BMJ open

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2011-000773
Article Type:	Research
Date Submitted by the Author:	06-Jan-2012
Complete List of Authors:	Kawashima, Shoji; Nagoya City University, Neurology Ito, Kengo; National Center for Geriatrics and Gerontology, Clinical and Experimental Neuroimaging Kato, Takashi; National Center for Geriatrics and Gerontology, Clinical and Experimental Neuroimaging
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Radiology and imaging, Diagnostics
Keywords:	Adult neurology < NEUROLOGY, Dementia < NEUROLOGY, Nuclear radiology < RADIOLOGY & IMAGING

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

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[*]Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI). As such, the investigators within ADNI contributed to the design and implementation of ADNI and/or provided data, but did not participate in the analyses or writing of this report. ADNI investigators include (complete listing available at www.loni.ucla.edu ¥ADNI¥Collaboration¥ADNI_Authorship_list.pdf).

[**]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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Keywords:

mild cognitive impairment; Alzheimer disease; neuropsychological tests; fluorodeoxyglucose; positron-emission tomography

Number of references = 35; number of figures = 4; number of tables = 3

Word count for the title = 19; word count for the abstract = 300; word count for the text = 3278

ARTICLE SUMMARY

Article focus

1) To aim at identifying neuroimaging measures associated with cognitive changes in healthy elderly and MCI patients, longitudinal multi-centre studies are ongoing in several countries.

2) 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 multi-centre studies (ADNI), are clarified.

Key messages

1) In association with criteria, SEAD-J recruited more patients with pre-dementia AD who had severe verbal memory deficits compared with ADNI.

2) 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.

3) 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

1) This study reinforces that the results of multi-centre studies should be interpreted carefully considering the impact of baseline profiles.

2) The present results were based on the analysis of data at the time of inclusion.

ABSTRACT

Background: Mild cognitive impairment (MCI) is considered to represent a transitional stage between aging and Alzheimer's Disease (AD). To aim at identifying neuroimaging measures associated with cognitive changes in healthy elderly and MCI patients, longitudinal multi-centre 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 were enrolled from United States.

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.

Conclusion: 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 multi-centre studies for early diagnosis of AD should be interpreted carefully considering profiles of patients.

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 aging 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 toward 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 multi-centre 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 United States and Canada (for additional information about ADNI, see 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 multi-centre 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

A total of 114 patients with MCI (mean age (± standard deviation), 70.8±7.5 years; 50 men, 64 women) were enrolled from nine facilities in Japan. A total of 56 normal age-matched subjects (20 men, 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 dataset of clinical and FDG-PET findings over a follow-up period of 2 years have recruited.

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, a LM II part 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

Datasets of clinical and baseline FDG-PET have 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/). Datasets 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 (≤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 normalized 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 normalized 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 (MediPhysics.com), then Z scores of FDG uptake were calculated voxel by voxel.

Three-dimensional stereotactic surface projections (3D-SSP)[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 datasets 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, 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 version 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 χ^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 were summarised in Table. (Table 1, Table 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 (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.

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

MMSE, Mini-Mental Status Examination; CDR memory, memory subscore for Clinical Dementia Rating; WMS-R LM I, Logical Memory part I subset of the Wechsler Memory Scale Revised; WMS-R LM II, Logical Memory part II subset of the Wechsler Memory Scale Revised; GDS, Geriatric Depression Scale; HAM-D, Hamilton Depression Rating Scale; *, see materials and methods.

Table 2 Demographic characteristics of patients at the time of inclusion

	SEAD-J	ADNI	p
Age (yrs.)	70.8±7.5	75.2±7.1	p<0.001
Gender (M:F)	50: 64	134: 66	p<0.001
Education (yrs.)	11.5±3.0	15.8±2.9	p<0.001
MMSE	26.4±1.9	27.2±1.7	p<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	p<0.001
GDS	4.3±2.2	1.6±1.4	p<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).

Baseline FDG-PET: group comparisons and correlation analyses

Compared to 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) (Fig. 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 (Fig. 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 (Fig. 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 (Fig. 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 correlations in the precuneus and left medial temporal region (Fig. 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 (Fig. 4A). As for correlations with age, both studies showed an inverse correlation in bilateral medial frontal regions (Fig. 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% versus 13.5%; χ^2=5.33; p<0.05). Conversely, conversion ratio over 2 years showed no difference between studies (SEAD-J, 35.6%; ADNI, 33.3%; χ^2=0.097; p=0.77). Comparing the baseline profiles associated with 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.

Table 3 Differences in baseline profiles between the converters to Alzheimer's disease and non-converters

	SEAD-J		ADNI	
1 year conversion	conv / non-conv		conv / non-conv	
MMSE	25.3±1.3 / 26.6±1.9	p=0.002	26.8±1.8 / 27.2±1.7	N.S.
Modified MMSE	21.6±1.3 / 22.6±1.8	p=0.012	21.8±1.7 / 22.5±1.5	N.S.
WMS-R LM	0.7±1.3 / 1.9±1.8	p=0.003	2.5±2.3 / 4.2±2.7	p=0.004
GDS	4.3±2.0 / 4.2±2.4	p=0.003	1.3±1.4 / 1.7±1.4	N.S.
AGE (yrs.)	70.6±6.9 / 71.6±6.7	N.S.	75.5±6.1 / 75.7±7.3	N.S.
Education (yrs.)	12.1±3.1 / 11.5±3.0	N.S.	15.8±2.8 / 15.9±2.9	N.S.
1-2 year conversion	conv / non-conv		conv / non-conv	
MMSE	25.9±1.8 / 26.4±1.9	p=0.01	27.1±1.6 / 27.3±1.6	N.S.
Modified MMSE	22.1±1.5 / 22.5±2.0	N.S.	22.5±1.5 / 22.5±1.4	N.S.
WMS-R LM	1.6±1.9 / 1.9±1.9	N.S.	3.8±2.7 / 4.3±2.7	N.S.
GDS	4.9±2.6 / 3.9±2.1	N.S.	1.6±1.2 / 1.5±1.4	N.S.
AGE (yrs.)	70.9±6.4 / 71.5±6.5	N.S.	73.7±7.6 / 75.9±6.8	N.S.
Education (yrs.)	12.4±3.4 / 11.7±3.1	N.S.	16.6±2.5 / 15.8±2.9	N.S.

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; conv, AD converters; non-conv, AD non-converters; N.S., no significance

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. i.e., 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, a 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 aging 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. However, there was no difference in conversion ratio seen within 2 years of follow-up period. 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.

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 datasets at the time of inclusion. To clarify further association between each patient' profile and risk of AD conversion, multimodal analyses of data are needed for longer follow-up period.

In conclusion, our study reinforces that different inclusion criteria provided heterogeneity in baseline profiles of MCI patients. SEAD-J included patients with more severe verbal memory deficits compared with ADNI. Furthermore, AD converters in SEAD-J within 1 year after inclusion showed more severe decrease of FDG uptake in bilateral inferior parietal regions compared with converters during the following year. The severity of memory deficit might cause increase of the rapid AD conversion. Therefore, the results of multicenter studies should be interpreted with consideration of the impact of baseline profile on patient samples.

Contributorship

Shoji Kawashima; substantial contributions to conception and design, acquisition of data, analysis, and drafting the article.

Kengo Ito; conception and design, acquisition of data, and drafting the article.

Takashi Kato; conception and design, acquisition of data, analysis, and drafting the article.

Data Sharing

There is no additional data available.

Acknowledgments

The authors thank Michio Senda, Kazunari Ishii, Kenji Ishii, Hidenao Fukuyama, Yasuomi Ouchi, Kennichi, Meguro, Yukihiko Washimi, Maeda Kiyoshi, Wataru Okumura, Yoshio Mitsuyama, Kennichi Shimada for their technical assistance and data acquisition of SEAD-J.

Competing interests:

None

Funding:

SEAD-J was supported by the Health Labour Sciences Research Grant from the Ministry of Health, Labour, and Welfare of Japan (H17-Tyojyu-023) and the Research Funding for Longevity Sciences from National Center for Geriatrics and Gerontology, Japan. Data collection for ADNI was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI; Principal Investigator: Michael Weiner; NIH grant U01 AG024904). ADNI was funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering (NIBIB), and through generous contributions from the following: Pfizer Inc., Wyeth Research, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, Merck & Co. Inc., AstraZeneca AB, Novartis Pharmaceuticals Corporation, Alzheimer' Association, Eisai Global Clinical Development, Elan Corporation plc, Forest Laboratories, and the Institute for the Study of Aging, with participation from the U.S. Food and Drug Administration. Industry partnerships are coordinated through the Foundation for the National Institutes of Health. The grantee organisation is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory of Neuro Imaging at the University of California, Los Angeles.

Ethics approval:

SEAD-J was approved by the medical ethics committee of the National Center for Geriatrics and Gerontology.

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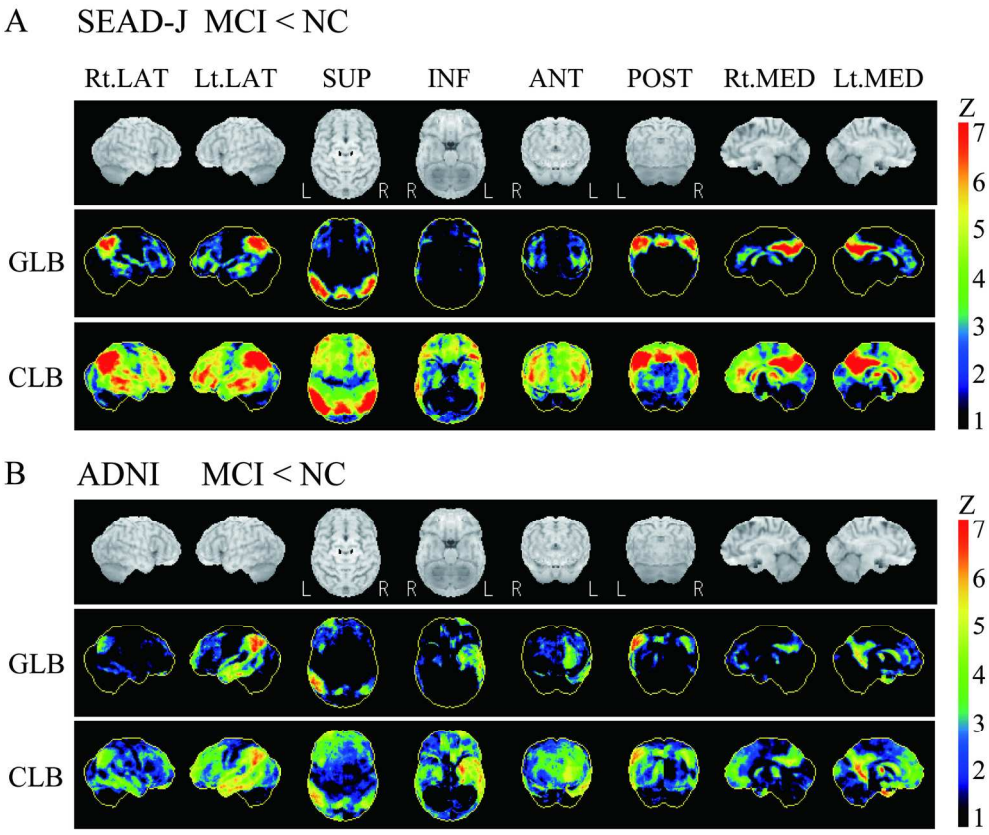
FIGURE LEGENDS

Fig. 1 3D-SSP analyses of baseline FDG-PET in SEAD-J (A) and 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 AD (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.

Fig. 2 3D-SSP analyses of baseline FDG-PET in SEAD-J. These are the results of group comparisons between 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.

Fig. 3 Statistical parametric mapping of the brain regions correlated with baseline profiles in SEAD-J and ADNI. The regions displayed in red indicate significant regional hypometabolism ($p<0.05$). A) Correlation between lower MMSE scores and glucose metabolism. B) Correlation between lower WMS-R LM scores and glucose metabolism.

Fig. 4 Statistical parametric mapping of the brain regions correlated with baseline profiles in SEAD-J and ADNI. The regions displayed in red indicate significant regional hypometabolism ($p<0.05$). A) Inverse correlation between GDS scores and glucose metabolism. B) Inverse correlation between age and glucose metabolism.



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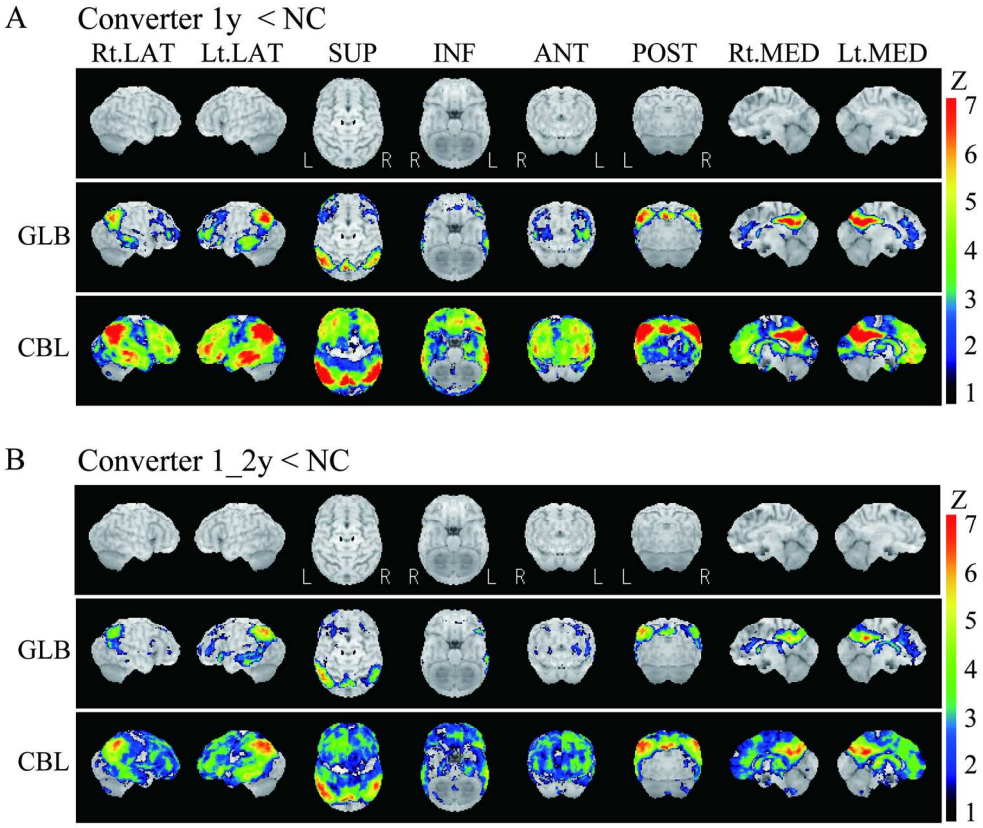

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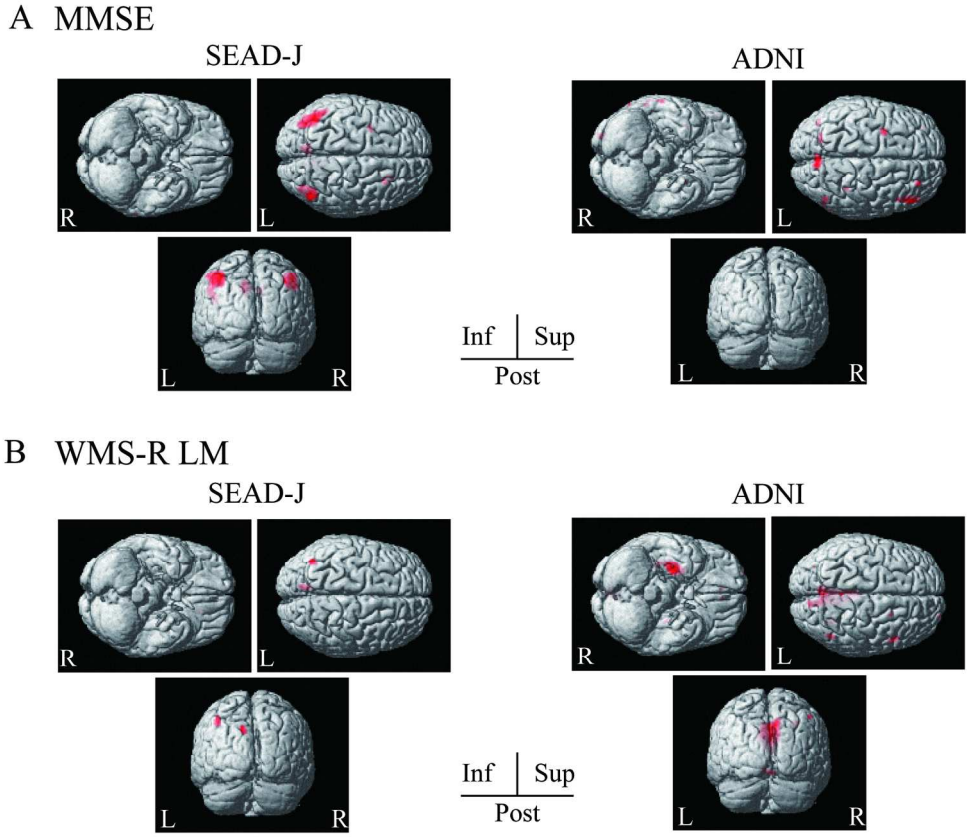

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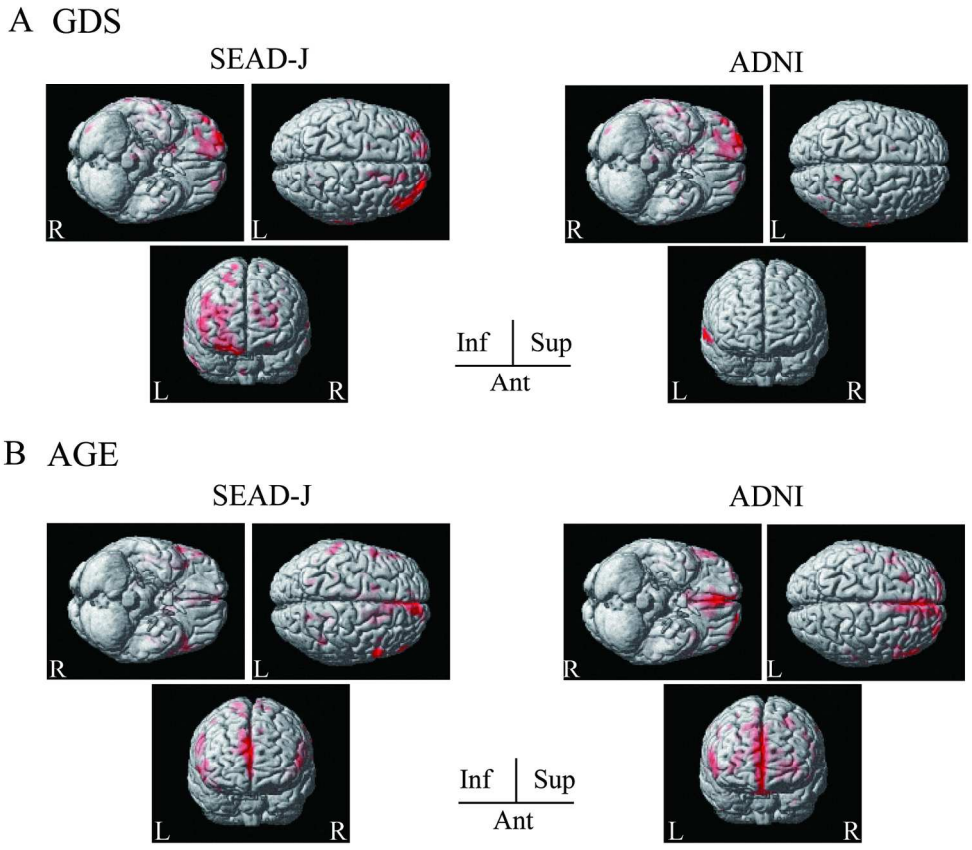

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6
Methods			
Study design	4	Present key elements of study design early in the paper	Page 7-9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5, 7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 7-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 7-9
Bias	9	Describe any efforts to address potential sources of bias	Page 7-9
Study size	10	Explain how the study size was arrived at	Page 7-9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 7-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 9
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed	Page 10

		eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 10
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	Page 10-14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 10-14
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 10-14
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 15-17
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 16-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 17-18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.