Alzheimer's & Dementia

Featured Article

Effects of sex, educational background, and chronic kidney disease grading on longitudinal cognitive and functional decline in patients in the Japanese Alzheimer's Disease Neuroimaging Initiative study

Atsushi Iwata[a,*], Takeshi Iwatsubo[b], Ryoko Ihara[b], Kazushi Suzuki[b], Yutaka Matsuyama[c], Naoki Tomita[d], Hiroyuki Arai[d], Kenji Ishii[e], Michio Senda[f], Kengo Ito[g], Takeshi Ikeuchi[h], Ryozo Kuwano[h], Hiroshi Matsuda[i], Alzheimer's Disease Neuroimaging Initiative[†], Japanese Alzheimer's Disease Neuroimaging Initiative[‡]

[a]*Department of Neurology, The University of Tokyo Hospital, Tokyo, Japan*
[b]*Unit for Early and Exploratory Clinical Development, The University of Tokyo Hospital, Tokyo, Japan*
[c]*Department of Biostatistics, School of Public Health, The University of Tokyo, Japan*
[d]*Department of Geriatrics & Gerontology, Division of Brain Science, Institute of Development, Aging and Cancer (IDAC), Tohoku University, Japan*
[e]*Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan*
[f]*Institute of Biomedical Research and Innovation, Kobe, Japan*
[g]*National Center for Geriatrics and Gerontology, Obu, Japan*
[h]*Niigata University, Niigata, Japan*
[i]*National Center for Neurology and Psychiatry, Kodaira, Japan*

Abstract

Introduction: The objective of this study was to determine whether sex or education level affects the longitudinal rate of cognitive decline in Japanese patients in the Alzheimer's disease Neuroimaging Initiative study with defined mild cognitive impairment (MCI).

Methods: We accessed the entire Japanese Alzheimer's Disease Neuroimaging Initiative data set of 537 individuals, among whom 234 had MCI and 149 had Alzheimer's disease. We classified participants into three categories of educational history: (1) low, 0 to 9 years; (2) moderate, 10 to 15 years; and (3) high ≥16 years. We examined the main effects and interactions of visit, sex, and educational achievement on scores for the Clinical Dementia Rating Sum of Boxes, Alzheimer's Disease Assessment Scale–cognitive subscale 13, Mini-Mental State Examination, and Functional Activities Questionnaire in a longitudinal manner.

Results: Women with MCI had a significantly faster rate of decline than men over a 3-year period. Highly educated men showed a significantly slower rate of decline than the other groups. Sex differences in the rates of decline remained after stratification by amyloid or apolipoprotein E (*APOE*) ε4 status but were absent in Alzheimer's disease over a 2-year period. Subtle differences in chronic kidney disease grade affected the rate of decline. A higher Fazekas periventricular hyperintensity score was associated with a lower estimated glomerular filtration rate in women only.

Discussion: In patients with MCI, sex and educational history significantly affected the rate of change in cognitive and clinical assessments. Furthermore, a subtle decline in chronic kidney

disease grade was associated with a faster rate of decline regardless of amyloid pathology in women.

1. Background

Successful completion of the Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI) project yielded a data set comprising 537 individuals, including 154 cognitively normal individuals, 234 individuals with late mild cognitive impairment (LMCI), and 149 individuals with mild Alzheimer's disease (AD). Previous publication has reported that the Japanese data set is generally comparable to the North American (NA)-ADNI data set, supporting the feasibility of a clinical trial bridging the prodromal stage of AD between Eastern and Western countries [1]. Moreover, the J-ADNI is the most comprehensive data set of this size, reflecting cognitive changes in older individuals from a Japanese (or Asian) population.

It is known that the incidence of AD does not seem to be affected by sex [2], whereas women have a higher life-time risk of AD owing to their longer life span than men [3]. In general, there is a lower incidence of AD among highly educated individuals compared with less educated individuals, suggesting that educational achievement confers some resistance to the development of the disease [4,5]. Nonetheless, highly educated subjects are thought to decline more quickly after they are diagnosed [6]. However, there has been almost no research into these factors among the elderly in the Japanese population. Therefore, we believe it is important to conduct an analysis of cognitive and functional changes in particular subgroups of Japanese people to explore the factors influencing them.

After publishing the initial analysis of the J-ADNI data set [1], we performed subanalyses with the aim of determining the effects of sex and education level on longitudinal decline in individuals with LMCI and AD. We analyzed various cognitive scales after stratifying them by sex and education level. Subsequently, we further analyzed the data according to amyloid positivity and other clinical and laboratory factors obtained in the study. Finally, we compared the data from the J-ADNI and NA-ADNI cohorts to investigate whether our findings are unique to the J-ADNI data set.

2. Methods

2.1. Sample

We obtained the J-ADNI data set from the National Bioscience Database Center with approval from its data access committee (https://humandbs.biosciencedbc.jp/en/ hum0043-v1). The inclusion criteria for J-ADNI were identical to those for NA-ADNI [7]. The follow-up period was 3 years for NC and LMCI and 2 years for AD. The antidementia drug prescription history of participants was obtained from the J-ADNI database (in preparation for publicization). We obtained the NA-ADNI data sets from ADNI1, AD-NIGO (Grand Opportunities), and ADNI2 from the Laboratory of Neuro Imaging with their approval. The data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu) (downloaded on June 15, 2017). 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 magnetic resonance imaging, positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD.

2.2. Assessments and clinical variables

From the several neuropsychological tests used in the J-ADNI cohort, we chose the Clinical Dementia Rating Sum of Boxes (CDR-SOB), Alzheimer's Disease Assessment Scale–cognitive subscale 13 (ADAS-cog13), Mini-Mental State Examination (MMSE), and Functional Activities Questionnaire (FAQ) to assess the longitudinal cognitive and functional status of participants. The clinical and laboratory data used for analysis included participants' sex, age, family history of dementia, marital status, smoking habits, Geriatric Depression Scale scores, fasting blood sugar level, low-density lipoprotein cholesterol level, high-density lipoprotein cholesterol level, glomerular filtration rate (GFR) calculated from serum creatinine, Fazekas periventricular hyperintensity (PVH) score, and deep and subcortical white matter hyperintensity scores from the screening magnetic resonance imaging scan (scored by a trained radiologist blind to clinical information), apolipoprotein E (*APOE*) ε4 allele status, and amyloid positivity. Amyloid positivity was clinically defined by visual inspection of amyloid PET images with Pittsburgh compound B as a ligand by trained radiologists who were blinded to any clinical information [8] and/or a cerebrospinal fluid amyloid-beta 42 ($A\beta_{42}$) value ≤ 333 pg/mL at baseline, using the cutoff value determined in a previous report [1]. When both data were available, we defined "positive" as at least one test having met "positive" criteria. When calculating the GFR, we used estimated glomerular filtration

rate (eGFR) for J-ADNI participants [9] and GFR-EPI (epidemiology collaboration) for the NA-ADNI participants [10]. These formulas are well established and validated in both the regions [9,10].

2.3. Statistical analyses

Data were analyzed using the JMP program (SAS Institute Inc, Cary, NC) or Prism 6.0c (GraphPad, La Jolla, CA). We assessed differences with chi-squared tests when analyzing demographic data, whereas longitudinal changes were analyzed using linear mixed-effects models. The interactive effect of group (high education vs. moderate education vs. low education, men vs. women, G1 vs. ≥G2) and time (months) on cognition and function was examined. Age at baseline and *APOE* ε4 carriage were included as covariates because they are known to be associated with cognition. Individuals were included as a random effect in the analyses. All *P* values shown in the figures were generated for the interactive effect between group and time. Differences with a *P* value of <.05 were considered significant.

2.4. Ethics

The study protocol was approved by the University of Tokyo Ethics Committee (11628).

3. Results

3.1. Sample characteristics

Table 1 presents detailed demographic data for the participants included in this study. In the included cohort, 49.6% of those with LMCI and 43.0% of those with AD were men. The mean ± standard deviation for the length of education was 13.0 ± 2.8 years in those with LMCI and 12.4 ± 3.1 years in those with AD, and there was no significant difference between the groups. We divided participants

into three groups: (1) low education level (0–9 years), (2) moderate education level (10–15 years), and (3) high education level (≥16 years). Regarding the subtypes of MCI, 2 out of 116 of the men and 4 out of 118 of the women had nonamnestic features. During the 3-year follow-up period, 50% of male and 54.7% of female LMCI subjects completed the study. For AD, 64.1% of male and 63.4% of female subjects completed the 2-year follow-up. Amyloid data were obtained from amyloid PET in 74 subjects with MCI and 57 with AD, from cerebrospinal fluid data in 88 with MCI and 55 with AD, and for both in 45 with MCI and 24 with AD. The positivity rate was 65.8% for MCI and 89.8% for AD. There were no sex differences in terms of average age, family history of dementia, amyloid positivity, or *APOE* ε4 frequency. However, we observed that significantly more men than women were highly educated in both the LMCI and AD groups.

3.2. Effects of sex and educational achievement on cognitive and functional decline

To evaluate the effect of sex on rates of cognitive and functional decline, we analyzed longitudinal changes in the CDR-SOB, ADAS-cog13, MMSE, and FAQ. As shown in Fig. 1A, ratings on all of these scales declined significantly more quickly in women with LMCI. There were no significant differences in longitudinal changes between the sexes for any of the scales in people with AD. These results imply that in the J-ADNI data set, women with LMCI experienced a faster rate of decline than men in terms of both cognition and function.

We next examined the effect of educational achievement on cognitive and functional changes. We observed significant differences in the rates of decline between the groups with different educational levels for all of the scales evaluated in those with LMCI (Fig. 1B). Specifically, the low and moderately educated groups showed similar trends,

Table 1
Detailed demographic data from participants with LMCI and AD from the J-ADNI cohort

| Characteristics | LMCI | | | | AD | | | | P value LMCI versus AD |
	Male	Female	Total	P value male versus female	Male	Female	Total	P value male versus female	
Total, n (%)	116 (49.6)	118 (50.4)	234 (100)		64 (43.0)	85 (57.0)	149 (100)		.2099
Average age years (SD)	72.8 (5.9)	72.9 (6.0)	72.8 (5.9)	.8403	73.3 (5.8)	73.8 (7.1)	73.6 (6.6)	.6522	.2253
Family history of dementia, n (%)	32 (27.6)	28 (23.7)	60 (25.6)	.5505	19 (29.7)	23 (27.1)	42 (28.2)	.8542	.6356
Educational years (SD)	14.1 (2.9)	11.9 (2.3)	13.0 (2.8)	<.0001	13.7 (3.7)	11.5 (2.3)	12.4 (3.1)	<.0001	.0663
Educational level, n (%)									
0–9 years	12 (10.3)	17 (14.4)	29 (12.4)	<.0001	10 (15.6)	21 (24.7)	31 (20.8)	<.0001	NA
10–15 years	43 (37.1)	88 (74.6)	131 (56.0)		27 (42.2)	58 (68.2)	85 (57.0)		
≥16 years	61 (52.6)	13 (11.0)	74 (31.6)		27 (42.2)	6 (7.1)	33 (22.1)		
Amyloid positive, n (%)	39 (62.9)	38 (69.1)	77 (65.8)	.5596	37 (90.2)	42 (89.4)	79 (89.8)	1	<.0001
Total available, n	62	55	117		41	47	88		
APOE ε4 positive, n (%)	57 (50.0)	64 (54.2)	121 (52.2)	.5992	41 (65.1)	47 (55.3)	88 (59.5)	.2417	.2051
Total available, n	114	118	232		63	85	148		

Abbreviations: AD, Alzheimer's disease; LMCI, late mild cognitive impairment; SD, standard deviation; NA, not available.
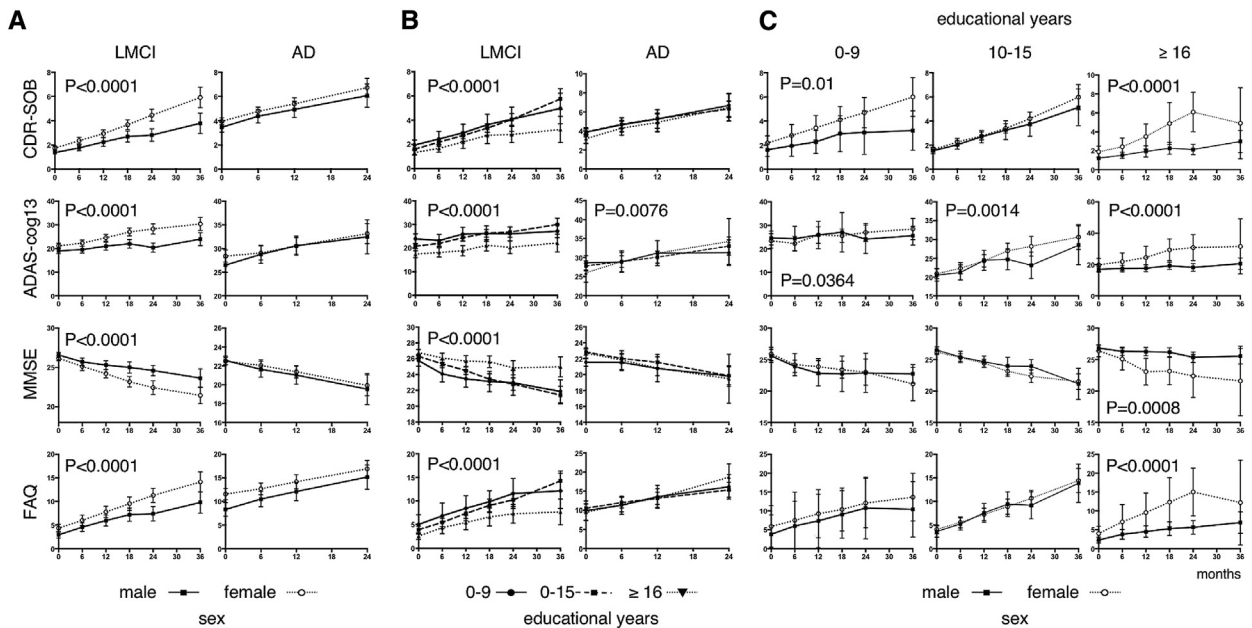
Fig. 1. (A) Longitudinal changes in CDR-SOB, ADAS-cog13, MMSE, and FAQ in participants with LMCI and AD, stratified by sex. The dotted lines represent women, and the solid lines represent men. The error bars represent 95% confidence intervals. The *P* values represent the results from an analysis of variance (ANOVA) investigating the main effects of visits and sex, as well as their interaction. (B) Longitudinal changes in participants with LMCI and AD, stratified by educational level. The solid lines represent participants with an education level of 0–9 years, the broken lines represent those with 10–15 years of education, and the dotted lines represent those with ≥16 years of education. The *P* values represent the results from an ANOVA investigating the main effects of visits and educational level, as well as their interaction. (C) Longitudinal changes in LMCI stratified by educational level and sex. The dotted lines represent women, and the solid lines represent men. Abbreviations: CDR-SOB, Clinical Dementia Rating Sum of Boxes; ADAS-cog13, Alzheimer's Disease Assessment Scale–cognitive subscale 13; MMSE, Mini-Mental State Examination; FAQ, Functional Activities Questionnaire; LMCI, late mild cognitive impairment; AD, Alzheimer's disease.

whereas the highly educated group showed a slower rate of decline in cognition and function. Again, there were no significant differences in longitudinal changes between the groups with different educational levels for any of the scales in those with AD, with the exception of slight differences in the ADAS-cog13 scores.

Given that there were significantly more highly educated men than women with LMCI (Table 1), sex differences in cognition and function may simply reflect educational differences between the sexes. To assess this issue, we further stratified the MCI group by educational level and sex. As shown in Fig. 1C, the trend for women to have a faster rate of decline remained for all scales, regardless of educational level. Highly educated women showed a significantly faster rate of decline in all scales than less educated women. Similarly, women with a low level of education showed a faster rate of decline in the CDR-SOB and ADAS-cog13 scales. Further analyses stratifying men and women by educational level revealed that in men, the CDR, MMSE, and FAQ showed a significant effect of educational level (*P* < .0001). However, none of the scales showed a significant effect of educational level in women (data not shown). This indicates that differences in the effects of educational achievement are not necessarily the reason for women showing a faster rate of decline than men.

3.3. Influence of amyloid positivity and APOE ε4 status

Subsequently, we aimed to understand the mechanisms underlying the differences between the sexes by examining whether amyloid positivity or the presence of the *APOE* ε4 allele affected the rates of cognitive and functional decline.

Among the participants with LMCI, 117 had amyloid data obtained using either amyloid PET or via cerebrospinal fluid Aβ₄₂. The rates of amyloid positivity were 62.9% and 69.1% in men and women, respectively, and these values were not significantly different between the groups (Table 1). Data regarding the presence of the *APOE* genotype were available for 232 participants with LMCI. We observed that 50.0% of men and 54.2% of women were *APOE* ε4 carriers, and these proportions did not differ significantly between the groups (Table 1). We further analyzed amyloid pathology and *APOE* ε4 positivity by educational level and observed no significant differences between the groups (Table 2).

To directly explore the effect of amyloid pathology and the presence of the *APOE* ε4 allele on the rate of cognitive decline, we stratified participants with LMCI according to these two components and compared longitudinal changes in cognition between the sexes. As shown in Fig. 2A, women still showed a significantly faster rate of decline in the CDR-SOB scale than men, regardless of amyloid positivity.

Table 2
Amyloid and *APOE* ε4 status stratified by educational level

Characteristics	Educational level years	Male			Female			Total, n (%)	*P* value male versus female
		Positive, n (%)	Negative, n (%)	Total, n	Positive, n (%)	Negative, n (%)	Total, n		
Amyloid pathology	0–9	0	0	0	8 (66.7)	4 (33.3)	12	8 (66.7)	NA
	10–15	14 (66.7)	7 (33.3)	21	27 (75.0)	9 (25.0)	36	41 (71.9)	.5506
	≥16	25 (61.0)	16 (39.0)	41	3 (42.9)	4 (57.1)	7	28 (58.3)	.4294
APOE ε4	0–9	6 (54.5)	5 (45.5)	11	10 (58.8)	7 (41.2)	17	16 (57.1)	1
	10–15	22 (51.2)	21 (48.8)	43	47 (53.4)	41 (46.6)	88	69 (52.7)	.8535
	≥16	29 (48.3)	31 (51.7)	60	7 (53.8)	6 (46.2)	13	36 (49.3)	.7676

Abbreviations: NA, not available; APOE, apolipoprotein E.

Amyloid-negative women also showed a faster rate of decline than men in the ADAS-cog13 and MMSE scales. Moreover, women with LMCI showed a significantly faster rate of decline than men in all the scales, except the FAQ, regardless of their *APOE* ε4 status (Fig. 2B).

We observed that statistical significance was not maintained for several scales after further stratification. However, we speculate that this is due to the relatively small number of participants in each group resulting from stratification because the trend toward significance for women to show a faster rate of decline remained for all scales, regardless of amyloid positivity or *APOE* ε4 status. Thus, we concluded that there was a rationale to seek further reasons for this trend.
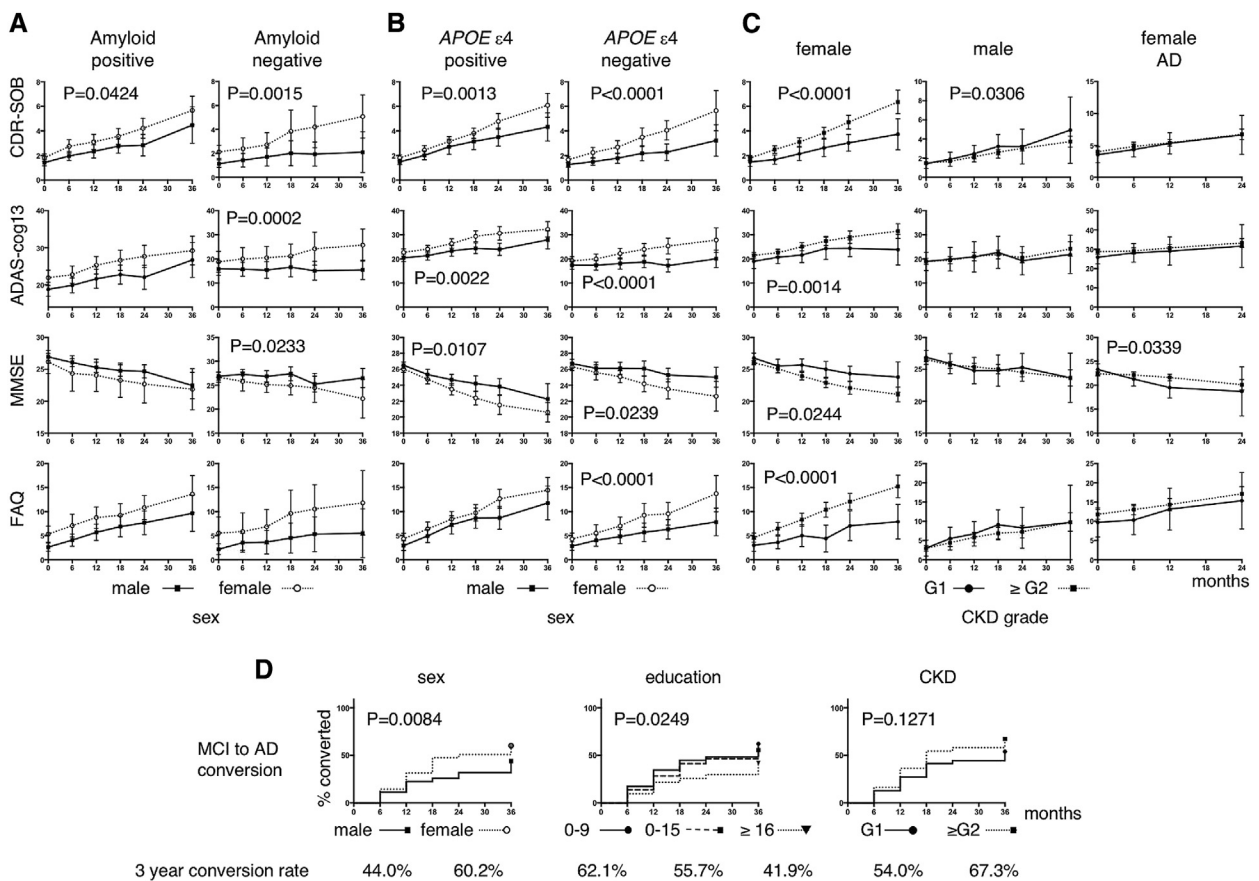

Fig. 2. (A) Longitudinal changes in LMCI stratified by sex and amyloid positivity. The dotted lines represent women, and the solid lines represent men. (B) Longitudinal changes in LMCI stratified by *APOE* ε4 allele status. (C) Longitudinal changes in LMCI and AD stratified by CKD grade. The solid lines represent CKD grade G1 and the dotted lines represent CKD grade ≥ G2. (D) Kaplan-Meyer plot of MCI to AD conversion stratified by sex, educational level, and CKD grades. Statistically significant differences were assessed using the log-rank test for sex and education; the log-rank test showed a trend toward significance for education level. The overall conversion rate is shown below the graphs. Abbreviations: LMCI, late mild cognitive impairment; AD, Alzheimer's disease; CKD, chronic kidney disease; APOE, apolipoprotein E.

3.4. Further factors leading to faster functional and cognitive decline

To elucidate the factors leading to faster functional and cognitive decline in women with LMCI, we divided female participants into quartiles according to the rate of decline in the CDR-SOB, ADAS-cog13, MMSE, or FAQ scores. Subsequently, we compared the age, years of education, family history, smoking history, body weight, body height, body mass index, blood test results (fasting blood sugar, creatinine, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, C-reactive protein, homocysteine, vitamin B12, and folic acid), amyloid positivity, APOE ε4 status, and chronic kidney disease (CKD) grade between the top and bottom quartiles.

The rate of decline was determined for each score from the baseline visit and last visit (this period was not necessarily 36 months for early dropouts, but all participants completed at least two visits). The results of this analysis suggested that individuals showing a fast rate of decline tended to have a lower CKD grade than participants showing a slower rate of decline. There were no other significant findings (data not shown).

Because there were few participants with a CKD grade above G3a (Table 3), we combined the CKD grades into a single group of $\geq$G2 (eGFR $<$ 90 mL/min/1.73 m^2) and analyzed patterns of declining cognition and function. As shown in Fig. 2C, female participants with a CKD $\geq$ G2 tended to show a faster rate of decline than those with a CKD of G1 for all the scales.

We then tested if sex, educational level, and CKD grade affected the MCI to AD conversion. As shown in Fig. 2D, sex and educational level had significant effects on conversion, whereas the effect of CKD grade was not significant.

3.5. Comparisons of J-ADNI and NA-ADNI

Finally, we investigated if similar findings could be observed in the NA-ADNI data set of 562 participants with LMCI (women, n = 344; men, n = 218).

Table 3
Participants' CKD grades

| CKD grade | LMCI | | AD | |
	Male, n (%)	Female, n (%)	Male, n (%)	Female, n (%)
G1	16 (13.8)	20 (16.9)	10 (15.6)	10 (11.8)
$\geq$G2	100 (86.2)	98 (83.1)	54 (84.4)	75 (88.2)
G2	82 (70.7)	79 (66.9)	43 (67.2)	62 (72.9)
G3a	13 (11.2)	18 (15.3)	10 (15.6)	10 (11.8)
G3b	5 (4.3)	0 (0)	1 (1.6)	3 (3.5)
G4	0 (0)	1 (0.8)	0 (0)	0 (0)
G5	0 (0)	0 (0)	0 (0)	0 (0)
Total	116 (100)	118 (100)	64 (100)	85 (100)

Abbreviations: AD, Alzheimer's disease; LMCI, late mild cognitive impairment; CKD, chronic kidney disease.

As shown in Fig. 3A, we did not observe a trend for women who were amyloid negative to perform worse within the 3-year follow-up period than male participants, although it has been reported that "overall," women with MCI declined faster in NA-ADNI population in the 8-year follow-up [11].

We observed a significant difference between the education level groups with regard to the scores for the CDR-SOB and ADAS-cog13 (Fig. 3B). Female participants with CKD $\geq$ G2 (according to the GFR-EPI formula) scored consistently worse on the ADAS-cog13 and MMSE scales than those with a CKD of G1, but there was no significant difference in the rate of decline (Fig. 3C).

These results indicate that educational achievement influenced cognition and function in individuals with LMCI from both the J-ADNI and NA-ADNI data sets, but the effects occurred in a slightly different manner. In addition, higher CKD grade was related to a faster rate of cognitive decline in female participants from both the cohorts. However, there was a more prominent difference in the rate of decline in the J-ADNI population.

Therefore, it remains to be determined what underlies these patterns. We speculate that a low eGFR could reflect chronic high blood pressure. Because the subjects' comprehensive past medical history was not available from the J-ADNI database, we attempted to determine whether there was any relationship between the Fazekas score obtained at the baseline magnetic resonance imaging scan and CKD grade. As shown in Fig. 3D, participants with a higher Fazekas PVH score had a lower eGFR, but this was only observed in women.

4. Discussion

Our findings from subanalyses of the J-ADNI data set suggest that women with LMCI showed a faster rate of decline than men with LMCI. Educational achievement also affected the speed of cognitive decline, and women with an eGFR of 90 mL/min/1.73 m^2 or less also showed a faster rate of decline. We did not observe the same differences in participants from the J-ADNI with AD, and these findings were only partially present in the NA-ADNI data set.

According to a previous systematic review, there are no sex differences in rates of cognitive decline in the normal aging process [12]. In contrast, the incidence of MCI is reported to be higher in men, although this is still controversial [13,14]. The precise pathological mechanisms underlying these patterns remain unknown. However, pathophysiological changes mediated by endocrine transition states, such as the menopause, which is both female-specific and age-related, may play a role [15]. Several previous reports have suggested that women with MCI tend to decline more quickly than do men across both a 1-year follow-up period [16] and a longer follow-up period of 8 years [11]. Our current results corroborate these previous findings in a Japanese population.
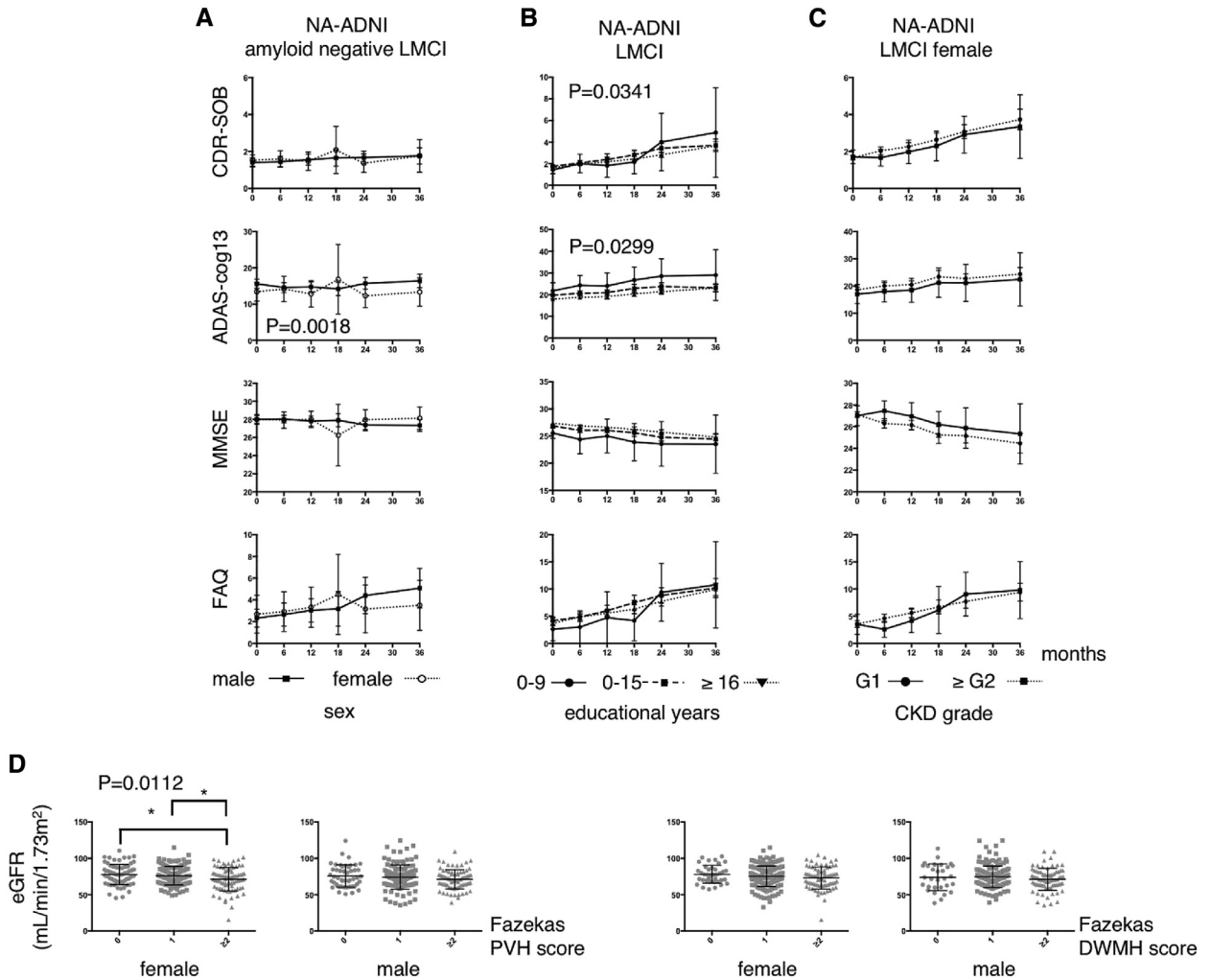
Fig. 3. (A) Longitudinal changes in CDR-SOB, ADAS-cog13, MMSE, and FAQ from participants who were amyloid negative from the NA-ADNI cohort. The dotted lines represent women, and the solid lines represent men. (B) Scale scores from participants with LMCI in the NA-ADNI cohort stratified by educational level. The solid lines represent participants with 0–9 years of education, the broken lines represent those with 10–15 years of education, and the dotted lines represent those with ≥16 years of education. The P values represent the results from an ANOVA investigating the main effects of visit and sex, as well as their interaction. (C) Scale scores of women with LMCI in the NA-ADNI cohort. The solid lines represent those with CKD grade G1 and the dotted lines represent those with CKD grade ≥ G2. The P values represent the results from an ANOVA investigating the main effect of sex throughout the visits. (D) Fazekas PVH and DWMH scores at baseline in patients from the J-ADNI cohort, with participants' CKD grade plotted. Differences were assessed using an ANOVA and the Tukey-Kramer method for multiple comparisons. *P = .0112. Abbreviations: CDR-SOB, Clinical Dementia Rating Sum of Boxes; ADAS-cog13, Alzheimer's Disease Assessment Scale–cognitive subscale 13; MMSE, Mini-Mental State Examination; FAQ, Functional Activities Questionnaire; LMCI, late mild cognitive impairment; PVH, periventricular hyperintensity; DWMH, deep white matter hyperintensity; CKD, chronic kidney disease; ANOVA, analysis of variance.

Several previous studies have investigated the relationship between educational level and risk of dementia. In general, lower educational achievement is related to a higher incidence of dementia, and risk decreases with each year increase in education [17,18]. In terms of cognitive decline among individuals with MCI, there are also several reports from cross-sectional studies indicating that higher education levels are associated with higher scores on cognitive scales [19,20]. In contrast, there have been very few reports regarding the longitudinal rate of cognitive decline and educational level in MCI populations [5]. Our current findings show that education level appears to affect the rate of cognitive decline in LMCI in both the J-ADNI and

NA-ADNI cohorts. One thing we should discuss here is that the protective effect of education was only positive in male LMCI subjects. The exact reason for this remains to be elucidated, but one explanation could be that highly educated women lack the protection that comes from occupational complexity. Indeed, among the 13 female subjects with an educational history of 16 years or more, seven subjects spent most of their lives as housewives.

It should be noted that in the J-ADNI data set, the rate of amyloid positivity was 66.7%, 70.7%, and 58.3%, in low, moderate, and highly educated individuals, respectively. There were fewer participants who were amyloid positive in the highly educated group, although this was not

statistically significant. This could affect the progression rate of LMCI among those in the highly educated group, regardless of their educational achievement. We attempted to account for this in our evaluation of cognitive decline; however, the number of participants was insufficient to perform statistical analyses. In addition, the number of participants with low education levels was very small in the NA-ADNI cohort. The percentages of low, moderate, and highly educated participants were 2.3%, 31.9%, and 65.8%, respectively, among those with LMCI, and 3.2%, 41.2%, and 55.6%, respectively, in those with AD. As such, the NA-ADNI cohort includes significantly more highly educated participants and fewer participants with a low level of education compared with the J-ADNI cohort. This limits comparisons between the two cohorts. Even in the J-ADNI cohort, which included more participants with a low level of education than the NA-ADNI cohort, the percentages of participants in each educational group were not equal (Table 1).

According to the Japanese government census, the male-to-female ratio of people over 65 years of age is 1:1.35, and the average years of education of people aged 65 to 85 years is approximately 10.9 years in men and 10.2 years in women [21]. Therefore, in J-ADNI cohort, the average age of participants was still higher than in the general population; compared to NA-ADNI cohort, it was much closer to that of the general population. Thus, further study is needed to evaluate the progression of LMCI in the general population in both the regions.

Our findings also suggest that women with LMCI show a faster rate of decline regardless of their amyloid or *APOE* ε4 status, indicating that there could be an independent factor affecting female cognitive decline other than amyloid pathology. Further analysis revealed that in women with LMCI, a CKD stage of G2 or higher was related to a faster rate of decline. This is of interest because a CKD stage of G2 reflects an eGFR lower than 90 mL/min/1.73 m^2, which does not necessarily indicate that these participants had CKD or even impaired renal function [22]. Indeed, only 7 women and 16 men fulfilled the criteria for CKD in the entire cohort of participants with LMCI. This indicates that even a subtle decline in eGFR is related to faster cognitive decline in Japanese women with LMCI. Because the serum creatinine levels used for the eGFR calculation could reflect low muscular volume, we tested the effects of differences in body height, body weight, and body mass index among women with CKD grade G1 and ≥G2 in the J-ADNI cohort but found no statistical difference between the two groups (body weight [mean ± standard deviation]: G1, 49.5 ± 7.9 kg and ≥G2, 48.1 ± 6.5 kg; body height: G1, 150.8 ± 5.1 cm and ≥G2, 150.7 ± 5.8 cm; body mass index: G1, 21.9 ± 3.7 and ≥G2, 21.2 ± 3.1). Another explanation was that there were fewer *APOE* ε4 carriers in the female G1 group than in other groups, but our analysis did not support this hypothesis (G1, 50.0% and ≥G2, 55.1%). Thus, eGFR seems to be related to cognitive decline in women with LMCI, independent of

amyloid pathology. Because antidementia drugs, such as donepezil, galantamine, rivastigmine, or memantine, could be prescribed to MCI subjects even before conversion to AD, we tested if prescription of those drugs affected the rate of cognitive decline. As shown in Table S1, the prescription rates, stratified by sex, educational level, or CKD grade, were not significantly different.

These findings were not replicated in the NA-ADNI data set. When analyzing the J-ADNI data set, we used eGFR to evaluate renal function [9] and GFR-EPI for the NA-ADNI data set [10]. These two GFR evaluation methods are widely used in each region. However, they gave completely different values when the data used for calculations were transposed. Nonetheless, even when we evaluated J-ADNI subjects with GFR-EPI and NA-ADNI subjects with eGFR, the results did not change.

In cross-sectional studies, CKD has been shown to be associated with cognitive decline [23–25] and cerebral cortical thinning [26]. Longitudinal studies of mild to moderate CKD found that an elevated serum creatinine level increased the risk of dementia [27]. We tried to explain this phenomenon by relating low eGFR to brain small vessel disease and found that in women with MCI only, participants with a high Fazekas PVH score had a significantly lower eGFR. The effect of high CKD grade on Fazekas PVH score was small, so other factors may underlie this finding, such as increased levels of inflammatory cytokines, oxidative stress, and alterations in lipid and homocysteine metabolism [27]. Alternatively, the simple Fazekas grading may not be precise enough to evaluate white matter disease, and precise volumetric measurements may be needed. It can be questioned why only women are affected by a low eGFR. One explanation could be that women with hypertension tend to have a lower GFR than men [28], or women may be more vulnerable to inflammatory cytokines or oxidative stress. There are sex differences in cardiovascular pathology. Plaque morphology of coronary arteries differs between men and women [29]. It has been reported that smoking and diabetes have a greater impact on atherosclerosis in women than in men [30]. Thus, this sex difference in atherosclerosis could also underlie this finding.

Moreover, it can be questioned why these relationships were only observed in Japanese women. At this point, it is not possible to answer this question satisfactorily. Further study is needed to determine whether the current results can be replicated in other cohorts.

Our study has several limitations that should be borne in mind. First, the number of participants with amyloid data was insufficient to further analyze the effects of this factor on cognitive decline in LMCI and AD cases. Second, the education level of participants was higher than that in the general population, which may make it difficult to generalize the findings. Third, we evaluated eGFR with serum creatinine levels only. Future studies could improve the evaluation by also incorporating serum cystatin C [31]. In participants

with LMCI in the J-ADNI cohort, there was no information about the disease duration in the database, and this could also be a limitation of our findings regarding differences in progression rate.

In this study, we successfully performed subanalyses of the J-ADNI data set. Our findings provide basic knowledge about Japanese individuals with MCI, which should provide a basis for future drug development in Alzheimer's disease and other dementias.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.trci.2018.06.008.

RESEARCH IN CONTEXT

1. Systematic review: We downloaded Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI) data and analyzed the cognitive decline rate of mild cognitive impairment (MCI) subjects to see if there is any effect of sex and educational level in the Japanese population similar to previously published studies from Western countries. The findings in J-ADNI data set were evaluated in North American (NA)-ADNI data set for comparison.

2. Interpretation: Female subjects declined faster than males. High educational status protected the subjects from worsening in men. Amyloid-negative subjects tend to decline faster when their kidney function was impaired more than G2 in chronic kidney disease (CKD) grade. Higher Fazekas scores in magnetic resonance imaging (MRI) were associated with higher CKD grade only in female MCI subjects, suggesting vascular factor in accelerated decline. This finding was not replicated in NA-ADNI data set.

3. Future directions: Findings partially corroborated with previously published results regarding sex and educational level. The effect of CKD grading and cognitive decline could be evaluated in a different cohort.

References

[1] Iwatsubo T, Iwata A, Suzuki K, Ihara R, Arai H, Ishii K, et al. Japanese and North American Alzheimer's Disease Neuroimaging Initiative studies: harmonization for international trials. Alzheimers Dement 2018; https://doi.org/10.1016/j.jalz.2018.03.009 [Epub ahead of print].

[2] Mielke MM, Vemuri P, Rocca WA. Clinical epidemiology of Alzheimer's disease: assessing sex and gender differences. Clin Epidemiol 2014;6:37–48.

[3] Seshadri S, Wolf PA, Beiser A, Au R, McNulty K, White R, et al. Lifetime risk of dementia and Alzheimer's disease. The impact of mortality on risk estimates in the Framingham Study. Neurology 1997;49:1498–504.

[4] Letenneur L, Launer LJ, Andersen K, Dewey ME, Ott A, Copeland JR, et al. Education and the risk for Alzheimer's disease: sex makes a difference. EURODEM pooled analyses. EURODEM Incidence Research Group. Am J Epidemiol 2000;151:1064–71.

[5] Vadikolias K, Tsiakiri-Vatamidis A, Tripsianis G, Tsivgoulis G, Ioannidis P, Serdari A, et al. Mild cognitive impairment: effect of education on the verbal and nonverbal tasks performance decline. Brain Behav 2012;2:620–7.

[6] Scarmeas N, Albert SM, Manly JJ, Stern Y. Education and rates of cognitive decline in incident Alzheimer's disease. J Neurol Neurosurg Psychiatry 2006;77:308–16.

[7] Petersen RC, Aisen PS, Beckett LA, Donohue MC, Gamst AC, Harvey DJ, et al. Alzheimer's Disease Neuroimaging Initiative (ADNI): clinical characterization. Neurology 2010;74:201–9.

[8] Yamane T, Ishii K, Sakata M, Ikari Y, Nishio T, Ishii K, et al. Inter-rater variability of visual interpretation and comparison with quantitative evaluation of (11)C-PiB PET amyloid images of the Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI) multicenter study. Eur J Nucl Med Mol Imaging 2017;44:850–7.

[9] Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009;53:982–92.

[10] Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.

[11] Lin KA, Choudhury KR, Rathakrishnan BG, Marks DM, Petrella JR, Doraiswamy PM, et al. Marked gender differences in progression of mild cognitive impairment over 8 years. Alzheimers Dement (N Y) 2015;1:103–10.

[12] Ferreira L, Ferreira Santos-Galduroz R, Ferri CP, Fernandes Galduroz JC. Rate of cognitive decline in relation to sex after 60 years-of-age: a systematic review. Geriatr Gerontol Int 2014;14:23–31.

[13] Caracciolo B, Palmer K, Monastero R, Winblad B, Backman L, Fratiglioni L. Occurrence of cognitive impairment and dementia in the community: a 9-year-long prospective study. Neurology 2008; 70:1778–85.

[14] Roberts RO, Geda YE, Knopman DS, Cha RH, Pankratz VS, Boeve BF, et al. The incidence of MCI differs by subtype and is higher in men: the Mayo Clinic Study of Aging. Neurology 2012;78:342–51.

[15] Brinton RD, Yao J, Yin F, Mack WJ, Cadenas E. Perimenopause as a neurological transition state. Nat Rev Endocrinol 2015;11:393–405.

[16] Holland D, Desikan RS, Dale AM, McEvoy LK, Alzheimer's Disease Neuroimaging I. Higher rates of decline for women and apolipoprotein E epsilon4 carriers. AJNR 2013;34:2287–93.

[17] Xu W, Tan L, Wang HF, Tan MS, Tan L, Li JQ, et al. Education and risk of dementia: dose-response meta-analysis of prospective cohort studies. Mol Neurobiol 2016;53:3113–23.

[18] Sharp ES, Gatz M. Relationship between education and dementia: an updated systematic review. Alzheimer Dis Assoc Disord 2011; 25:289–304.

[19] Jones RN, Gallo JJ. Education and sex differences in the mini-mental state examination: effects of differential item functioning. J Gerontol B Psychol Sci Soc Sci 2002;57:P548–58.

[20] Doraiswamy PM, Krishen A, Stallone F, Martin WL, Potts NL, Metz A, et al. Cognitive performance on the Alzheimer's Disease Assessment Scale: effect of education. Neurology 1995;45:1980–4.

[21] Japan PCPCBCToI. Population 15 years of age and over, by school attendance and type of last school completed (6 groups), age (five-year groups), marital status (4 groups) and sex - Japan*. Statistics of Japan.

[22] Chapter 1: definition and classification of CKD. Kidney Int Suppl 2011;2013:19–62.

[23] Kurella M, Yaffe K, Shlipak MG, Wenger NK, Chertow GM. Chronic kidney disease and cognitive impairment in menopausal women. Am J Kidney Dis 2005;45:66–76.

[24] Khatri M, Nickolas T, Moon YP, Paik MC, Rundek T, Elkind MS, et al. CKD associates with cognitive decline. JASN 2009;20:2427–32.

[25] Martens RJ, Kooman JP, Stehouwer CD, Dagnelie PC, van der Kallen CJ, Koster A, et al. Estimated GFR, albuminuria, and cognitive performance: the Maastricht Study. Am J Kidney Dis 2017; 69:179–91.

[26] Chen CH, Chen YF, Chiu MJ, Chen TF, Tsai PH, Chen JH, et al. Effect of kidney dysfunction on cerebral cortical thinning in elderly population. Sci Rep 2017;7:2337.

[27] Kurella M, Chertow GM, Fried LF, Cummings SR, Harris T, Simonsick E, et al. Chronic kidney disease and cognitive impairment in the elderly: the health, aging, and body composition study. JASN 2005;16:2127–33.

[28] Muiesan ML, Ambrosioni E, Costa FV, Leonetti G, Pessina AC, Salvetti M, et al. Sex differences in hypertension-related renal and cardiovascular diseases in Italy: the I-DEMAND study. J Hypertens 2012; 30:2378–86.

[29] Yahagi K, Davis HR, Arbustini E, Virmani R. Sex differences in coronary artery disease: pathological observations. Atherosclerosis 2015; 239:260–7.

[30] Mathur P, Ostadal B, Romeo F, Mehta JL. Gender-related differences in atherosclerosis. Cardiovasc Drugs Ther 2015;29:319–27.

[31] Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012;367:20–9.