PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Inclusion criteria provide heterogeneity in baseline profiles of patients with mild cognitive impairment: Comparison of two prospective cohort studies
AUTHORS	Shoji, Kawashima; Nagoya City University, Neurology Kengo, Ito; National Center for Geriatrics and Gerontology, Clinical and Experimental Neuroimaging Takashi, Kato; National Center for Geriatrics and Gerontology, Clinical and Experimental Neuroimaging

VERSION 1 - REVIEW

REVIEWER	Danielle Harvey Associate Professor University of California, Davis USA
REVIEW RETURNED	03-Feb-2012

THE STUDY	Some sentences and choice of wording are awkward, so the meaning may get lost. An example would be "data were recruited". I would think "data were acquired" would be more clear.
GENERAL COMMENTS	The authors might want to clarify in the Setting and Participants section of the abstract that there were 200 ADNI patients with FDG-PET (since ADNI recruited ~400 MCI patients).

REVIEWER	Alan Zonderman NIA
REVIEW RETURNED	15-Feb-2012

GENERAL COMMENTS	The authors compared the baseline characteristics and the rates of Alzheimer's disease in two separate multi-site studies of small samples conducted in Japan and United States. They found that the Japanese study recruited patients with poorer verbal memory performance and greater depressive symptoms. They also found that the Japanese sample had less FDG activity in the precuneus, posterior cingulate, parietotemporal, and frontal areas. The authors seem to have in mind several purposes for this manuscript. First, they examine the extent to which inclusion and diagnostic criteria are associated with the incidence of Alzheimer's disease. This seems self evident. It would be news if the incidence of Alzheimer's disease was not greater in groups with greater susceptibility symptoms. Second, they compare national differences between multi-site studies to show that inclusion criteria is associated with brain activity (or lack thereof). Finally, they show that severity of Alzheimer's disease assessed by neuropsychological tests were a function of the initial patient recruitment criteria.

	It is unclear how this manuscript contributes to our understanding of the pathogenesis of Alzheimer's disease or to our understanding of the predictors of who is at risk for Alzheimer's disease or the rate of change in the disease after it is established. It is self-evident (perhaps axiomatic) that sample selection is a crucial consideration in determining the results; perhaps more importantly, it is crucial in how we interpret the results and to whom the results generalize.

VERSION 1 – AUTHOR RESPONSE

Response to the managing editor:

1) The authorship should be clarified. If the ADNI group had any direct involvement in conducting the specific research reported in the paper then they should be included in the contributorshp statement but not in the byline (list of authors) unless they were full authors.

Following the reviewer's comment, we excluded the ADNI group from list of authors, and included them in the contributorship statement. The investigators within ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. We had completely followed the review for ADNI Publications Policy. Before submitting, our paper was reviewed by ADNI Data and Publications Committee (ADNI DPC). ADNI DPC approved it acceptable for submission to a journal.

2) The funding statement should include information relevant to this article - i.e. who funded the article to be written? If the authors are part of SEAD-J is OK to report that funding; only report the ADNI funding if you are part of the ADNI group.

Following the reviewer's comment, we rewrote the funding statement. Because of the authors are part of the SEAD-J group, not are ADNI group, we limited the funding information relevant to this article.

3) The information provided by the asterisked statements about where the data came from should be in the methods.

Following the reviewer's comment, we added the statements about where the data came from.

"Dataset of SEAD-J used was obtained from the nine facilities in Japan. All data was checked and quality controlled at National Center for Geriatrics and Gerontology."
(revised manuscript; page 7, lines 3-4)

"Data used in the preparation of this article were obtained from the ADNI database (www.loni.ucla.edu/ADNI)."
(revised manuscript; page 7, lines 21-22)

4) The conclusions of the paper are quite basic, as the second reviewer indicates: the two studies had different inclusion criteria, the participants have different baseline characteristics and so the studies are likely to produce different outcomes and messages. The paper would therefore be strengthened if you could explain more clearly why this paper was written.

We fully agree with the reviewer. We rewrote ambiguous conclusions following reviewer's suggestion as below.

"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 multi-centre 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."
(revised manuscript; page 17, lines 15-23)

Response to the reviewer: Associate Professor Danielle Harvey

1) Some sentences and choice of wording are awkward, so the meaning may get lost. An example would be "data were recruited". I would think "data were acquired" would be more clear.

Following the reviewer's comment, we rewrote the choice of wording as below.

"All dataset of clinical and FDG-PET findings over a follow-up period of 2 years have acquired."
(revised manuscript; page 7, lines 8-9)

2) The authors might want to clarify in the Setting and Participants section of the abstract that there were 200 ADNI patients with FDG-PET (since ADNI recruited ~400 MCI patients).

Following the reviewer's comment, we rewrote the setting and participants section of the abstract as below.

"A total of 200 patients in ADNI patients with FDG-PET were enrolled from United States."
(revised manuscript; page 4, lines 11-12)

Response to the reviewer: Dr. Alan Zonderman

1) The authors seem to have in mind several purposes for this manuscript. First, they examine the extent to which inclusion and diagnostic criteria are associated with the incidence of Alzheimer's disease. This seems self evident. It would be news if the incidence of Alzheimer's disease was not greater in groups with greater susceptibility symptoms. Second, they compare national differences between multi-site studies to show that inclusion criteria is associated with brain activity (or lack thereof). Finally, they show that severity of Alzheimer's disease assessed by neuropsychological tests were a function of the initial patient recruitment criteria.

We agree with the reviewer's comment that our conclusion seems self evident. It is not novel proposal that inclusion and diagnostic criteria are associated with the incidence of Alzheimer's disease. However, to date, our research provides first evidence to demonstrate the impact of differences in criteria in two multi-center studies aimed at identifying neuroimaging measures in MCI and AD subjects. Furthermore, we thought our result is noteworthy in the point that the difference in AD conversion ratio was differed due to follow up period. We revealed that SEAD-J patients exhibited a significantly higher rate of conversion within 1 year after inclusion, on the contrary, there was no difference in conversion ratio within 2 years of follow-up. We added the new statement in discussion and rewrote conclusion as below following the reviewer's suggestions.

"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 Alzheimer's disease may not have greater difference in groups with greater susceptibility symptoms, if there are no operational criteria as for prevalence in genotype."
(revised manuscript; page 16, line 22- page 17, line 6)

"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 multi-centre 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."
(revised manuscript; page 17, lines 15-23)

2) It is unclear how this manuscript contributes to our understanding of the pathogenesis of Alzheimer's disease or to our understanding of the predictors of who is at risk for Alzheimer's disease or the rate of change in the disease after it is established. It is self-evident (perhaps axiomatic) that sample selection is a crucial consideration in determining the results; perhaps more importantly, it is crucial in how we interpret the results and to whom the results generalize.

We agree with the reviewer's comment. We rewrote the manuscript to associate the pathogenesis of Alzheimer's disease with FDG-PET findings in discussion section, and added a new reference as below.

"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 Alzheimer's disease may not have greater difference in groups with greater susceptibility symptoms, if there are no operational criteria as for prevalence in genotype."
(revised manuscript; page 16, line 22- page 17, line 6)

VERSION 2 – REVIEW

REVIEWER	Danielle Harvey, PhD Associate Professor UC Davis USA
REVIEW RETURNED	12-Mar-2012

THE STUDY	There are still a couple of places where the wording is awkward. For example, page 7, lines 18-21 and line 50. Suggested rewording include "All clinical and FDG-PET data over a follow-up period of 2 years have been acquired" and "Clinical and baseline FDG-PET data acquired from a total of 200..."