatric Depression Scale. Psychopharmacol Bull 1988; 24: 709-11.
23. Hirata Y, Matsuda H, Nemoto K et al. Voxel-based morphometry to discriminate early Alzheimer's disease from controls. Neurosci Lett 2005; 382: 269-74.
24. Matsuda H. Role of neuroimaging in Alzheimer's disease, with emphasis on brain perfusion SPECT. J Nucl Med 2007; 48: 1289-300.
25. Matsuda H. The role of neuroimaging in mild cognitive impairment. Neuropathology 2007; 27: 570-7.
26. Mueller EA, Moore MM, Kerr DC et al. Brain volume preserved in healthy elderly through the eleventh decade. Neurology 1998; 51: 1555-62.
27. Scahill RI, Frost C, Jenkins R, Whitwell JL, Rossor MN, Fox NC. A longitudinal study of brain volume changes in normal aging using serial registered magnetic resonance imaging. Arch Neurol 2003; 60: 989-94.
28. Jonsson M, Edman A, Lind K, Rolstad S, Sjögren M, Wallin A. Apathy is a prominent neuropsychiatric feature of radiological white-matter changes in patients with dementia. Int J Geriatr Psychiatry 2010; 25: 588-95.
29. Perneczky R, Pohl C, Sorg C et al. Impairment of activities of daily living requiring memory or complex reasoning as part of the MCI syndrome. Int J Geriatr Psychiatry 2006; 21: 158-62.
30. Cobb JL, Wolf PA, Au R, White R, D'Agostino RB. The effect of education on the incidence of dementia and Alzheimer's disease in the Framingham study. Neurology 1995; 45: 1707-12.
31. Baroncelli L, Braschi C, Spolidoro M, Begenisic T, Sale A, Maffei L. Nurturing brain plasticity: impact of environmental enrichment. Cell Death Differ 2010; 17: 1092-103.
32. Black JE, Isaacs KR, Anderson BJ, Alcantara AA, Greenough WT. Learning causes synaptogenesis, whereas motor activity causes angiogenesis, in cerebellar cortex of adult rats. Proc Natl Acad Sci USA 1990; 87: 5568-72.
33. van Praag H, Shubert T, Zhao C, Gage FH. Exercise enhances learning and hippocampal neurogenesis in aged mice. J Neurosci 2005; 25: 8680-5.
34. Colcombe SJ, Erickson KI, Scalf PE et al. Aerobic exercise training increases brain volume in aging humans. J Gerontol A Biol Sci Med Sci 2006; 61: 1166-70.

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# Inclusion criteria provide heterogeneity in baseline profiles of patients with mild cognitive impairment: comparison of two prospective cohort studies

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*Research group of the Studies on Diagnosis of Early Alzheimer's Disease—Japan (SEAD-J) comprised investigators from nine different facilities. The investigators contributed to the design and implementation of SEAD-J and/or provided data but did not participate in the analyses of this report.

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## ABSTRACT

**Background:** Mild cognitive impairment (MCI) is considered to represent a transitional stage between ageing and Alzheimer's disease (AD). To aim at identifying neuroimaging measures associated with cognitive changes in healthy elderly and MCI patients, longitudinal multicentre studies are ongoing in several countries. The patient profiles of each study are based on unique inclusion criteria.

**Objectives:** The purpose of the study is to clarify differences in baseline profiles of MCI patients between Studies on Diagnosis of Early Alzheimer's Disease—Japan (SEAD-J) and Alzheimer's Disease Neuroimaging Initiative (ADNI) and to examine the association between baseline profiles and risk of early conversion to AD.

**Design:** Prospective cohort study.

**Setting and participants:** SEAD-J recruited 114 patients from nine facilities in Japan. A total of 200 patients in ADNI with fluorodeoxyglucose–positron emission tomography (FDG-PET) were enrolled from the USA.

**Methods:** Baseline profiles were statistically analysed. For FDG-PET at a time of inclusion, associations between each profile and cerebral metabolic rate for glucose (CMRgl) were examined using SPM5 software. In each study, the ratio of conversion to AD within the 1-year and 2-year period after inclusion was investigated and differences in baseline profiles between AD converters and non-converters were analysed.

**Results:** SEAD-J included MCI patients with more severe verbal memory deficits and extracted patients with higher depressive tendencies. These differences were likely to be associated with criteria. SEAD-J exhibited a higher rate of conversion within 1 year compared with ADNI (24.5% vs 13.5%). In FDG-PET analyses of SEAD-J, AD converters within 1 year showed more severe decrease of FDG uptake in bilateral inferior parietal regions compared with non-converters.

**Conclusions:** Different inclusion criteria provided differences in baseline profiles. The severity of memory deficit might cause increase of the AD conversion within 1 year. Clinical outcomes of multicentre studies for early diagnosis of AD should be interpreted carefully considering profiles of patients.

## ARTICLE SUMMARY

### Article focus

- To aim at identifying neuroimaging measures associated with cognitive changes in healthy elderly and MCI patients, longitudinal multicentre studies are ongoing in several countries.
- The differences in baseline profiles of MCI patients between Studies on Diagnosis of Early Alzheimer's Disease—Japan (SEAD-J) and Alzheimer's Disease Neuroimaging Initiative (ADNI) multicentre studies are clarified.

### Key messages

- In association with criteria, SEAD-J recruited more patients with pre-dementia AD who had severe verbal memory deficits compared with ADNI.
- In SEAD-J, AD converters within 1 year showed more severe decrease of FDG uptake in bilateral inferior parietal regions compared with non-converters. SEAD-J exhibited a higher rate of conversion within 1 year.
- These results suggested that MCI patients with severe memory loss at the time of inclusion had an increased risk of early transition to AD.

### Strengths and limitations of this study

- This study reinforces that the results of multicentre studies should be interpreted carefully considering the impact of baseline profiles.
- The present results were based on the analysis of data at the time of inclusion.

## INTRODUCTION

The increasing prevalence of patients with dementia is a growing social problem. In particular, Alzheimer's disease (AD) is a common disease that causes progressive dementia. Mild cognitive impairment (MCI) is considered to represent a transitional stage between ageing and AD,[1] and patients with MCI tend to progress to AD at a rate of approximately 10%–15% per year.[2 3] In this context, early diagnosis of patients who show

an increased risk of future conversion to AD represents an important step towards preventing progression of AD pathology when disease-modifying therapies for AD are finally developed.

Although the clinical evidence is not yet well established, fluorodeoxyglucose–positron emission tomography (FDG-PET) has recently been reported to provide useful findings of the cerebral metabolic rate for glucose (CMRgl) in both patients with AD[4 5] and MCI patients.[6] A pattern of CMRgl reduction in the posterior cingulate cortex and precuneus has been reported in MCI patients,[7] and hypometabolism in these regions might contribute to prediction of clinical AD conversion.[8] Furthermore, AD converters from among pre-MCI patients have shown correlations between CMRgl and future memory decline.[9] Likewise, FDG-PET appears potentially useful for distinguishing MCI patients with increased risk of progressive dementia from patients with lower risk of future AD conversion.

Alzheimer's Disease Neuroimaging Initiative (ADNI) is a multicentre study aimed at identifying neuroimaging measures and biomarkers associated with cognitive and functional changes in healthy elderly, MCI and AD subjects.[10] ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies and non-profit organisations, as a $60 million 5-year public–private partnership. ADNI is the results of efforts by many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the USA and Canada (for additional information about ADNI, see http://www.adni-info.org). Studies on Diagnosis of Early Alzheimer's Disease—Japan (SEAD-J) was launched in 2005 by the National Center for Geriatrics and Gerontology. SEAD-J represents an ongoing follow-up of MCI patients, with the aim of achieving early prediction of AD conversion. Both studies have been investigating changes of serial neuroimaging findings and neuropsychological assessments, based on different patient samples enrolled with unique inclusion criteria to extract patients at increased risk of AD. Such differences in criteria appear likely to affect AD conversion.[11] However, the impact of difference in baseline profiles of MCI patients for AD conversion has not been studied yet. The purpose of the study was to clarify this, comparing the results of statistical and imaging analyses of different multicentre studies: SEAD-J and ADNI. We investigated baseline profiles and AD conversion ratio within the 1-year and 2-year period after inclusion and then statistically analysed differences in baseline profiles between AD converters and non-converters.

## MATERIALS AND METHODS

### SEAD-J participants

Data set of SEAD-J was obtained from nine facilities in Japan. All data were checked and quality controlled at National Center for Geriatrics and Gerontology. A total of 114 patients with MCI (mean age (±SD), 70.8±7.5 years; 50 men, 64 women) were enrolled. A total of 56 normal age-matched subjects (20 men and 36 women) without evidence of neuropsychiatric impairment based on interviews were included to construct a normative imaging database. All participants provided informed consent in accordance with the trust ethics committee of National Center for Geriatrics and Gerontology. All data sets of clinical and FDG-PET findings over a follow-up period of 2 years have acquired.

Diagnosis of MCI was based on an interview with neurologists that contained evidence of reduced cognitive capacity, normal activities of daily living and absence of dementia.[12] All patients were free of significant underlying medical, neurological or psychiatric illness. Patients were initially accessed using a neuropsychological test battery, including Mini-Mental Status Examination (MMSE), Clinical Dementia Rating (CDR),[13] Geriatric Depression Scale (GDS)[14 15] and Logical Memory subset of the Wechsler Memory Scale Revised (WMS-R LM).[16] In accordance with the inclusion criteria, MCI patients were between 50 and 80 years old, with an MMSE score ≥24, a GDS score ≤10, a WMS-R LM I score ≤13, an LM II parts A and part B score (maximum, 50) ≤8 and a CDR memory box score restricted to 0.5. Patients with an educational level, defined as the number of completed years of formal education, <6 years were excluded.

### ADNI participants

Data used in the preparation of this article were obtained from the ADNI Database (http://www.loni.ucla.edu/ADNI). Data sets of clinical and baseline FDG-PET recruited from a total of 200 MCI patients (mean age, 75.2±7.1 years; 134 men, 66 women) were downloaded from the ADNI public website (http://www.loni.ucla.edu/ADNI/). Data sets of baseline FDG-PET from 102 normal subjects were used as reference data to perform group comparisons of FDG-PET between these studies. MCI patients were without any other neuropsychological disease or symptoms and between 55 and 90 years old, with an MMSE score ≥24, verbal memory deficit as measured by WMS-R LM II part A score (maximum, 25) and a CDR memory box score 0.5 or 1. LM II part A score was used to select patients with verbal memory deficit measured by education-adjusted scores ≤8/25 (for ≥16 years of education, n=133), ≤4/25 (for 8–15 years of education, n=66) or ≤2/25 (for ≤7 years of education, n=1). In addition, patients who had experienced major depression or bipolar disorder within the past year were excluded, and patients with a Hamilton Depression Rating Scale[17] score ≤12 (from a total of 17 items) were recruited.

### Neuropsychological test batteries

The neuropsychological test batteries used in each study had three differences, regarding MMSE, WMS-R LM II and GDS scores. In different subscores of MMSE,

patients in SEAD-J were scored using serial subtraction of 7 from 100 (5 points), while patients in ADNI were scored by reverse repetition of the word 'earth' (5 points). To adjust for this difference, modified MMSE score (maximum, 25) was calculated without the subscores from these 5-point subsets.

WMS-R LM II score contains parts A and B and reflects verbal memory deficits. The total score is 50 points. In SEAD-J, the cut-off score of WMS-R LM II for inclusion was ≤8/50. In ADNI, it was determined using the algorithm described above. For comparison of both profiles, only part A score (25 points) was used for analysis, and the normalised cut-off score for inclusion were calculated using a following calculation that took into account each weighting for the educational level: $\sum$ (cut-off score × patient number of each category)/total patient number. Using this measurement, the normalised cut-off score for ADNI was estimated as ≤6.65/25, while that for SEAD-J was ≤4/25. The difference also indicated that SEAD-J used more severe criteria to include patients with memory deficits.

To evaluate depressive tendencies, ADNI used the Hamilton Depression Rating Scale and GDS, while SEAD-J used a 15-item questionnaire (GDS-15). A higher GDS score (≥11) reflects depressive tendencies and represents a reliable instrument to diagnose depressive disorder.[14 15] GDS-15 was considered a suitable short-form test for an elderly population.[18] A higher GDS-15 score (≥6) was evaluated as having >90% sensitivity and specificity for depression in elderly individuals.[19]

### FDG-PET and analyses

In SEAD-J, FDG-PET data at the time of inclusion were consolidated onto local servers. Scans were performed in a resting state in a dark room, 40–60 min after venous injection of FDG. Scans of MCI patients were compared with a normative reference database, controlling for global activity using iSSP software (http://MediPhysics.com) and then Z scores of FDG uptake were calculated voxel by voxel.

Three-dimensional stereotactic surface projections[20] of Z scores were generated to visualise imaging differences for MCI patients compared with age-matched controls and AD converters compared with age-matched controls. In line with the same procedure mentioned above, we performed a comparison for scans of MCI patients in ADNI, using data sets restricted to participants <80 years old, to reduce differences in age for comparisons of results.

We also performed correlation analyses to investigate the impact of baseline patient profiles on CMRgl reduction using SPM5 software (http://www.fil.ion.ucl.ac.uk/spm/). Each image was deformed to the Montreal Neurological Imaging template and then normalised for variations in whole-brain measurements using proportionate scaling. Post-processed images were smoothed to a spatial resolution of 8 mm full width at half maximum. Analyses were conducted using MMSE score, WMS-R LM II score, GDS score and age as independent variables and CMRgl as the dependent variable. Statistical parametric maps for each of the contrasts and correlations were used in computations. The level of significance was set at $p<0.01$ (uncorrected).

### Statistical analyses

SPSS V.17.0 was used for the analyses of baseline profiles. Independent sample t-tests were used to assess differences in clinical and cognitive variables. The $\chi^2$ test was used for the analysis of gender difference between studies and used to determine group differences in the ratio of AD conversion (AD converters vs non-converters; MCI stables) within the 1-year and 2-year period after inclusion.

## RESULTS

### Differences in criteria and clinical profiles

The inclusion criteria of SEAD-J and ADNI and the differences in demographic characteristics of MCI patients are summarised in tables 1 and 2. In comparisons of neuropsychological test batteries at the time of inclusion, mean MMSE score was lower for SEAD-J patients (26.4±1.9) than for ADNI patients (27.2±1.7, $p<0.001$), and mean WMS-R LM score was lower for SEAD-J patients (1.8±1.8) than for ADNI patients (4.0±2.7, $p<0.001$). However, modified MMSE score did not differ significantly between studies, suggesting that there is little difference in global cognitive function compared with verbal memory deficits.

MCI patients in SEAD-J showed a lower educational level (SEAD-J, 11.5±3.0 years; ADNI, 15.8±2.9 years, $p<0.001$). The percentage of patients with education level ≥16 years (corresponding to post-university) was 18.4% in SEAD-J and 66.5% in ADNI, indicating the inclusion of a larger proportion of patients with higher education in ADNI. A positive correlation between WMS-R LM score and education level was found in ADNI patients ($r=0.30$, $p<0.001$) but not in SEAD-J patients

**Table 1** Differences in inclusion criteria for mild cognitive impairment

| | SEAD-J | ADNI |
|---|---|---|
| Age (yrs) | 50–80 | 55–90 |
| MMSE | 24–30 | 24–30 |
| CDR memory | 0.5 | 0.5 or 1 |
| WMS-R LM I | 0–13 | None |
| WMS-R LM II | 0–8 | * |
| GDS | 0–10 | None |
| HAM-D | None | 0–12 |

*See the Materials and methods section.
ADNI, Alzheimer's Disease Neuroimaging Initiative; CDR memory, memory subscore for Clinical Dementia Rating; GDS, Geriatric Depression Scale; HAM-D, Hamilton Depression Rating Scale; MMSE, Mini-Mental Status Examination; SEAD-J, Studies on Diagnosis of Early Alzheimer's Disease—Japan; WMS-R LM II, Logical Memory part II subset of the Wechsler Memory Scale Revised; WMS-R LM I, Logical Memory part I subset of the Wechsler Memory Scale Revised.

## Comparison of baseline profiles of MCI patients between SEAD-J and ADNI

**Table 2** Demographic characteristics of patients at the time of inclusion

| | SEAD-J | ADNI | p Value |
|---|---|---|---|
| Age (yrs) | 70.8±7.5 | 75.2±7.1 | <0.001 |
| Gender (M:F) | 50:64 | 134:66 | <0.001 |
| Education (yrs) | 11.5±3.0 | 15.8±2.9 | <0.001 |
| MMSE | 26.4±1.9 | 27.2±1.7 | <0.001 |
| Modified MMSE | 22.4±1.7 | 22.5±1.5 | 0.642 |
| WMS-R LM | 1.8±1.8 | 4.0±2.7 | <0.001 |
| GDS | 4.3±2.2 | 1.6±1.4 | <0.001 |

Values are mean±SD. The Modified MMSE represents the sum of total scores except for different subscores in both studies (maximum 25). WMS-R LM is taken as the score for the Logical Memory II part A (maximum 25).
ADNI, Alzheimer's Disease Neuroimaging Initiative; GDS, Geriatric Depression Scale; MMSE, Mini-Mental Status Examination; SEAD-J, Studies on Diagnosis of Early Alzheimer's Disease—Japan; WMS-R LM, Logical Memory subset of the Wechsler Memory Scale Revised.

(r=0.04, p=0.67). No association with MMSE scores was found in either study.

Regarding depressive tendencies using GDS, mean score was higher in SEAD-J patients (4.3±2.2) than in ADNI patients (1.6±1.4, p<0.001). In SEAD-J, 18 patients (9%) were over the cut-off for GDS-15 (6/15 points), while in ADNI, no patients were over the cut-off (11/30 points). Thus, SEAD-J included more patients with higher depressive tendency compared with ADNI. The difference in GDS score might have been caused by the exclusive criteria using the Hamilton Depression Rating Scale. The mean age of patients was younger in SEAD-J (70.8±7.5 years) compared with ADNI (75.2±7.1 years, p<0.001), presumably due to the inclusion criteria for age.

### Baseline FDG-PET: group comparisons and correlation analyses

Compared with normal controls, MCI patients in SEAD-J showed considerably lower CMRgl in the regions preferentially affected by AD, including the precuneus, posterior cingulate and parietotemporal regions (AD-associated hypometabolism) (figure 1A). In ADNI, MCI patients exhibited similar patterns of reduced CMRgl in these regions. The CMRgl reduction was also found in medial temporal regions with left dominance (figure 1B). In both studies, MCI patients showed lower CMRgl in bilateral frontal regions compared with normal subjects. Furthermore, in SEAD-J, FDG-PET analysis revealed that the converters during 1 year after inclusion showed AD-associated hypometabolism compared with non-converters. The difference in hypometabolism was more severe in the converters within 1 year compared with the converters within the following 1 year (figure 2).

In correlation analyses for FDG-PET, the association between patient profiles and glucose metabolism are depicted in figures 3 and 4. In SEAD-J, bilateral inferior parietal regions correlated with MMSE score, whereas ADNI showed no specific regions (figure 3A). Both studies showed different patterns of correlation with WMS-R LM score. In SEAD-J, a correlation was found in the left inferior parietal region, while ADNI showed

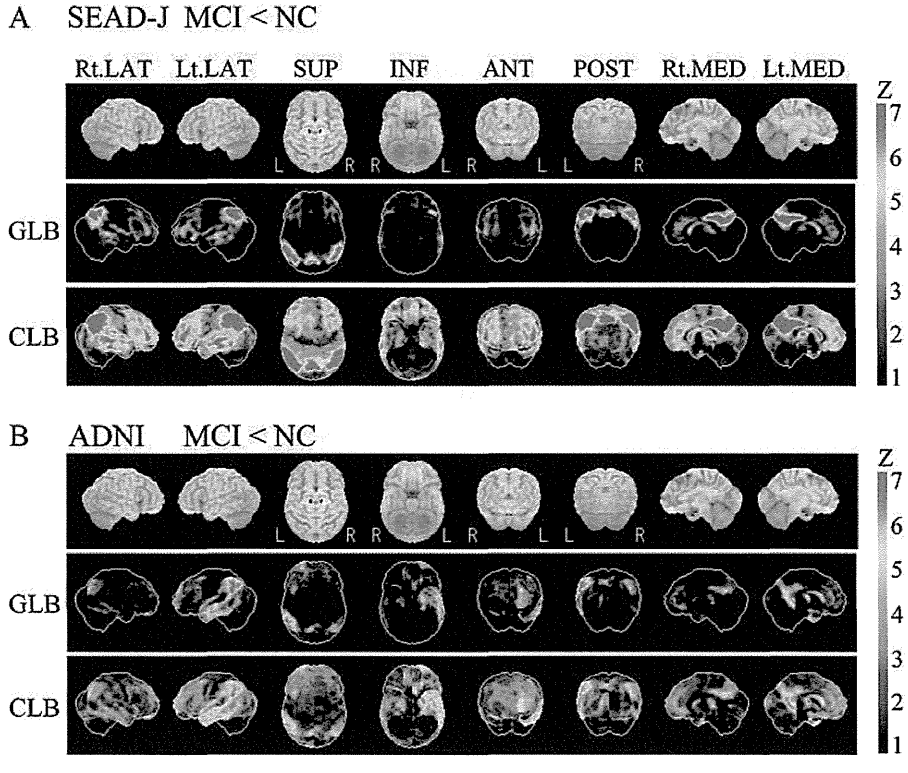


**Figure 1** 3D-SSP analyses of baseline fluorodeoxyglucose—positron emission tomography in Studies on Diagnosis of Early Alzheimer's Disease—Japan (SEAD-J) (A) and Alzheimer's Disease Neuroimaging Initiative (ADNI) (B). These are the results of group comparison between MCI patients and normal controls (NC). MCI patients showed a significant decrease of the cerebral metabolic rate for glucose (CMRgl) not only in the regions preferentially affected by Alzheimer's disease (including the inferior parietal lobules and precuneus) but also in the frontal lobules. Colour bar indicates the mean Z score of CMRgl. LAT, lateral view; SUP, superior view; INF, inferior view; ANT, anterior view; POST, posterior view; MED, medial view; GLB, reference region in global brain; CLB, reference region in cerebellum.

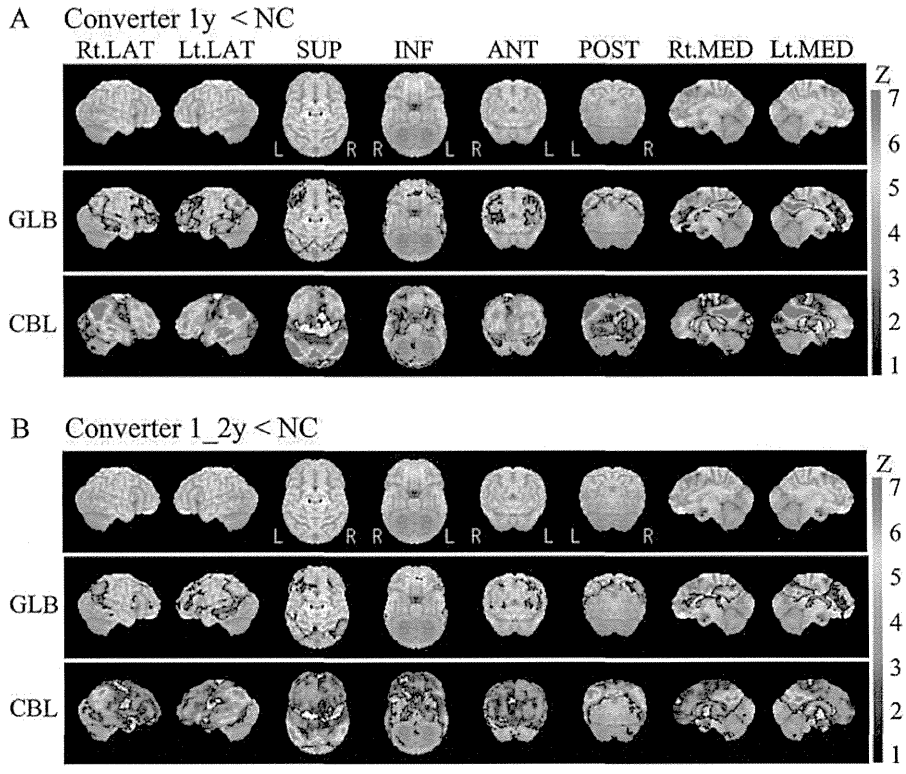


**Figure 2** 3D-SSP analyses of baseline fluorodeoxyglucose–positron emission tomography in Studies on Diagnosis of Early Alzheimer's Disease—Japan. These are the results of group comparisons between Alzheimer's disease (AD) converters and non-converters. AD converters show a greater reduction in glucose metabolism for AD-associated and frontal regions. This hypometabolism was more evident in the converters within 1 year after inclusion compared with the converters from 1 year to 2 years after inclusion. (A) AD converters within 1 year after inclusion and non-converters. (B) AD converters from 1 year to 2 years after inclusion and non-converters.

correlations in the precuneus and left medial temporal region (figure 3B). Furthermore, GDS score showed an inverse correlation in the frontal regions. In SEAD-J, regions with significant correlations showed a greater distribution over the lateral and inferior frontal regions (figure 4A). As for correlations with age, both studies

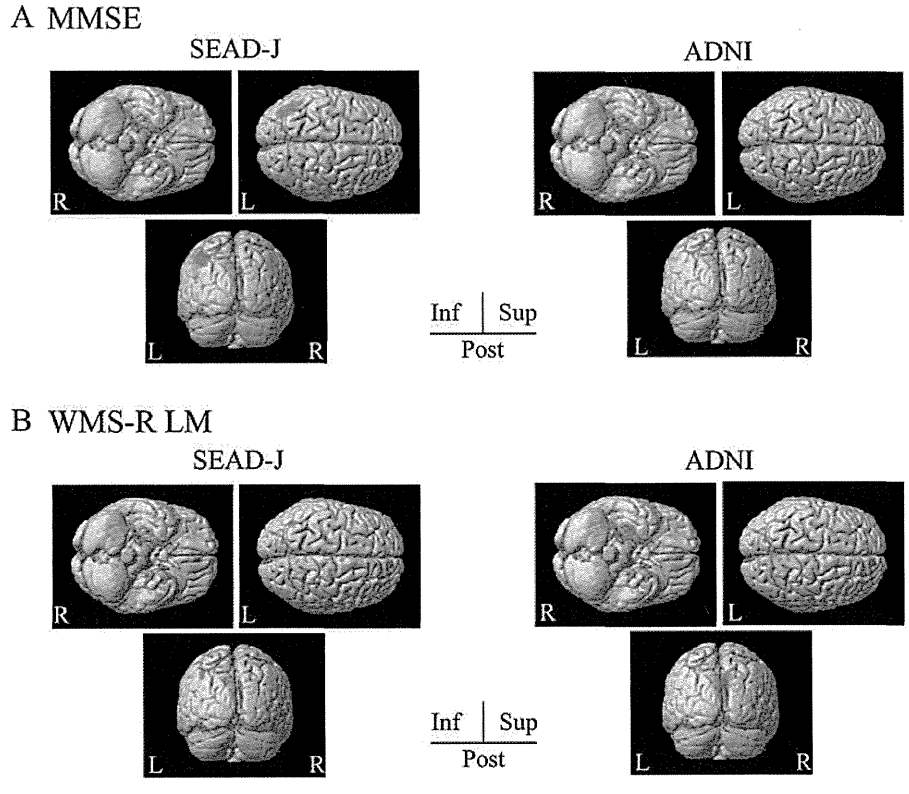


**Figure 3** Statistical parametric mapping of the brain regions correlated with baseline profiles in Studies on Diagnosis of Early Alzheimer's Disease—Japan (SEAD-J) and Alzheimer's Disease Neuroimaging Initiative (ADNI). The regions displayed in red indicate significant regional hypometabolism ($p<0.05$). (A) Correlation between lower Mini-Mental Status Examination (MMSE) scores and glucose metabolism. (B) Correlation between lower Logical Memory subset of the Wechsler Memory Scale Revised (WMS-R LM) scores and glucose metabolism.

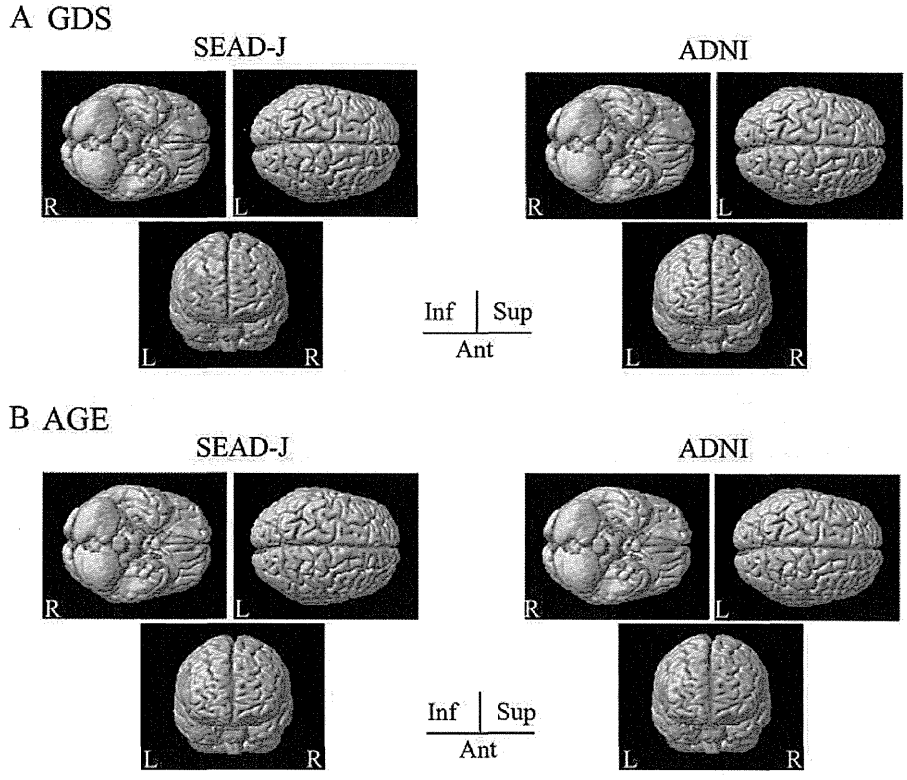


**Figure 4** Statistical parametric mapping of the brain regions correlated with baseline profiles in Studies on Diagnosis of Early Alzheimer's Disease—Japan (SEAD-J) and Alzheimer's Disease Neuroimaging Initiative (ADNI). The regions displayed in red indicate significant regional hypometabolism ($p<0.05$). (A) Inverse correlation between Geriatric Depression Scale (GDS) scores and glucose metabolism. (B) Inverse correlation between age and glucose metabolism.

showed an inverse correlation in bilateral medial frontal regions (figure 4B).

### Differences between AD converters and non-converters

In comparisons with AD conversion within 2 years, we revealed the difference in profiles between converters and non-converters (table 3). Patients who had dropped out or returned to normal were excluded from statistical analysis. In terms of patients to follow-up and patients dropping out, the studies did not show any significant differences in clinical profiles. The conversion ratio during 1 year was higher in SEAD-J than in ADNI (24.5% vs 13.5%; $\chi^2=5.33$, $p<0.05$). Conversely, conversion ratio over 2 years showed no difference between studies (SEAD-J, 35.6%; ADNI, 33.3%; $\chi^2=0.097$, $p=0.77$). Comparing the baseline profiles associated with

**Table 3** Differences in baseline profiles between the converters to AD and non-converters

| | SEAD-J | | ADNI | |
|---|---|---|---|---|
| | Conv/non-conv | p Value | Conv/non-conv | p Value |
| 1-year conversion | | | | |
| MMSE | 25.3±1.3/26.6±1.9 | 0.002 | 26.8±1.8/27.2/1.7 | NS |
| Modified MMSE | 21.6±1.3/22.6±1.8 | 0.012 | 21.8±1.7/22.5±1.5 | NS |
| WMS-R LM | 0.7±1.3/1.9±1.8 | 0.003 | 2.5±2.3/4.2±2.7 | 0.004 |
| GDS | 4.3±2.0/4.2±2.4 | 0.003 | 1.3±1.4/1.7±1.4 | NS |
| Age (yrs) | 70.6±6.9/71.6±6.7 | NS | 75.5±6.1/75.7±7.3 | NS |
| Education (yrs) | 12.1±3.1/11.5±3.0 | NS | 15.8±2.8/15.9±2.9 | NS |
| 1–2-year conversion | | | | |
| MMSE | 25.9±1.8/26.4±1.9 | 0.001 | 27.1±1.6/27.3±1.6 | NS |
| Modified MMSE | 22.1±1.5/22.5±2.0 | NS | 22.5±1.5/22.5±1.4 | NS |
| WMS-R LM | 1.6±1.9/1.9±1.9 | NS | 3.8±2.7/4.3±2.7 | NS |
| GDS | 4.9±2.6/3.9±2.1 | NS | 1.6±1.2/1.5±1.4 | NS |
| AGE (yrs) | 70.9±6.4/71.5±6.5 | NS | 73.7±7.6/75.9±6.8 | NS |
| Education (yrs) | 12.4±3.4/11.7±3.1 | NS | 16.6±2.5/15.8±2.9 | NS |

Values are mean±SD. 1-year conversion, AD conversion within 1 year after inclusion; 1–2-year conversion, AD conversion from 1 year to 2 years after inclusion.
AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; Conv, AD converters; GDS, Geriatric Depression Scale; MMSE, Mini-Mental Status Examination; non-conv, AD non-converters; NS, no significance; SEAD-J, Studies on Diagnosis of Early Alzheimer's Disease—Japan; WMS-R LM, Logical Memory subset of the Wechsler Memory Scale Revised.

conversion during 1 year of follow-up, SEAD-J converters showed significantly lower MMSE and WMS-R LM scores than non-converters ($p<0.01$). In ADNI, WMS-R LM score was lower in converters ($p<0.01$), but no difference in MMSE score was evident. Regarding the profiles associated with conversion from 1 year to 2 years after inclusion, MMSE score was lower for SEAD-J converters than for non-converters ($p<0.05$). Among ADNI converters, no profiles showed significant differences.

## DISCUSSION

From analyses of baseline profiles, SEAD-J included patients with more severe verbal memory deficits and extracted patients with higher depressive tendencies compared with ADNI. These differences in profiles of MCI patients were likely to be associated with operating criteria. In FDG-PET, both studies showed considerably lower CMRgl in the regions preferentially affected by AD and the frontal cortices. The baseline profiles provided characteristic pattern of correlations between CMRgl on baseline FDG-PET and scores of neuropsychological tests.

Despite some studies have reported associations between lower MMSE score of AD patients and higher Z score in the regions preferentially affected by AD,[21 22] such associations in MCI patients have not been demonstrated. In this study, MCI patients in SEAD-J had association between hypometabolism in bilateral inferior parietal regions and MMSE score. The modified MMSE score showed same pattern of correlation (data not shown). However, we could not find any association between MMSE score of patients in ADNI and CMRgl, as a result of previous report.[23] In WMS-R LM score, SEAD-J showed a weak regional correlation in the part of right inferior parietal cortex, while ADNI showed correlations in the precuneus and right dominant medial–temporal cortices. These results might reflect difference in disease severity of the patient samples, that is, how close an individual is to a clinical transition to AD.

Concerning the hypometabolism in frontal cortices, it might be an additional finding associated with the conversion from MCI to AD.[8] In patients with depressed mood disorders, an FDG-PET study has shown a lower CMRgl in bilateral frontal and temporal cortices, inferior parietal lobules and left cingulate cortex.[24] In AD patients with depressive syndrome, a greater decrease of CMRgl has been found in right suprafrontal lobules than in non-depressive AD.[25] In our analyses, CMRgl in the right dominant suprafrontal regions showed an inverse correlation with GDS scores. In particular, the SEAD-J, which included patients with higher depressive tendencies, showed wider regions with correlation compared with ADNI. Although the prevalence of patients with depressive tendencies was not as high in SEAD-J, the inclusion of patients with depressive tendencies might affect CMRgl. In addition, CMRgl in medial frontal regions showed an inverse correlation with age, indicating the ageing effect of glucose metabolism,[26] or possibly containing a partial volume effect.[27] These results reflected patient demographics of each study.

In baseline profiles, high educational level was another characteristic of patients in ADNI. The WMS-R LM score for ADNI patients correlated with educational level. This correlation was likely to be associated with categorical inclusion criteria for educational level. High education might mask expression of dementia symptoms. Several studies have supported the hypothesis that highly educated subjects tend to cope better with the onset of dementia.[28–30] In FDG-PET studies, higher education has been documented as a proxy for brain functional reserve.[31 32] The impact of educational level might complicate the interpretation of subtle changes in neuropsychological test results for patients with high education. A combination of neuropsychological testing with FDG-PET might thus help the accuracy for AD diagnosis in such cases. One study reported an association between higher education and lower CMRgl in the temporoparietal cortex and precuneus in AD and MCI converters.[33] However, we did not find evidence that high education affected AD conversion in MCI patients. The impact of education remains controversial and might depend on the patient sample.[34]

We revealed that SEAD-J patients exhibited a significantly higher rate of conversion within 1 year after inclusion compared with ADNI. Deficits in verbal memory and psychomotor speed/executive function abilities might be associated with conversion to AD.[35] Actually, in the present analyses, comparisons of baseline profiles between AD converters and non-converters revealed that SEAD-J converters had lower global cognitive and verbal memory compared with ADNI converters. Furthermore, in SEAD-J, AD converters during 1 year after inclusion showed more severe CMRgl reductions in bilateral inferior parietal regions compared with converters during the following year. Based on these results, the difference in AD conversion ratio might be dependent on the severity of pre-dementia AD, reflecting that MCI patients with severe baseline memory deficits rapidly converted to AD. It suggested that inclusion and diagnostic criteria were likely to be associated with the incidence of AD. However, there was no difference in conversion ratio seen within 2 years of follow-up period. Concerning the discrepancy due to follow-up period, it is likely that the difference in AD conversion ratio may not be limited by criteria only but be affected by another factor such as genotype in MCI population. The CMRgl reductions in AD-associated regions have been reported in cognitively normal people with the apolipoprotein E ε4 allele, a common AD susceptibility gene, many years before the onset of symptoms of cognitive disturbance.[36] It suggests that FDG-PET findings may associate with pathogenesis of AD. Although our observation was too short to make clear the impact of criteria and baseline profiles on the risk of AD conversion, it is likely that the incidence of AD may not have greater difference in groups with greater

susceptibility symptoms, if there are no operational criteria as for prevalence in genotype.

In our analyses, these comparisons of different multicenter studies have some limitations. Quality control protocols for data acquisition caused different pattern of CMRgl in comparison of FDG-PET between SEAD-J and ADNI. We carried out the analyses comparing the baseline FDG-PET between two studies. However, the result contaminated non-specific changes especially in the frontal and parietal regions. In this reason, we presented the difference in glucose metabolism between MCI patients and normal subjects, in each study. In addition, the present results were based on data sets at the time of inclusion. To clarify further association between each patient's profile and risk of AD conversion, multimodal analyses of data are needed for longer follow-up period.

In conclusion, our study revealed that the participants of each study showed some differences in baseline profiles because the two studies applied own original inclusion criteria to MCI patients. SEAD-J had more strict criteria to include patients with severe verbal memory deficits. The characteristics of baseline profiles are closely related to AD conversion ratio within 1 year after inclusion. Furthermore, we compared national differences between multicentre studies to show that inclusion criteria were associated with pattern of regional glucose metabolism. We suggest that severity of AD assessed by neuropsychological tests were a function of the recruitment criteria. To evaluate the value of neuroimaging measures in the early diagnosis of AD, the results of multicenter studies, even though focusing on amnestic MCI, should be compared carefully considering difference in characteristics of inclusion criteria and profiles.

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**Competing interests** None.

**Ethics approval** SEAD-J was approved by the medical ethics committee of the Center for Development of Advanced Medicine for Dementia, National Center for Geriatrics and Gerontology.

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## REFERENCES

1. Petersen RC, Smith GE, Waring SC, *et al.* Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999;56:303–8.
2. Bowen J, Teri L, Kukull W, *et al.* Progression to dementia in patients with isolated memory loss. *Lancet* 1997;349:763–5.
3. Petersen RC, Stevens JC, Ganguli M, *et al.* Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2001;56:1133–42.
4. Hoffman JM, Welsh-Bohmer KA, Hanson M, *et al.* FDG PET imaging in patients with pathologically verified dementia. *J Nucl Med* 2000;41:1920–8.
5. Silverman DH, Small GW, Chang CY, *et al.* Positron emission tomography in evaluation of dementia: regional brain metabolism and long-term outcome. *JAMA* 2001;286:2120–7.
6. Drzezga A, Grimmer T, Riemenschneider M, *et al.* Prediction of individual clinical outcome in MCI by means of genetic assessment and (18)F-FDG PET. *J Nucl Med* 2005;46:1625–32.
7. Mosconi L, Tsui WH, Herholz K, *et al.* Multicenter standardized 18F-FDG PET diagnosis of mild cognitive impairment, Alzheimer's disease, and other dementias. *J Nucl Med* 2008;49:390–8.
8. Drzezga A, Lautenschlager N, Siebner H, *et al.* Cerebral metabolic changes accompanying conversion of mild cognitive impairment into Alzheimer's disease: a PET follow-up study. *Eur J Nucl Med Mol Imaging* 2003;30:1104–13.
9. Caselli RJ, Chen K, Lee W, *et al.* Correlating cerebral hypometabolism with future memory decline in subsequent converters to amnestic pre-mild cognitive impairment. *Arch Neurol* 2008;65:1231–6.
10. Mueller SG, Weiner MW, Thal LJ, *et al.* Ways toward an early diagnosis in Alzheimer's disease: he Alzheimer's Disease Neuroimaging Initiative (ADNI). *Alzheimers Dement* 2005;1:55–66.
11. Saxton J, Snitz BE, Lopez OL, *et al.* Functional and cognitive criteria produce different rates of mild cognitive impairment and conversion to dementia. *J Neurol Neurosurg Psychiatry* 2009;80:737–43.
12. Petersen RC, Doody R, Kurz A, *et al.* Current concepts in mild cognitive impairment. *Arch Neurol* 2001;58:1985–92.
13. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* 1993;43:2412–14.
14. Yesavage JA, Brink TL, Rose TL, *et al.* Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res* 1982;17:37–49.
15. Nyunt MS, Fones C, Niti M, *et al.* Criterion-based validity and reliability of the Geriatric Depression Screening Scale (GDS-15) in a large validation sample of community-living Asian older adults. *Aging Ment Health* 2009;13:376–82.
16. Sullivan K. Estimates of interrater reliability for the Logical Memory subtest of the Wechsler Memory Scale-Revised. *J Clin Exp Neuropsychol* 1996;18:707–12.
17. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56–62.
18. de Craen AJ, Heeren TJ, Gussekloo J. Accuracy of the 15-item geriatric depression scale (GDS-15) in a community sample of the oldest old. *Int J Geriatr Psychiatry* 2003;18:63–6.
19. Fountoulakis KN, Tsolaki M, Iacovides A, *et al.* The validation of the short form of the geriatric depression scale (GDS) in Greece. *Aging (Milano)* 1999;11:367–72.
20. Minoshima S, Frey KA, Koeppe RA, *et al.* A diagnostic approach in Alzheimer's disease using three-dimensional stereotactic surface projections of fluorine-18-FDG PET. *J Nucl Med* 1995;36:1238–48.
21. Hanyu H, Sato T, Hirao K, *et al.* The progression of cognitive deterioration and regional cerebral blood flow patterns in Alzheimer's disease: a longitudinal SPECT study. *J Neurol Sci* 2010;290:96–101.
22. Chase TN, Foster NL, Fedio P, *et al.* Regional cortical dysfunction in Alzheimer's disease as determined by positron emission tomography. *Ann Neurol* 1984;(15 Suppl):S170–4.
23. Langbaum JB, Chen K, Lee W, *et al.* Categorical and correlational analyses of baseline fluorodeoxyglucose positron emission tomography images from the Alzheimer's Disease Neuroimaging Initiative (ADNI). *Neuroimage* 2009;45:1107–16.
24. Hosokawa T, Momose T, Kasai K. Brain glucose metabolism difference between bipolar and unipolar mood disorders in depressed and euthymic states. *Prog Neuropsychopharmacol Biol Psychiatry* 2009;33:243–50.
25. Lee DY, Choo IH, Jhoo JH, *et al.* Frontal dysfunction underlies depressive syndrome in Alzheimer disease: a FDG-PET study. *Am J Geriatr Psychiatry* 2006;14:625–8.
26. Aston JA, Cunningham VJ, Asselin MC, *et al.* Positron emission tomography partial volume correction: estimation and algorithms. *J Cereb Blood Flow Metab* 2002;22:1019–34.
27. Kantarci K, Senjem ML, Lowe VJ, *et al.* Effects of age on the glucose metabolic changes in mild cognitive impairment. *AJNR Am J Neuroradiol* 2010;31:1247–53.

28. Wilson RS, Li Y, Aggarwal NT, *et al.* Education and the course of cognitive decline in Alzheimer disease. *Neurology* 2004;63:1198–202.
29. Bennett DA, Wilson RS, Schneider JA, *et al.* Education modifies the relation of AD pathology to level of cognitive function in older persons. *Neurology* 2003;60:1909–15.
30. Roe CM, Xiong C, Miller JP, *et al.* Education and Alzheimer disease without dementia: support for the cognitive reserve hypothesis. *Neurology* 2007;68:223–8.
31. Stern Y, Alexander GE, Prohovnik I, *et al.* Inverse relationship between education and parietotemporal perfusion deficit in Alzheimer's disease. *Ann Neurol* 1992; 32:371–5.
32. Perneczky R, Drzezga A, Diehl-Schmid J, *et al.* Schooling mediates brain reserve in Alzheimer's disease: findings of fluoro-deoxy-glucose-positron emission tomography. *J Neurol Neurosurg Psychiatry* 2006;77:1060–3.
33. Garibotto V, Borroni B, Kalbe E, *et al.* Education and occupation as proxies for reserve in a MCI converters and AD: FDG-PET evidence. *Neurology* 2008;71:1342–9.
34. Landau SM, Harvey D, Madison CM, *et al.* Comparing predictors of conversion and decline in mild cognitive impairment. *Neurology* 2010;75:230–8.
35. Tabert MH, Manly JJ, Liu X, *et al.* Neuropsychological prediction of conversion to Alzheimer disease in patients with mild cognitive impairment. *Arch Gen Psychiatry* 2006;63:916–24.
36. Reiman EM, Chen K, Alexander GE, *et al.* Correlations between apolipoprotein E ε4 gene dose and brain-imaging measurements of regional hypometabolism. *Proc Natl Acad Sci U S A* 2005;102:8299–302.

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# 地域在住高齢者の身体活動と認知機能に関する縦断的研究

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発表研究論文

# 地域在住高齢者の身体活動と認知機能に関する縦断的研究

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## 1. 緒　言

老年期の認知症は発症後の治療が非常に困難であり，予防に努めることが重要であると考えられる．認知症の発症および進行を遅らせる有効な予防法があれば，認知症高齢者の生活の質（quality of life：QOL）の改善，自立した生活の継続，また経済的社会負担の軽減などの効果をもたらすことが予想される．

身体活動や運動は，高齢者にとって，健康の維持に必要なものであり，身体機能の改善をもたらすだけでなく，認知機能や脳機能低下の予防の手段として，その適用が期待されており，運動や余暇活動に注目した研究が数多くされてきた[1-8]．しかし，日常身体活動には運動や余暇活動だけでなく家事・仕事身体活動も含まれているため，それらの要因を考慮した検討が必要とされる．日常の身体活動の内容は男女で異なり，加齢によるその内容の変化にも性差があると考えられる．

仕事身体活動と認知機能との関連についてこれまでの研究は，関連があるとする報告[9)]やないとする報告[10)]に分かれているが，いずれも家事のような家庭内の身体活動が含まれてないか，性差に注目した検討は行われていない．

そこで，本研究では地域在住の60歳以上の男女を対象とした縦断的検討により，認知機能と余暇および家事・仕事身体活動との関連について性差による検討を行った．

## 2. 方　法

### 1）対象

対象者は，「国立長寿医療研究センター・老化に関する長期縦断疫学研究（NILS-LSA：National Institute for Longevity Sciences -Longitudinal Study of Aging）」[11)]の第2次調査（2000～2002）および6年後の第5次調査(2006～2008)に共に参加した60～81歳の男女のうち，第2次調査のMMSE得点が28点以上の668人(男:339人，女：329人，平均67.9 ± 5.5歳）である．NILS-LSAは愛知県大府市（人口約70,000人）および知多郡東浦町（人口約40,000人）の地域住民を対象とした老化と老年病に関する縦断的コホート研究である．本研究の参加者は，年齢別・性別に層化無作為抽出されている．

本研究は国立長寿医療研究センターにおける倫理委員会の了承の下に参加者に対して事前に調査・検査内容とその意義についての説明を行い，調査への参加の文書による同意（informed consent）の得られた者を対象として行われている．

### 2）測定項目

#### (1) 身体活動

過去1年間の身体活動内容は質問紙[12)]を用いて，専門スタッフの聞き取り形式によって調査した．対象者の1日の生活状況を把握する上で，1週間あたりの身体活

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動を2ヶ月ごとにまとめ，最終的には1年にわたる余暇，家事・仕事身体活動時間（家事の時間＋仕事の時間）を強度別に把握した．まず，2.5 Mets以上の余暇身体活動時間と2.5 Mets以上の家事・仕事身体活動時間を算出し，この合計を2.5 Mets以上の総身体活動時間とした．さらに4.5 Mets以上の総身体活動時間についても同様にして求めた．

(2) 認知機能

認知機能評価はMMSE (Mini-Mental State Examination) [13]を用いた．認知機能の低下の判断基準としてcut-off pointは27/28とした[14]．MMSE検査は主に記憶力，計算力，言語力，見当識（現在の日時や，自分がどこにいるかなどの状況把握力）を測定するためのテストである．

(3) 統計解析

各変数の測定結果は平均±値標準偏差で示した．連続変数の群間比較にはt検定を，カテゴリー変数の群間比較には$\chi 2$検定を用いた．また，第5次調査時MMSE得点の27点以下への低下の有無を目的変数とし，説明変数は第2次調査時の2.5 Mets以上の総身体活動時間，4.5 Mets以上の総身体活動時間，2.5 Mets以上の余暇身体活動時間，2.5 Mets以上の家事・仕事身体活動時間を2分位で上位群，下位群に分け，それぞれの影響について多重ロジスティック回帰分析を用いて性別に検討した．調整因子は，第2次調査時の年齢，糖尿病，狭心症・心筋梗塞，高脂血症，脳卒中既往，慢性関節リウマチの既往歴の有無，BMI，教育年数とした．統計処理はSAS ver 9.1.3を利用し，有意水準は$p<0.05$とした．

## 3. 結　果

本研究の結果，第2次調査時の対象者の特性を男女別に表1に示した．2.5 Mets以上の余暇身体活動時間は男性の方が有意に高かった．一方，2.5 Mets以上の総身体活動時間や2.5 Mets以上の家事・仕事身体活動時間においては女性の方が高い値を示した．4.5 Mets以上の総身体活動時間には有意な性差は認められなかった（表1）．

図表1　対象者の特性

| | 男性 (n= 339) | 女性 (n= 329) | p |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| 年齢 | 67.5 ± 5.4 | 68.2 ± 5.6 | 0.099 |
| BMI | 22.9 ± 2.6 | 22.8 ± 2.9 | 0.419 |
| MMSE | 28.2 ± 1.6 | 28.3 ± 1.7 | 0.322 |
| 教育年数（年） | 11.7 ± 2.8 | 10.5 ± 2.2 | <0.0001 |
| 身体活動時間（分／日） | | | |
| 2.5Mets以上 | | | |
| 総身体活動時間（分／日） | 149.9 ± 110.7 | 222.7 ± 104.9 | <0.0001 |
| 余暇身体活動時間（分／日） | 48.9 ± 49.1 | 30.2 ± 40.7 | <0.0001 |
| 家事・仕事身体活動時間（分／日） | 101.0 ± 112.4 | 192.5 ± 104.1 | <0.0001 |
| 4.5Mets以上 | | | |
| 総身体活動時間（分／日） | 35.7 ± 55.2 | 28.6 ± 44.0 | 0.069 |
| 既往歴（%） | | | |
| 高血圧 | 114 (33.6) | 118 (36.1) | 0.506 |
| 狭心症・心筋梗塞 | 26 (7.7) | 27 (8.3) | 0.788 |
| 高脂血症 | 54 (16.0) | 88 (26.9) | 0.001 |
| 糖尿病 | 37 (10.9) | 18 (5.5) | 0.011 |
| 脳卒中 | 19 (5.6) | 8 (2.5) | 0.040 |
| 慢性関節リウマチ | 29 (8.6) | 60 (18.4) | 0.000 |

性差の検定は，連続変数の場合はt検定を，カテゴリー変数の場合は$\chi 2$検定を用いた．2.5Mets以上の総身体活動時間＝2.5Mets以上の余暇身体活動時間＋2.5Mets以上の家事・仕事身体活動時間．

追跡期間中MMSE得点が27点以下に低下した人は，男性82（24.9%）人，女性76（22.4%）人であった．また，ロジスティック回帰分析の結果では，女性の場合，家事・仕事身体活動時間が上位群（毎日150分以上）に比べ下位群（毎日150分未満）の方がMMSE得点の27点以下への低下リスクが約2倍であった（オッズ比：1.878, 95%信頼区間：1.022-3.452, p= 0.0423）．しかし，2.5Mets以上の総身体活動時間や2.5Mets以上の余暇身体活動時間および4.5Mets以上の総身体活動時間はMMSE得点の27点以下への低下と関連は認められなかった．また，男性の場合はどの項目においても有意な関連が認められなかった（表2）．

## 4. 考察

本研究では，無作為抽出された地域在住中高年者を対象として2.5 Mets以上の総身体活動時間を4.5 Mets以上の身体活動時間，2.5 Mets以上の余暇や家事・仕事身体活動時間に分け，それぞれ認知機能との関連について検討を行った．その結果，2.5 Mets以上の家事・仕事身体活動時間が毎日150分未満である女性は，認知機能の低下するリスクが約2倍となり，普段から家事を含めた仕事身体活動量を一定に保つことは認知機能低下の予防に繋がる可能性が示唆された．

近年，毎日の雑用や介護などで多くのエネルギーを消費している高齢者は，加齢による認知機能低下が生じにくいことが明らかになった[15]．運動と思わずに行っていることでも，心拍数を上げ，血流を増加させる効果があるとしている．また，正式な運動プログラムが優れていることに変わりはないが，残りの時間の活動の重要性を見逃してはならないと指摘している．本研究におい

表2 MMSEの得点と身体活動との関連

| 項目 | | | n (%) | オッズ比 | 95% 信頼区間 | p |
|---|---|---|---|---|---|---|
| 男性 | | | | | | |
| | 2.5Mets 以上 | | | | | |
| | 総身体活動時間 | 下位群 | 168 (49.6) | 0.981 | 0.550 - 1.749 | 0.948 |
| | | 上位群 | 171 (50.4) | 1 | Referent | |
| | 余暇身体活動時間 | 下位群 | 167 (50.6) | 1.263 | 0.699 - 2.282 | 0.440 |
| | | 上位群 | 163 (49.4) | 1 | Referent | |
| | 仕事身体活動時間 | 下位群 | 169 (50.6) | 0.652 | 0.362 - 1.174 | 0.154 |
| | | 上位群 | 165 (49.4) | 1 | Referent | |
| | 4.5Mets 以上 | | | | | |
| | 総身体活動時間 | 下位群 | 166 (49.4) | 1.024 | 0.578 - 1.816 | 0.935 |
| | | 上位群 | 170 (50.6) | 1 | Referent | |
| 女性 | | | | | | |
| | 2.5Mets 以上 | | | | | |
| | 総身体活動時間 | 下位群 | 156 (48.5) | 1.01 | 0.550 - 1.856 | 0.974 |
| | | 上位群 | 166 (51.5) | 1 | Referent | |
| | 余暇身体活動時間 | 下位群 | 160 (50.0) | 1.032 | 0.575 - 1.853 | 0.917 |
| | | 上位群 | 160 (50.0) | 1 | Referent | |
| | 仕事身体活動時間 | 下位群 | 158 (49.2) | 1.878 | 1.022 - 3.452 | 0.042 |
| | | 上位群 | 163 (50.8) | 1 | Referent | |
| | 4.5Mets 以上 | | | | | |
| | 総身体活動時間 | 下位群 | 161 (50.2) | 1.476 | 0.819 - 2.659 | 0.195 |
| | | 上位群 | 160 (49.8) | 1 | Referent | |

解析方法：各身体活動は上位群，下位群の2分位によってカテゴリー化した．年齢，既往歴，（高血圧，狭心症・心筋梗塞，高脂血症，糖尿病，脳卒中，慢性関節リウマチ），教育年数を調整したロジスティック回帰分析を用いた．

て女性で，家事を含めた仕事身体活動時間と認知機能との関連が認められたことは，余暇活動の時間が短くても家事などで2.5 Mets以上の身体活動時間を維持することで多くのエネルギーを消費し，認知機能低下を予防できる可能性が示唆されたと考えられる．

一方，Rovioらの報告[10]では，認知機能の低下は仕事身体活動との関連は認められず余暇身体活動との関連について認めている．その原因として，退職後の身体活動内容の変化や仕事の機械化による仕事身体活動の強度が低いことを指摘している．本研究において男性の場合，仕事身体活動と認知機能低下との関連が認められなかったのは先行研究と同じ原因が考えられる．

身体活動の内容は性差を含め加齢にともなってその内容が変化し，生活に現れるそれぞれの身体活動が示す割合も変わっていく．そのため，それらの要因を考慮し，認知機能のどの側面と関連しているかについてさらなる検討が望まれる．

## 5. 結　論

地域在住の60歳以上の男女を対象とし縦断的研究により，認知機能と家事・仕事身体活動および余暇身体活動との関連について検討した．2.5 Mets以上の家事・仕事身体活動時間が毎日150分未満の女性高齢者は，150分以上である女性高齢者と比べて認知機能の低下するリスクが約2倍であった．

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＊参考文献

1) Kramer, A. and Kirk, I. : Capitalizing on cortical plasticity : influence of physical activity on cognition and brain function. Trends Cogn Sci. 11 (8) : 342-348, 2007.
2) Larson, E.B., Wang, L., Bowen, J.D. et al. : Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Ann. In- tern. Med. 144 (2) : 73-81, 2006.
3) Lytle, M.E., Vander, Bilt, J., Pandav, R.S. et al. : Exercise level and cognitive decline : the MoVIES project. Alzheimer Dis. Assoc. Disord. 18 (2) : 57-64, 2004.
4) Weuve, J., Kang, J.H., Manson, J.E. et al. : Physical activity, including walking, and cognitive function in older women. JAMA 292 : 1454-1461, 2004.
5) Laurin, D., Verreault, R., Lindsay, J. et al. : Physical activity and risk of cognitive impairment and dementia in elderly persons. Arch. Neurol. 58 (3) : 498-504, 2001.
6) Rovio, S., Kåreholt, I., Helkata, E. et al. : Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. Lancet Neurol. 4 : 705-711, 2005.
7) Colcombe, S., Kramer, A.F. : Fitness effects on the cognitive function of older adults : a meta-analytic study. Psychol. Sci. 14 (2) : 125-30, 2003.
8) Verghese, J., Lipton, R.B., Katz, M.J. et al. : Leisure activities and the risk of dementia in the elderly. N. Engl. J. Med. 348 : 2508-2516, 2003.
9) Anttila, T., Helkala, E.L., Kivipelto, M. et al. : Midlife income, occupation, APOE status, and dementia : a population-based study. Neurology 59 : 887-893, 2002.
10) Rovio, S., Kåreholt, I., Viitanen, M. et al. : Work-related physical activity and the risk of dementia and Alzheimer's disease. Int. J. Geriatr. Psychiatry 22 (9) : 874-82, 2007.
11) Shimokata, H., Ando, F. and Niino, N. : A new comprehensive study on aging-the National Institute for Longevity Sciences, Longitudinal Study of Aging (NILS-LSA) . J. Epidemiol 10 (1 Suppl) : S1-9, 2000.
12) Iwai, N., Yoshiike, N., Saitoh, S. et al. : Leisure-time physical activity and related lifestyle characteristics among middle-aged Japanese. J. Epidemiol. 10 : 226-233. 2000.
13) Folstein, M.F., Folstein, S.E. and McHugh, P.R. : "Mini-mental state" : a practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12 : 189-198, 1975.
14) Sid, E., Joy, D., Glenn, E. et al. : Detecting Dementia with the Mini-Mental State Examination in Highly Educated Individuals Arch. Neurol. 65 (7) : 963-967, 2008.
15) Middleton, L.E., Manini, T.M., Simonsick, E.M. et al. : Activity Energy Expenditure and Incident Cognitive Impairment ir Older Adults. Arch. Intern. Med. 171 (14) : 1251-1257, 2011.