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Featured Article

Japanese and North American Alzheimer's Disease Neuroimaging Initiative studies: Harmonization for international trials

Takeshi Iwatsubo[a,b,*], Atsushi Iwata[c], Kazushi Suzuki[a], Ryoko Ihara[a], Hiroyuki Arai[d], Kenji Ishii[e], Michio Senda[f], Kengo Ito[g], Takeshi Ikeuchi[h], Ryozo Kuwano[h], Hiroshi Matsuda[i], Japanese Alzheimer's Disease Neuroimaging Initiative[1], Chung-Kai Sun[j], Laurel A. Beckett[k], Ronald C. Petersen[l], Michael W. Weiner[m], Paul S. Aisen[j], Michael C. Donohue[j], Alzheimer's Disease Neuroimaging Initiative

[a]*Unit for Early and Exploratory Clinical Development, The University of Tokyo Hospital, Tokyo, Japan*
[b]*Department of Neuropathology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan*
[c]*Department of Neurology, The University of Tokyo Hospital, Tokyo, Japan*
[d]*Department of Geriatrics, Tohoku University, Sendai, Japan*
[e]*Research Team for Neuroimaging, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan*
[f]*Division of Molecular Imaging, Institute of Biomedical Research and Innovation, Kobe, Japan*
[g]*Department of Clinical and Experimental Neuroimaging, National Center for Geriatrics and Gerontology, Obu, Japan*
[h]*Department of Molecular Genetics, Bioresource Science Branch, Center for Bioresources, Brain Research Institute, Niigata University, Niigata, Japan*
[i]*Integrative Brain Imaging Center, National Center for Neurology and Psychiatry, Kodaira, Japan*
[j]*Alzheimer's Therapeutics Research Institute, University of Southern California, San Diego, CA, USA*
[k]*Division of Biostatistics, Department of Public Health Sciences, University of California, Davis, Davis, CA, USA*
[l]*Department of Neurology, Mayo Clinic, Rochester, MN, USA*
[m]*Department of Veterans Affairs Medical Center, Center for Imaging of Neurodegenerative Diseases, University of California, San Francisco, CA, USA*

Abstract

Introduction: We conducted Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI) and compared the basic characteristics and progression profiles with those of ADNI in North America.
Methods: A total of 537 Japanese subjects with normal cognition, late amnestic mild cognitive impairment (LMCI), or mild Alzheimer's disease (AD) were enrolled using the same criteria as ADNI. Rates of changes in representative cognitive or functional measures were compared for amyloid positron emission tomography- or cerebrospinal fluid amyloid β(1–42)-positive LMCI and mild AD between J-ADNI and ADNI.
Results: Amyloid positivity rates were significantly higher in normal cognition of ADNI but at similar levels in LMCI and mild AD between J-ADNI and ADNI. Profiles of decline in cognitive or functional measures in amyloid-positive LMCI in J-ADNI (n = 75) and ADNI (n = 269) were remarkably similar, whereas those in mild AD were milder in J-ADNI (n = 73) compared with ADNI (n = 230).
Discussion: These results support the feasibility of bridging of clinical trials in the prodromal stage of AD between Asia and western countries.
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Keywords: Alzheimer's disease; ADNI; Mild cognitive impairment; Biomarker; Amyloid PET imaging; Harmonization; Japan

1. Background

The significance of neuroimaging and fluid biomarkers in the early diagnosis and prediction of clinical progression during the very early stages of Alzheimer's disease (AD)

[1]The full membership of the Japanese ADNI investigators is listed at https://humandbs.biosciencedbc.jp/en/hum0043-j-adni-authors.

*Corresponding author. Tel.: 81-3-5841-3541; Fax: 81-3-5841-3613.
E-mail address: iwatsubo@m.u-tokyo.ac.jp

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has been highlighted [1], as pathogenic molecules causative to AD (e.g., amyloid β [Aβ]) were discovered, and therapeutic strategies against the neurodegenerative process of AD (i.e., disease-modifying therapies [DMTs]) have been developed [2]. Because of the recent failures in large-scale clinical trials of DMTs in AD patients at the dementia stage [3–5], the target population of DMT trials is being shifted to earlier stages, i.e., mild cognitive impairment (MCI) [6] or even the asymptomatic stage (i.e., preclinical AD [7]), where the clinical progression is expected to be slower, and the drug efficacies harder to evaluate.

To develop methods to detect the progression of AD in its early stages (i.e., MCI and mild AD) in a multicenter trial setting using neuroimaging (e.g., positron emission tomography [PET] scan, magnetic resonance imaging [MRI]), and biomarkers (e.g., cerebrospinal fluid [CSF]) and establish a database delineating the natural history of the early stage of AD, AD Neuroimaging Initiative (ADNI) has been conducted in North America since 2004. ADNI has firmly established the basis for the current global clinical trials of DMTs for AD in its prodromal and mild stages [8].

A dramatic increase in the elderly population and those suffering from AD is also a common and imminent issue in Asian countries, especially Japan, where patients are already being involved in global clinical trials for AD DMTs. However, there have not been any large-scale observational studies of the early stages of AD including MCI in the Asian population, which has its own ethnic characteristics (e.g., lower prevalence of apolipoprotein E (*APOE*) ε4 alleles [9], difference in language and cultures). Furthermore, to validate the ADNI data obtained primarily in Caucasian populations in the United States, a replication of the ADNI study in a second cohort, especially in a non-Caucasian population, has long been awaited. To this end, we initiated the Japanese (J-) ADNI study, closely discussing the harmonization of the protocol and procedures with the ADNI core members from 2006. We launched J-ADNI as a multicenter, longitudinal observational study using an almost identical protocol to ADNI's in 2008. We have recently made publicly available the J-ADNI database obtained from 537 individuals of AD, MCI, and normal cognition (CN), supported in a database (National Bioscience Database Center, Japan) available for worldwide data sharing. In this article, we describe the basic characteristics and clinical progression profiles of the J-ADNI population and compare the data with those of ADNI to determine if any differences exist between the Japanese and North American populations with the goal of international harmonization for clinical trials of DMTs for AD.

2. Methods

2.1. J-ADNI participants

Approval for the J-ADNI study protocol (UMIN000001374) was obtained from the local ethics committees or institutional review committees at the 38 participating clinical sites, including the principal investigator's site (The University of Tokyo). Informed written consent was obtained from all participants at each clinical site.

To characterize the clinical, neuroimaging, and biomarker measures in subjects with CN, late amnestic MCI [6] (LMCI), or mild AD in the Japanese elderly population, volunteer participants between the ages of 60 and 84 years fluent in Japanese were diagnosed and enrolled using generally identical inclusion and exclusion criteria to those of ADNI [10]. Briefly, the subjects with LMCI or AD both had memory complaints, whereas CN had none. On Mini–Mental State Examination (MMSE), the range for CN and LMCI was 24–30 and for AD, 20–26 (all are inclusive). The Clinical Dementia Rating (CDR) global score for CN was 0, LMCI was 0.5 (memory domain 0.5 mandatory), and the rating for AD was 0.5 or 1. Delayed recall of the Logical Memory IIA subscale of the Wechsler Memory Scale-Revised was used for a memory criterion with cutoff scores based on education: For CN subjects, ≧9 for 16 years of education, ≧5 for 10–15 years, and ≧3 for 0–9 years. For subjects with LMCI or AD, Logical Memory IIA scores were ≦8 for 16 years of education, ≦4 for 10–15 years, and ≦2 for 0–9 years. The subjects with LMCI had to be largely intact with regard to general cognition and functional performance and could not meet diagnostic criteria for a dementia diagnosis, thus they were classified as single- or multi-domain amnestic MCI. J-ADNI did not recruit participants with early MCI, so this ADNI group was excluded from analysis. The subjects with mild AD had to satisfy the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for probable AD [11]. Psychoactive drugs were prohibited or restricted as defined in the protocol, and exceptions were approved and recorded. The participant should have Hachinski Ischemic Score of ≦4, and should not be depressed (Geriatric Depression Scale score ≦6). Of 715 people assessed for eligibility, 537 met criteria and were enrolled (Fig. 1).

At baseline, the following cognitive and functional measures based on the National Alzheimer's Coordinating Center Uniform Data Set, as used in ADNI, were examined: Digit Span, Category Fluency, Trail Making A and B, Digit Symbol Substitution Test of the Wechsler Adult Intelligence Scale III, Boston Naming Test, Clock Drawing Test, Neuropsychiatric Inventory-Q, AD Assessment Scale-Cognitive Subscale (ADAS-Cog), and Functional Assessment Questionnaire (FAQ). Audio-Visual Learning Test was not performed in J-ADNI. Participants who were CN or MCI were evaluated every 6 or 12 months for 36 months, and those with AD for 24 months, as in ADNI. Clinical conversion from LMCI to dementia was primarily diagnosed by clinical site investigators at every visit and verified by an adjudication committee.

All subjects received a structural MRI scan at 1.5 Tesla signal strength based on three-dimensional magnetization-

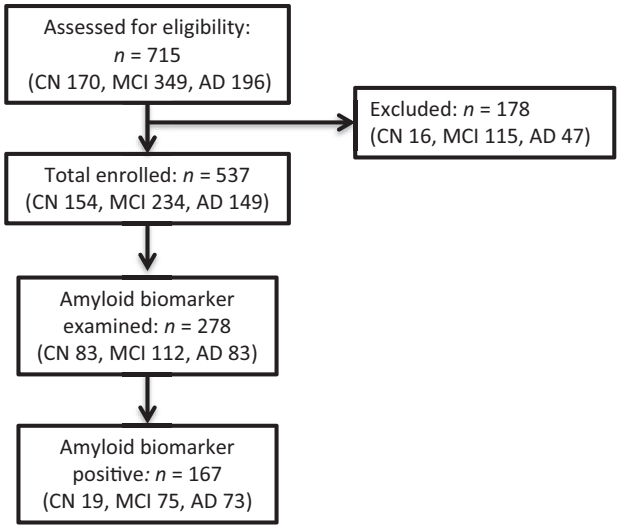

Fig. 1. Diagram showing the number and flow of participants in J-ADNI. Abbreviations: J-ADNI, Japanese Alzheimer's Disease Neuroimaging Initiative; CN, normal cognition; MCI, mild cognitive impairment; AD, Alzheimer's disease.

prepared rapid acquisition with gradient echo sequence using ADNI protocol at all visits [12]. Three-hundred and forty cases (63.3% of total) received a ^{18}F-fluorodeoxyglucose PET scan at baseline and had follow-up scans at every 6 or 12 months; 189 cases (35.2%) had a ^{11}C-Pittsburgh compound B (PiB) amyloid PET scan at baseline and had additional scans at every 12 months. One hundred and ninety-eight cases (36.9%) underwent a lumbar puncture at baseline, and some had another lumbar puncture at month 12. CSF samples were assayed for Aβ(1–42), total tau, and phosphorylated tau by using multiplex xMAP Luminex platform (Luminex Corp, Austin, TX) with Innogenetics (INNO-BIA AlzBio3; Ghent, Belgium) immunoassay kit-based reagent as validated previously [13] at the J-ADNI biomarker core at Niigata University. Blood samples were obtained at each visit, and plasma samples were stored at −80°C degrees. *APOE* genotyping was performed by using polymerase chain reaction as described [9].

All data uploaded by each site were transmitted online to the J-ADNI data center through a virtual private network and underwent standard quality check procedures. The primary outcome measures were the rates of progression from LMCI to AD as well as a variety of clinical and psychometric measures, and imaging and chemical biomarkers.

2.2. Statistical methods

Baseline characteristics were summarized by frequencies and percentages for categorical variables. Continuous variables were summarized by mean and standard deviation. Group comparisons for continuous variables were performed using the Wilcoxon rank-sum test. Fisher's exact test was used for categorical data. All tests were done under the nominal significance level $\alpha = 0.05$.

The progression of the continuous outcomes was modeled to assess differences between geographic region (i.e., J-ADNI and ADNI) using mixed models of repeated measures [14] controlling for age, *APOE* genotype, and education. The variance-covariance structure was selected by Akaike information criterion [15] from among those with heterogeneous or homogeneous variance, and unstructured, compound symmetric, or autoregressive order one correlation structures. Rates of conversion from amyloid-positive MCI to AD by region were estimated using Kaplan-Meier plots and compared using the log-rank test and the Cox proportional hazards model [16] controlling for age, *APOE*, and education. All hypotheses were tested at the two-sided significance level $\alpha = 0.05$. Statistical software *R* was used for statistical analysis.

Rates of change in representative cognitive composite measures were compared for amyloid-positive LMCI and mild AD individuals between the J-ADNI and ADNI populations. J-ADNI data were obtained from the National Bioscience Database Center Human Database, Japan (Research ID: hum0043.v1, 2016). ADNI data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

2.3. Assessment of amyloid positivity

Amyloid positivity was defined as visual reads of the PiB PET scans being not negative [17], or baseline CSF Aβ42 < 333 pg/mL in J-ADNI and as baseline AV45 (florbetapir) PET mean cortical standardized uptake value ratios (SUVRs) > 1.11 [18] or baseline CSF Aβ42 < 192 pg/mL in ADNI [13], respectively. SUVR of PiB in J-ADNI was calculated based on the J-ADNI PET images according to the published method, and the cutoff line has been defined at 1.48 [17]. J-ADNI used visual reads of PiB PET scans as criteria for amyloid deposition, because visual reads, not SUVR, has been approved for interpretation of PET images with ^{18}F-labeled amyloid PET diagnostic drugs, to which PiB presents similar distribution, by the Food and Drug Administration and by the Japanese guideline. The cutoff for CSF Aβ(1–42) in J-ADNI was determined to be 333 pg/mL by a Receiver Operating Characteristic analysis of baseline CSF Aβ(1–42) levels from 35 AD and 53 CN cases (specificity, 0.87; sensitivity, 0.89). The κ statistic was used to quantify agreement between dichotomous measurements (SUVR of PiB vs. CSF Aβ[1–42]) relative to what would be expected by chance in J-ADNI.

3. Results

3.1. Baseline characteristics of J-ADNI participants in comparison with ADNI

A total of 537 subjects (154 CN, 234 LMCI, and 149 mild AD), out of 715 screened, were enrolled at baseline in J-ADNI at 38 clinical sites during August 2008 and April 2012 and followed up until March 2014. Among these, 83 CN (54%), 112 LMCI (48%), and 83 mild AD (56%) were tested either by PiB PET or CSF assay for Aβ(1–42) for amyloid positivity. Nineteen CN (23% of tested), 75 LMCI (67%), and 73 mild AD (88%) were judged to be amyloid positive either by PET or CSF, a significantly lower rate than ADNI CN (44%, $P < .001$) but not significantly different from ADNI LMCI and mild AD (75% and 92%) (Fig. 1). Family history, however, was similar in the CN but more frequently reported in ADNI LMCI and mild AD (54% and 47%, respectively) compared to J-ADNI (26% and 30%).

A scatterplot of baseline mean cortical SUVR of PiB PET and CSF Aβ(1–42) levels from 81 J-ADNI participants who had both PET scan and CSF sampling at baseline demonstrated good agreement of these amyloid biomarkers ($\kappa = 0.73$) (Fig. 2). This was consistent with the previous ADNI results on PiB PET and CSF Aβ(1–42) [19] ($\kappa = 0.74$) and florbetapir and CSF Aβ(1–42) [20] ($\kappa = 0.72$), supporting our definition and interpretation of amyloid-positive cases in this study. The percentages of *APOE* ε4-positive individuals (i.e., homozygous or heterozygous) in the total CN, LMCI, and mild AD in J-ADNI were 24, 52, and 60%, and 25, 49, and 59% in those with amyloid biomarker data, respectively, which were at comparable levels to those with amyloid biomarker data in ADNI (28, 55, and 68%).

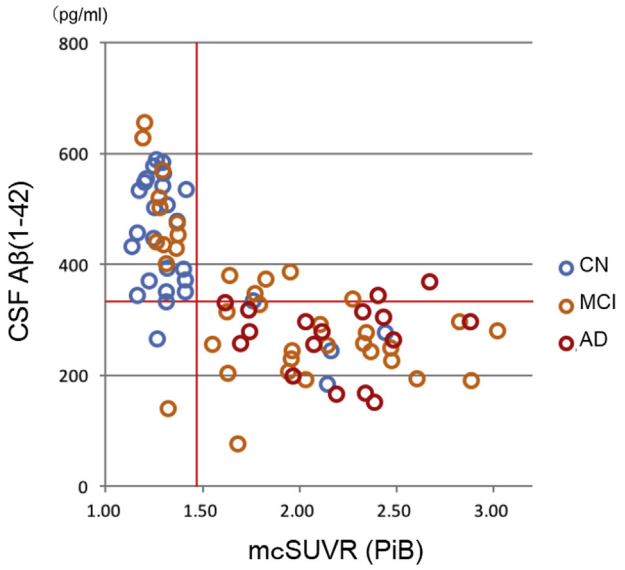

Fig. 2. Mean cortical ^{11}C-PiB SUVR (mcSUVR) plotted against CSF Aβ(1–42) in J-ADNI subjects. Cutoffs for PiB SUVR (1.48) and CSF Aβ(1–42) (333 pg/mL) are marked on each axis in red lines and have been defined as described in the text. Blue, orange, and red circles represent levels of each biomarker at baseline in individual J-ADNI subjects of CN, LMCI, and mild AD groups, respectively. Abbreviations: J-ADNI, Japanese Alzheimer's Disease Neuroimaging Initiative; CN, normal cognition; LMCI, late amnestic mild cognitive impairment; PiB, Pittsburgh compound B; CSF, cerebrospinal fluid; SUVR, standardized uptake value ratios; Aβ amyloid β; MCI, mild cognitive impairment.

The baseline characteristics of J-ADNI and ADNI participants with amyloid biomarker data are shown in Table 1. Of note, the mean age was younger in J-ADNI CN, and education in ADNI was higher in all three diagnostic groups; the percentages of mild AD individuals with CDR global score 0.5 and 1 were almost even at 48% and 51%, respectively, in ADNI, whereas those with score 0.5 were predominant (70%) compared with those with score 1 (30%) in J-ADNI ($P = .001$). J-ADNI participants with mild AD also had better mean baseline scores on ADAS-Cog (16.0 vs. 19.7) and FAQ (9.7 vs. 13.1) but not on other performance tests. LMCI and CN participants showed mixed results at baseline, with most mean scores similar but occasional significant differences, not consistent in direction.

3.2. Comparison of the progression profiles of J-ADNI and ADNI participants

Patients in the J-ADNI LMCI (234 cases enrolled, 232 at baseline) progressed to dementia in 12 months at a rate (95% confidence interval) of 28.8% (22.6%, 34.5%) per year, more rapidly than in ADNI (20.2% [16.7%, 23.5%]). The significantly higher rate of conversion to dementia in J-ADNI persisted until 18 months (39.7% [32.8%, 45.9%] in J-ADNI vs. 27.4% [23.4%, 31.1%] in ADNI), whereas the rate in ADNI caught up after 24 months, reaching 45.1% (38.0%, 51.3%) in J-ADNI and 40.9% (36.3%, 45.0%) in ADNI at 36 months, respectively (Fig. 3A). The progression of conversion in amyloid-positive LMCI showed a similar trend to that in the total LMCI (Fig. 3B): amyloid-positive J-ADNI LMCI (75 cases at baseline) progressed to dementia in 12 months at a rate (95% confidence interval) of 30.4% (18.9%, 40.2%) per year, more rapidly than in ADNI (24.7% [19.2%, 29.8%]). The higher rate of conversion to dementia in J-ADNI persisted until 18 months (43.4% [30.6%, 53.9%] in J-ADNI, and 31.2% [25.1%, 36.7%] in ADNI), and the rate in ADNI was relatively similar after 24 months, reaching 63.5% [49.9%, 73.4%] in J-ADNI and 60.0% [53.0%, 66.0%] at 36 months, respectively (Fig. 3B). In a Cox proportional hazards model adjusting for age, education, and *APOE* the hazard ratio (HR) for progression to dementia in J-ADNI compared with ADNI was HR = 1.28 [1.01 to 1.63, $P = .044$] among total LMCI; and HR = 1.06 [0.74 to 1.53, $P = .748$] among amyloid-positive LMCI.

Clinical trials for AD DMTs increasingly focus on the population of amyloid-positive LMCI (i.e., prodromal AD [21]) and mild AD. In this group, cognitive and functional decline are frequently used as a more sensitive endpoint

Table 1
Baseline characteristics of the J-ADNI and ADNI participants with amyloid biomarker information

Baseline diagnosis groups	CN			MCI			AD		
Cohorts	ADNI	J-ADNI		ADNI	J-ADNI		ADNI	J-ADNI	
Number of non-missing values	N = 402	N = 83	*P* value	N = 358	N = 112	*P* value	N = 251	N = 83	*P* value
Age (years)	73.71 (5.93)	67.93 (5.23)	<.001*	73.41 (7.55)	72.54 (5.82)	.185*	74.72 (8.06)	74.28 (6.24)	.564*
Education	16.39 (2.65)	13.86 (2.42)	<.001*	16.13 (2.84)	13.49 (2.84)	<.001*	15.50 (2.94)	12.61 (3.26)	<.001*
Pt gender			.399†			.187†			.097†
Male	190 (47%)	44 (53%)		218 (61%)	60 (54%)		146 (58%)	39 (47%)	
Family history	204 (51%)	36 (43%)	.23†	194 (54%)	29 (26%)	<.001†	119 (47%)	25 (30%)	.007†
ApoE4			.809†			.189†			.311†
0	289 (72%)	62 (75%)		161 (45%)	57 (51%)		79 (32%)	34 (41%)	
1	104 (26%)	19 (23%)		150 (42%)	47 (42%)		117 (47%)	35 (42%)	
2	9 (2%)	2 (2%)		47 (13%)	8 (7%)		52 (21%)	14 (17%)	
MMSE	29.04 (1.18)	29.24 (1.15)	.044*	27.23 (1.84)	26.62 (1.78)	.002*	23.27 (2.02)	22.53 (1.71)	.002*
CDR-SB	0.041 (0.142)	0.060 (0.164)	.232*	1.634 (0.933)	1.598 (0.922)	.726*	4.420 (1.640)	3.610 (1.510)	<.001*
CDR global						1†			.001†
0	402 (100%)	83 (100%)		1 (0%)	0 (0%)				
0.5				356 (99%)	112 (100%)		121 (48%)	58 (70%)	
1				1 (0%)	0 (0%)		129 (51%)	25 (30%)	
2							1 (0%)	0 (0%)	
FAQ	0.28 (1.04)	0.11 (0.47)	.067*	3.76 (4.38)	3.82 (4.29)	.516*	13.08 (6.94)	9.67 (5.57)	<.001*
ADAS-Cog11	5.92 (2.95)	4.55 (2.43)	<.001*	11.65 (4.72)	10.49 (4.41)	.023*	19.69 (6.91)	16.01 (4.93)	<.001*
ADAS-Cog13	9.24 (4.35)	7.64 (3.90)	.001*	18.81 (6.70)	19.24 (6.51)	.48*	30.02 (8.27)	27.25 (5.73)	.011*
GDS Scale	0.84 (1.10)	1.27 (1.32)	.003*	1.70 (1.38)	1.82 (1.48)	.585*	1.66 (1.43)	2.23 (1.59)	.003*
Category fluency Animal	20.46 (5.46)	19.58 (5.14)	.173*	16.47 (4.94)	14.54 (4.10)	<.001*	12.40 (5.02)	11.94 (4.07)	.342*
Category fluency Vegetables	14.36 (3.76)	16.22 (4.04)	.002*	10.80 (3.37)	11.19 (3.56)	.48*	8.17 (3.35)	9.96 (3.79)	.001*
TMT A	34.5 (11.9)	37.6 (12.7)	.02*	43.9 (21.3)	53.0 (25.2)	<001*	64.7 (35.6)	66.1 (32.0)	.315*
TMT B	85.3 (42.8)	95.3 (36.9)	<.001*	128.0 (72.0)	159.7 (78.1)	<.001*	197.7 (86.3)	199.3 (79.7)	.818*
BNT	28.03 (2.21)	28.98 (1.71)	<.001*	25.81 (3.87)	26.51 (4.18)	.003*	22.54 (5.93)	24.12 (5.28)	.021*
Clock drawing	4.647 (0.635)	4.765 (0.676)	.018*	4.159 (0.996)	4.339 (1.045)	.018*	3.380 (1.370)	4.000 (1.280)	<.001*
Amyloid positive	177 (44%)	19 (23%)	<.001†	269 (75%)	75 (67%)	.112†	230 (92%)	73 (88%)	.382†
CSF Aβ (1–42) pg/mL	199.9 (51.7)	467.8 (141.8)	‡	161.4 (52.6)	337.2 (134.3)	‡	139 (39)	270 (94)	‡

Abbreviations: J-ADNI, Japanese Alzheimer's Disease Neuroimaging Initiative; CN, normal cognition; PET, positron emission tomography; MCI, mild cognitive impairment; MMSE, Mini–Mental State Examination; CDR, Clinical Dementia Rating; ADAS-Cog, Assessment Scale-Cognitive Subscale; FAQ, Functional Assessment Questionnaire; CSF, cerebrospinal fluid; AD, Alzheimer's disease; Aβ, amyloid β; TMT, trail making test; BNT, Boston Naming Test; GDS, Geriatric Depression Scale; *APOE*, apolipoprotein E.

NOTE. Mean scores for age*, education*, number of females†, incidence of family history†, number of *APOE*ε4 alleles†, scores for MMSE*, CDR-SB*, CDR global score†, FAQ*, ADAS-Cog11*, ADAS-Cog13*, GDS*, Category Fluency–Animal and Vegetables*, TMT A and B*, BNT*, and Clock Drawing* are shown. Amyloid positive† denotes the number of individuals who were positive either for amyloid PET or CSF Aβ(1–42) in each group. Statistical tests used are shown as superscript of the *P* values.

*Wilcoxon test (standard deviation in parenthesis).

†Fisher's exact test (percentage in parenthesis).

‡Note that the cutoff values of CSF Aβ(1–42) in ADNI and J-ADNI were 192 and 333 pg/mL, respectively.

than progression to dementia. Moreover, decline may be less sensitive than baseline levels to biases from education or culture. To this end, we compared the progression profiles of the four major composite measures, representing cognition (MMSE and ADAS-Cog13), cognition and function (CDR-Sum of Boxes), and function in daily living (FAQ) in amyloid-positive LMCI and mild AD in J-ADNI and ADNI. The patterns in decline and the 3-year mean changes [95% confidence interval] in MMSE (−1.52/y [−1.89, −1.14]), CDR-SB (1.18/y [0.92, 1.45]), ADAS-Cog13 (2.73/y [1.91, 3.56]), and FAQ (3.01/y [2.36, 3.65]) in amyloid-positive MCI in J-ADNI were remarkably similar to those in ADNI (−1.40/y [−1.61, −1.18], 1.02/y [0.87, 1.16], 3.15/y [2.69, 3.62] and 2.93/y [2.58, 3.29], respectively), only with significantly lower score in MMSE at 12 months in J-ADNI (Fig. 4, left in each panel). Two-year mean changes in MMSE (−1.42/y [−2.02, −0.82]), CDR-SB (1.47/y [1.09, 1.85]), and ADAS-Cog13 (2.54/y [1.37, 3.72]) in amyloid-positive mild AD in J-ADNI were significantly slower than those in ADNI (−2.55/y [−2.93, −2.16], 1.92/y [1.66, 2.17], 5.88/y [5.11, 6.65], respectively) and that of FAQ (3.28/y [2.53,

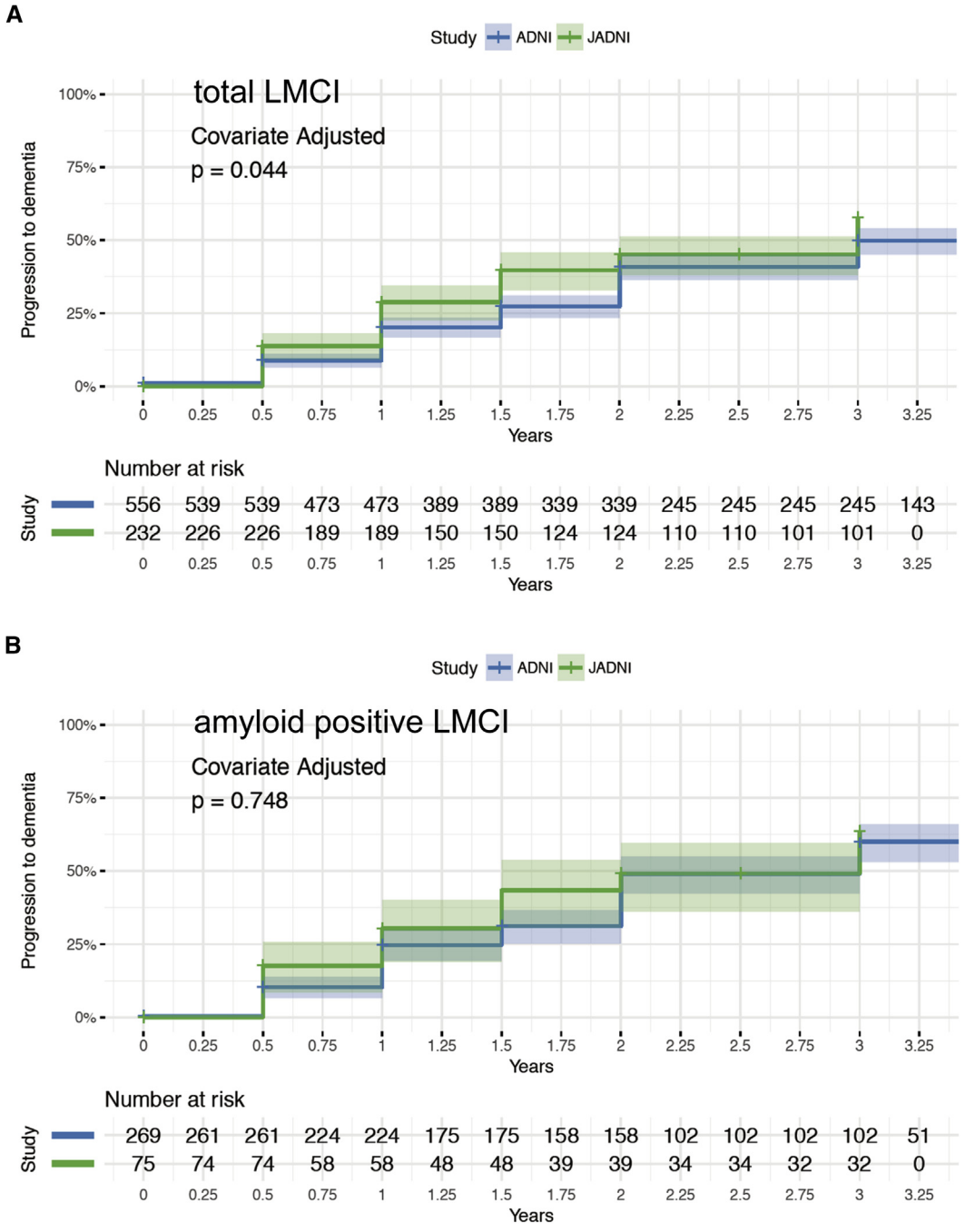

Fig. 3. Progression rates from LMCI to dementia in J-ADNI (green) and ADNI (blue) LMCI individuals over the 3-year follow-up. Panel (A) shows the progression patterns in total LMCI cases (J-ADNI, 232 cases; ADNI, 556 cases; including those without amyloid biomarker information; hazard ratio 1.28 [95% confidence interval 1.01 to 1.63, $P = .044$] adjusted for age, education, and *APOE* indicating nominally higher rate in J-ADNI). Panel (B) shows progression in amyloid-positive LMCI cases (J-ADNI, 75 cases; ADNI, 267 cases; adjusted hazard ratio 1.06 [95% confidence interval 0.74 to 1.53, $P = .748$]). Kaplan-Meier estimated rates over time (lines) with 95% confidence intervals (shaded areas) are shown, and the numbers at risk at each time point (years) are shown below the panel. Abbreviations: J-ADNI, Japanese Alzheimer's Disease Neuroimaging Initiative; LMCI, late amnestic mild cognitive impairment.

4.04]) in J-ADNI was similar to that (3.82/y [3.33, 4.31]) in ADNI (Fig. 4, right in each panel). The mean scores in CDR-SB, ADAS-Cog13, and FAQ in amyloid-positive mild AD in J-ADNI were significantly lower than those in ADNI at all four time points during the longitudinal follow-up. In contrast, CN populations in J-ADNI and ADNI exhibited minimal movements in the cognitive scores (*P* values for scores in amyloid-positive CN of J-ADNI vs. ADNI at baseline, 6, 12, 24, and 36 months were as follows: MMSE: 0.60, 0.13, 0.23, 0.19, and 0.50; ADAS-Cog13: 0.57, 0.48, 0.84, 0.98, and 0.34; CDR-SB: 0.47, 0.15, 0.16, 0.36, and 0.16; FAQ: 0.68, 0.21, 0.48, 0.50, and 0.92, respectively).

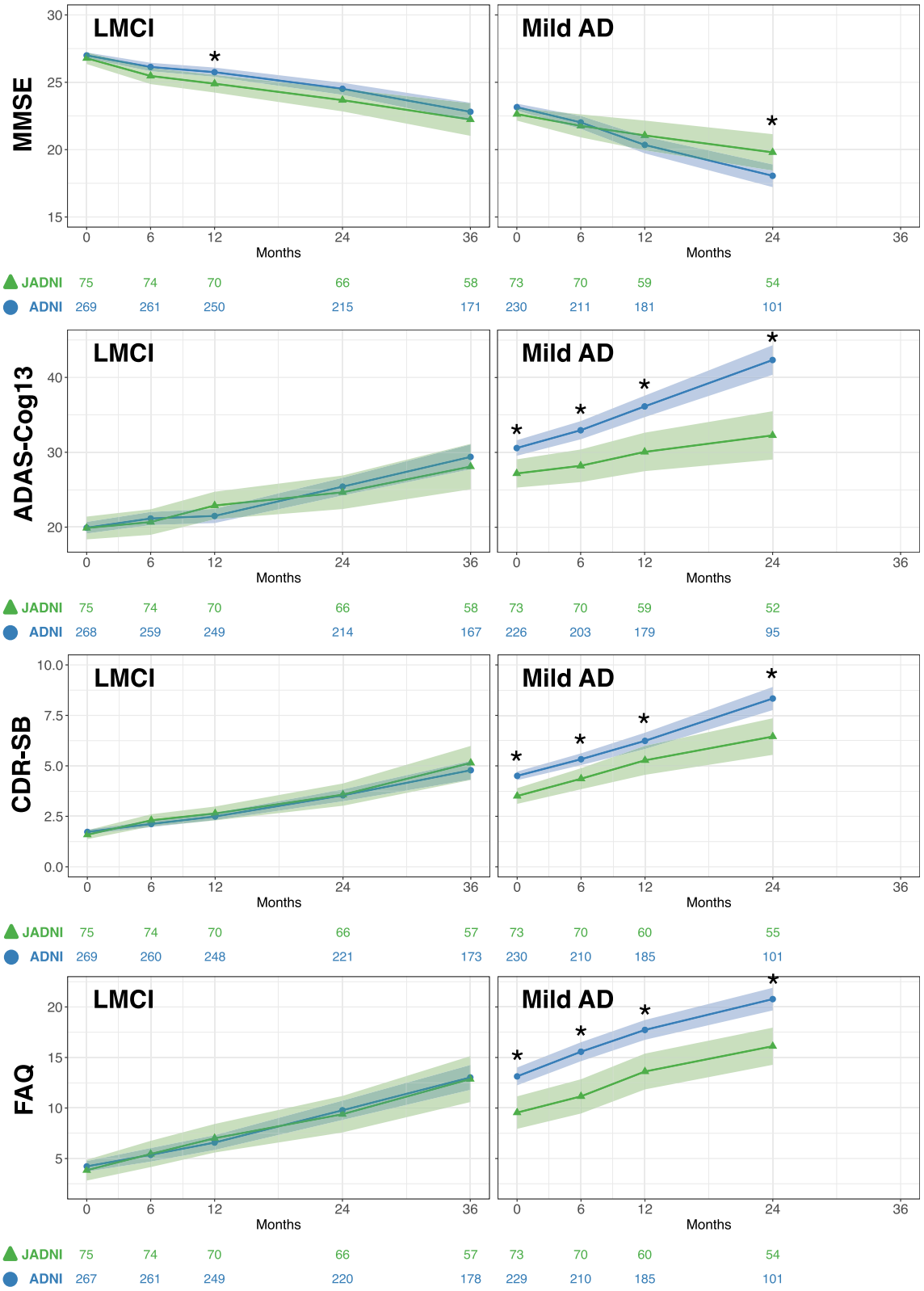

Fig. 4. Comparison of the progression profiles of MMSE, ADAS-Cog13, CDR-SB, and FAQ in subjects of amyloid-positive LMCI (left in each panel) and mild AD (right in each panel) in J-ADNI and ADNI. The mean trajectories over time in J-ADNI (green) and ADNI (blue) are plotted as modeled with MMRM controlling for age, *APOE*, and education. Scales in x-axis (duration, months) and y-axis (scores) were adjusted between LMCI and mild AD for each test (note that LMCI and mild AD groups were separately studied, without any transition or overlap in participants). Asterisks indicate statistically significant differences, and shaded areas in green and blue represent range of standard deviation. The numbers of subjects analyzed at each time point in J-ADNI and ADNI are shown below each panel. Abbreviations: J-ADNI, Japanese Alzheimer's Disease Neuroimaging Initiative; LMCI, late amnestic mild cognitive impairment; MMSE, Mini–Mental State Examination; CDR, Clinical Dementia Rating; ADAS-Cog, Assessment Scale-Cognitive Subscale; FAQ, Functional Assessment Questionnaire; MMRM, mixed models of repeated measures; AD, Alzheimer's disease.

4. Discussion

We show that J-ADNI successfully recruited cohorts of CN, subjects with LMCI and mild AD with generally comparable baseline characteristics and progression profiles with those of ADNI, with some differences. Notably, the four representative cognitive, clinical, and functional composite measures, i.e., MMSE, ADAS-Cog13, CDR-SB, and FAQ, showed almost similar progression profiles in terms of scores and rate of changes in amyloid-positive LMCI (i.e., MCI due to AD or prodromal AD [21]) between J-ADNI and ADNI, supporting the notion that LMCI due to AD in Japanese and Caucasian populations shares comparable characteristics beyond region or ethnicity and that the progression in cognitive and functional decline can be evaluated using the same methods and criteria. Even though there were some differences, e.g., in the education level, we have been able to define LMCI groups that are comparable in objective measures of cognitive and functional status and change that would be key measures in a clinical trial targeted at delaying these aspects of disease progression in this early disease stage. This supports the feasibility of multisite clinical trials in Caucasian and Asian (Japanese) populations, with such measures as outcomes in this particular group.

The faster LMCI to dementia conversion rate in the total as well as amyloid-positive J-ADNI LMCI populations compared with ADNI was the only apparent difference in terms of the symptomatic progression in LMCI (Fig. 3). This is not consistent with the similar levels of CDR-SB scores in amyloid-positive LMCI in J-ADNI and ADNI. One possible explanation is that J-ADNI clinicians defined the clinical cutoff for AD more sensitively. Under this scenario, people with borderline symptoms would be classified as progressing to AD earlier in J-ADNI than in ADNI. In this context, the time-to-event outcome in MCI trials (i.e., conversion to dementia) might sometimes be problematic because the criteria for clinical judgment are difficult to harmonize and implement. The time-to-event endpoint is also prone to be underpowered relative to repeated continuous outcome measures [22].

In contrast to LMCI, the J-ADNI mild AD showed generally better scores in MMSE, ADAS-Cog13, CDR-SB, and FAQ throughout the 2-year follow-up, and the speed of decline in the cognitive composites (MMSE and ADAS) also were slower compared with ADNI despite the higher education in mild AD patients in ADNI. This trend was consistent with the significantly higher percentage of mild AD with CDR score 0.5 (70%) in J-ADNI, compared with that in ADNI (49%) ($P = .001$, see Table 1). It is possible that the mild AD patients enrolled in J-ADNI were slightly earlier in the disease stage because of a minor difference in the dividing line between LMCI and AD, with J-ADNI investigators setting a slightly earlier cut point on initial diagnosis, although the J-ADNI protocol used the identical criteria of MCI as ADNI [6]. In support of this idea, we note that the LMCI individuals in ADNI do "catch up" after a year or two when we look at the conversion rates to dementia (Fig. 3).

A variety of factors may potentially underlie these discrepancies, including the clinical division of LMCI and AD between J-ADNI and ADNI. Because one criterion for AD (dementia) is limitation in being able to function in daily living, the "background setting" may be different in J-ADNI and ADNI. A number of environmental factors, for example, differences in life style and social welfare systems, should also be considered. A deeper look at the CDR-SB or FAQ items, as well as the clinical records, may help to clarify this point. The higher education in ADNI compared with J-ADNI may be an additional factor for differential rates of progression in mild AD; higher cognitive reserve may cause slower decline at an early stage but faster progression subsequently in AD dementia stage when pathology overwhelmed the reserve. Another possibility is that the underlying disease process is actually different. Notably, it is increasingly well recognized that the neuropathology of AD may be somewhat heterogeneous, with most people having mixed pathology at an advanced stage. It may be that the neuropathological characteristics are slightly different between the Japanese and US AD participants from the early stages, leading to differences in the clinical progression; this aspect should be verified by further comparing the extent of neurodegeneration by atrophy or CSF tau levels, and vascular lesions in MRI images, as well as by future clinicopathological studies. Regarding the methodological aspects, the difference in cognitive or functional scales translated from English to Japanese might have affected the assessment of the participants, which will require further linguistic validation. Development of instruments that can quantify cognition beyond language will also be needed. Further harmonization and consensus in clinical judgment (within Japan as well as internationally), e.g., on the diagnosis of MCI and decisions on conversion to dementia, might improve the consistency in the evaluation of the different populations. Finally, in addition to the difference in the incidence of *APOE*ε4 genotype, other genetic characteristics of the Japanese or Asian population should be revealed by further genomic analysis in J-ADNI.

In view of the continuum in the progression profiles of cognitive and functional decline in mild AD with those of the later stage of LMCI both in J-ADNI and ADNI, the present results may justify the current trend to combine LMCI due to AD (prodromal AD) and mild AD as the target population in clinical trials of DMTs in the early stage of AD [23,24]. However, comparison of treatment effects on symptom progression should also be carefully assessed, given the differing progression rates between Japanese and Caucasian ADNI cohorts in the mild AD population.

CN populations in J-ADNI and ADNI exhibited similar characteristics with minimal changes in the cognitive scores during the 3-year follow-up, although the percentage of amyloid-positive CN individuals (i.e., preclinical AD [7]) was significantly higher in ADNI (44%) compared with J-ADNI (23%; $P < .001$). The higher ages (mean, 73.7 years) in ADNI CN compared with J-ADNI (mean, 67.9 years) might have affected the results, although the *APOE*ε4 positivity rates were similar (28% in ADNI vs. 25% in J-ADNI), suggesting the involvement of additional factors, e.g., bias in enrollment due to volunteering of the high-risk individuals in US or other genetic and environmental differences. Another contributing factor to the higher amyloid positivity in ADNI CN is the high CSF positivity (154/370 = 42%) compared with the PET positivity (95/285 = 33%); a careful reevaluation of the CSF and PET positivity criteria in CN may be required to resolve this discrepancy. Further characterization of the preclinical AD population in Asian and Caucasian populations should also be pursued through the large-scale prevention trials, e.g., the A4 study [25], in which Japan also is participating.

There are some limitations in J-ADNI. First, the smaller size of the study in J-ADNI might have caused some of the differences observed in baseline demographics (e.g., age in CN groups) and progression rates and biomarker data between ADNI and J-ADNI, although the total number of participants (537 cases) provided adequate power for planned comparisons, and 95% confidence intervals showed good precision for estimates of differences (e.g., HRs for MCI to dementia conversion). Second, the duration of observation in J-ADNI was limited to 2–3 years, and a longer follow-up, which should provide a more realistic delineation of the natural history, was not available. Third, the difference in the criteria for amyloid positivity (i.e., PiB PET and/or CSF in J-ADNI vs. florbetapir PET and/or CSF in ADNI) might have biased the results, although the correlation between PET and CSF measures in J-ADNI was comparable to that in ADNI. Indeed, the Alzheimer's Association quality program (in which the J-ADNI Niigata laboratory is also participating) has shown a considerable between-laboratory variability in CSF Aβ(1–42) measurements, which makes the definition of a universal cutoff value difficult [26]; the approximate 1.73-fold difference in the cutoff values for amyloid positivity between J-ADNI (333 pg/mL) and ADNI (192 pg/mL) may lie within this variability range.

In sum, we have conducted ADNI study in Japan, which demonstrated the similarity and differences in LMCI and mild AD populations between Japanese and Caucasian, as well as the feasibility of multicenter clinical studies and trials using neuroimaging and fluid biomarkers in different regions in the world. The overall purpose of ADNI consists in the validation of biomarkers for AD clinical trials, which is being achieved by correlating biomarker values, e.g., MRI, fluorodeoxyglucose or amyloid PET, and CSF Aβ(1–42) or tau, with clinical or cognitive data in individual ADNI projects and thus will work as an internal validation. Further comparison of such correlations between the ADNIs in different regions will provide us with external validity of biomarkers in the trials of early stages of AD. Such comprehensive analyses will lend support to the successful bridging of AD clinical trial data among Asia, North America, and Europe.

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RESEARCH IN CONTEXT

1. Systematic review: We have searched for the NCBI PubMed database for existing evidence and the "progress reports" of Alzheimer's Disease Neuroimaging Initiative (ADNI) published yearly in Alzheimer's and Dementia.
2. Interpretation: The clinical criteria of mild cognitive impairment (MCI) have widely been established and used worldwide since the late 20th century. The basic characteristics and progression profiles of MCI, especially of amnestic MCI that often precedes the onset of dementia symptoms in Alzheimer's disease (AD), were examined in a large-scale longitudinal observational studies combining neuroimaging and biomarker studies in western countries, as exemplified by the ADNI study in US, Australian Imaging Biomarker and Lifestyle Study of Ageing study in Australia, and similar studies in Europe. This led to the emergence of worldwide ADNI studies, based on the standard methodologies established by ADNI and other related studies. However, none, including activities in other western countries or Asia, except for Japanese ADNI, has replicated the standard protocol of ADNI for the investigation of MCI in a second cohort or in other regions.
3. Future directions: Japanese ADNI, study has replicated the basic findings of ADNI, especially those on the characteristics of MCI due to AD, in the Japanese population and has demonstrated that the ADNI findings and methodologies, now becoming widely applied to global clinical trials of disease-modifying therapies for AD, are applicable to the Asian population. To ascertain the nature of the similarities and differences between the early stages of Asian and Caucasian AD, further detailed analyses combining the magnetic resonance imaging, positron emission tomography, cerebrospinal fluid, and genomic information are underway.

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