Disease progression modelling from preclinical Alzheimer's disease (AD) to AD dementia

Soo Hyun Cho
Samsung Medical Center
Sookyoung Woo
Samsung Medical Center
Changsoo Kim
Yonsei University College of Medicine
Hee Jin Kim
Samsung Medical Center
Hyemin Jang
Samsung Medical Center
Byeong C. Kim
Chonnam National University Medical School
Si Eun Kim
Inje University College of Medicine
Seung Joo Kim
Gyeongsang National University Hospital
Jun Pyo Kim
Samsung Medical Center
Young Hee Jung
Samsung Medical Center
Samuel Lockhart
Wake Forest University School of Medicine
Rik Ossenkoppele
VU medisch centrum School of Medical Sciences
Susan Landau
University of California Berkeley
Duk L. Na
Samsung Medical Center
Michael Weiner
University of California San Francisco
Seonwoo Kim
Samsung Medical Center
Sang Won Seo (sw72.seo@samsung.com)

samsung medical center

Research

Keywords: Alzheimer's disease, Disease progression modelling, preclinical Alzheimer's disease, AD dementia, sex and APOE ε4

Posted Date: December 23rd, 2019

DOI: https://doi.org/10.21203/rs.2.19451/v1

Abstract

Background: To characterize the course of Alzheimer's disease (AD) over a longer time interval, we aimed to construct a disease course model for the entire span of the disease using two separate cohorts ranging from preclinical AD to AD dementia.

Methods: We used longitudinal data from 127 participants with preclinical AD and 309 participants with mild cognitive impairments (MCI) due to AD from the Alzheimer's Disease Neuroimaging Initiative. In order to develop a model of progression from preclinical AD to AD dementia, we estimated Alzheimer's Disease Assessment Scale–Cognitive Subscale 13 (ADAS-cog 13) scores according to the follow-up time for each cohort, determined the time point at which the estimated scores of ADAS-cog 13 for the two cohorts first overlapped, and shifted the ADAS-cog 13 scores for the latter cohort at this time point to connect the two cohorts and to combine the data into a single unified progression course.

Results: The estimated years for progression from the median ADAS-cog 13 score in the preclinical AD cohort (9.3 points) to the median ADAS-cog 13 score at the time of progression in the participants who progressed from preclinical AD to MCI due to AD (16.0 points) was 7.8 years. The estimated years for progression from preclinical AD to the median ADAS-cog 13 score at the time of progression in those who progressed from MCI to due AD to AD dementia (26.8 points) was 15.2 years. ADAS-cog 13 scores deteriorated most rapidly in female APOE ε4 carriers and most slowly in male APOE ε4 non-carriers ($p < 0.001$).

Conclusion: Our results suggest that disease progression modelling from preclinical AD to AD dementia may help clinicians to estimate where patients are in the disease course and provide information on variation in the disease course by sex and APOE ε4 status.

Background

Understanding the course of disease progression across the whole Alzheimer's disease (AD) continuum including preclinical AD, mild cognitive impairment (MCI) due to AD, and AD dementia will help in designing clinical trials to test preventative interventions. Some studies have investigated the progression in preclinical AD [1], MCI due to AD [2] and AD dementia [3] separately. However, their mean follow-up durations of 1.4–6.2 years were too short to understand the progression across the entire AD spectrum. Unfortunately, following a single cohort for several decades is difficult, though not impossible (as demonstrated in the Nun Study [4], Framingham study [5] etc).

A potential approach would be to use cross sectional and longitudinal data from many individuals across the disease spectrum from no AD pathology to AD dementia, to estimate a single disease progression model across. This method is advantageous, as it allows us to construct a disease course model for the whole time span over a longer period using multiple separate cohorts. As far as we know, no such analysis has been used to the study of AD progression. Successfully constructing a model of the entire

AD spectrum would allow an analysis of potential covariates that have been suggested to influence the disease process.

In the present study, we developed a model of AD progression across its entire spectrum using two separate cohorts. To investigate whether APOE ε4 and sex influence rates of cognitive decline across the AD continuum, we also constructed the disease models by APOE ε4 and sex.

Methods

Participants

All data used in the present study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) website (www.adni-info.org) as of May 2017. ADNI is a multisite longitudinal biomarker study that has enrolled cognitively normal (CN), older individuals; people with early MCI (EMCI) and late MCI (LMCI) which are determined using the Wechsler Memory Scale Logical Memory II and people with early AD. EMCI defined as milder episodic memory impairment than the LMCI group. The present study consisted of 1091 participants enrolled in the ADNI-1, ADNI-GO and ADNI-2 cohorts who had available data for ADAS-cog13 testing and had ^{18}F-AV45 (Florbetapir) PET to assess amyloid-β (Aβ) deposition. According to the National Institute on Aging-Alzheimer's Association criteria [6–8], Aβ (+) CN or subjective memory concerns (SMC) were defined as preclinical AD and Aβ (+) EMCI or LMCI were defined as MCI due to AD. In the present study, we included participants who were categorized as preclinical AD and MCI due to AD by their baseline diagnosis

We excluded the following conditions: 1) 54 participants whose amyloid PET result changes; their amyloid PET result changed from positive to negative. 2) 40 participants in whom the ADAS-cog13 scores were obtained only once. Therefore, all enrolled participants performed ADAS-cog 13 at least two times. 3) 445 participants with amyloid pet negative result because amyloid negative CN could become amyloid positive then it is hard to make disease progression model with amyloid negative MCI. 4)116 participants with dementia at baseline were not included because their median time of follow-up was short (12 months) and ADAS-cog 13 scores for AD dementia participant were in the range of ADAS-cog 13 scores for participants who progressed from MCI due to AD to AD dementia (Fig. 1) [9].

All protocols were approved by Institutional Review Board in each participating sites and participants signed written informed consent at the time of enrolment. The authors obtained approval from the ADNI Data Sharing and Publications Committee for data use and publication.

Neuropsychological evaluation

For neuropsychological testing, participants undergo ADAS-Cog 13 at baseline, 6, 12, and ongoing annually performed for CN, MCI participants. We used ADAS-cog 13, which includes tests of attention and concentration, planning and executive function, verbal memory, nonverbal memory, praxis, delayed word recall, and number cancellation or maze tasks. ADAS-cog 13 scores range from 0 to 85. The ADAS-cog 13

is more responsive to disease progression than the ADAS-cog 11 in subjects with AD and similar or slightly more responsive in subjects with pre-dementia syndromes [10, 11].

Image acquisition and processing

We downloaded amyloid (florbetapir) PET data from the ADNI website. Florbetapir imaging consisted of four 5-min frames (dynamic 3D scan) acquired 50–70 min after injection of 370 MBq (10 mCi) of tracer; frames were realigned, averaged, resliced to a common voxel size (1.5 mm × 1.5 mm × 1.5 mm) and smoothed to a common resolution of 8 mm^3. MPRAGE images acquired concurrently with baseline florbetapir images and used as a structural template to define cortical and reference regions in native space for each subject with FreeSurfer. More detailed information can be found at http://www.loni.ucla.edu. A florbetapir cortical summary measurement (SUVR) was calculated by dividing cortical uptake by a whole cerebellum as a reference region. We included only amyloid-positive individuals with an Amyloid SUVR of 1.11 [12] or higher in our analysis.

APOE genotyping

APOE genotyping was performed on DNA obtained from participant blood samples with an APOE genotyping kit as described at the ADNI site (see http://www.adni-info.org for detailed information on blood sample collection, DNA preparation, and genotyping methods). APOE ε4 non-carriers were defined as no APOE ε4 allele and APOE ε4 carriers as one or two APOE ε4 alleles.

Statistical analysis

In order to model the disease progression course from preclinical AD to AD dementia using two cohorts, we carried out the following three steps: 1) estimating a model of ADAS-cog 13 scores according to the follow-up time for each cohort; 2) determining the time interval until the ADAS-cog 13 regions of the two cohorts overlapped, enabling the two cohorts to be combined into an entire course of disease progression; and 3) developing an AD progression model for the whole spectrum. In the first step, for each cohort, we examined the pattern of ADAS-cog 13 values of individuals with preclinical AD and MCI due to AD (Fig. 2a) and estimated a model for each cohort using a linear mixed model considering time as a fixed effect and subject as a random effect (Fig. 2b). In the development of the model, ADAS-cog 13 scores were square root–transformed due to a highly skewed distribution, and outliers with an absolute studentized residual larger than 3 were excluded. In the second step, we generated a estimated ADAS-cog 13 score and 95% confidence interval (CI) for each subject at each follow-up time based on the estimated model. Using these estimated values, we identified overlapping ranges of the estimated ADAS-cog 13 scores between the two cohorts (Fig. 2c). The estimated value of ADAS-cog 13 at which the 95% CI of the estimated values of the subjects in the two cohorts overlapped was identified, and the time corresponding to this ADAS-cog 13 score was determined. Then, the ADAS-cog 13 scores of the patients with MCI due to AD were shifted to this time (Fig. 2d). Finally, a single model for the entire course of AD was estimated by analysing data from the second step using a linear mixed model that included the same effect terms as the individual cohort models. In this model, the duration and its 95% CI for progression from preclinical AD to MCI due to AD and to AD dementia was calculated in terms of the time corresponding to the

median ADAS-cog 13 scores and the 95% CI for the progressed groups. To investigate the effect of sex and APOE ε4 status on ADAS-cog 13 decline, another progression model of the entire AD continuum was developed using a linear mixed model that included the combined effects of sex and APOE ε4 carrier status, as well as a time effect. The time from preclinical AD to AD dementia was also calculated with this model.

In a sensitivity analysis, we also adjusted for learning effects (LEs), because LEs related to repeated measurements may obscure cognitive decline and delay the detection of conversion to MCI [13] and AD. The magnitude of LEs was estimated and tested with six alternative linear mixed models according to the covariates of age at baseline, sex, and education level [14]. ADAS-cog 13 scores adjusted for LEs were used for the sensitivity analysis.

P-values were corrected for multiple testing using the Bonferroni method. Continuous and categorical variables were summarized as median (inter-quartile range (IQR, 1st quartile-3rd quartile) and frequency (percentage), respectively. A two-tailed P-value < 0.05 was considered to indicate statistical significance. The statistical analysis was performed with SAS 9.1.3 (SAS Institute Inc, Cary, NC, USA) and the R3.4.1 package (Vienna, Austria).

Results

Demographic and clinical characteristics of participants

The preclinical AD cohort included 127 participants, while the MCI due to AD cohort included 309 participants (Table 1). The median age of participants with preclinical AD was 74.6 years (IQR 70.8–78.5), while that of participants with MCI due to AD was 73.6 years (68.5–78.1). In the preclinical AD cohort and in the MCI due to AD cohort, 57 participants (44.9%) and 210 participants (68.0%) were APOE ε4 carriers, respectively. Women comprised 79 participants (62.2%) in the preclinical AD cohort, and 130 (42.1%) in the MCI due to AD cohort. The median years of education was 16 for both the preclinical AD cohort and the MCI due to AD cohort. The number of visits (median (IQR)) per participant was 5 (3–7) in the preclinical AD cohort and 6 (4–7) in the MCI due to AD cohort. The follow-up period was 48 (24–60) months in the preclinical AD cohort and 48 (36–60) months in the MCI due to AD cohort. The median (IQR) ADAS-cog 13 scores were 9.3 (6.7–12.0) in the preclinical AD cohort and 17 (12.0–21.0) in the MCI due to AD cohort. In the preclinical AD cohort, 37 participants (29.1%) progressed to MCI due to AD and 13 (10.2%) progressed to AD dementia. In the MCI due to AD cohort, 134 participants (43.4%) progressed to AD dementia.

Table 1
Demographics and clinical features of participants with AD

Diagnosis	Preclinical AD	MCI due to AD
Participants no. (%)	127 (29.2)	309 (70.9)
Age (year), median (IQR)	74.6 (70.8–78.5)	73.6 (68.5–78.1)
APOE ε4 carriers, no. (%)	57 (44.9)*	210 (68.0)*
Female, no. (%)	79 (62.2)*	130 (42.1)*
Education (year), median (IQR)	16 (14–18)	16 (14–18)
Follow up		
Number of visits per participant, median (IQR)	5 (3–7)	6 (4–7)
Follow up month, median (IQR)	48 (24–72)	48 (36–60)
ADAS-cog 13		
median (IQR)	9.3 (6.7–12.0)*	17 (12.0–21.0)*
Conversion to		
MCI due to AD, no (%)	37 (29.1)	
AD dementia, no (%)	13 (10.2)	134 (43.4)
Age, education, ADAS-cog 13 and month of follow-up are expressed as median (IQR).		
Categorical variables are expressed as no (%).		
Statistical analyses are performed with Chi-squared tests for APOEε4 carriers and sex. Mann Whitney test for age, education and ADAS-cog 13.		
*p < 0.05 between preclinical AD vs. MCI due to AD		
Abbreviations: AD = Alzheimer's Disease; ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale; APOE = Apolipoprotein E; IQR = interquartile range; MCI = mild cognitive impairment		

Disease progression modelling from preclinical AD to AD dementia

The median ADAS-cog 13 score was 16.0 points at the time of progression for participants who progressed from preclinical AD to MCI due to AD and 26.8 points at the time of progression for participants who progressed from MCI due to AD to AD dementia. The estimated years (95% CI) for progression from the median ADAS-cog 13 score in the preclinical AD cohort (9.3 points) to the median ADAS-cog 13 at the time of progression in participants who progressed from preclinical AD to MCI due to AD (16.0 points) was 7.8 (6.1–10.0) years. The estimated years for progression from preclinical AD to the median ADAS-cog 13 at the time of progression in the participants who progressed from MCI due to AD

to AD dementia (26.8 points) was 15.2 (14.1–15.9) years (Fig. 3). Additionally, when the calculation was performed using the median ADAS-cog 13 score for LMCI (19 points), the estimated time to progress from preclinical AD to LMCI was 8.9 years.

APOE ε4 effects on the course of disease progression by sex

We analysed differences in the rate of cognitive decline stratified by sex and APOE ε4 status (Fig. 4). APOE ε4 carriers had a steeper decline in ADAS-cog 13 scores than did APOE ε4 non-carriers regardless of sex ($p < 0.001$). Women also had a steeper decline in ADAS-cog 13 scores than men, irrespective of APOE ε4 carrier status ($p < 0.001$). ADAS-cog 13 scores deteriorated most rapidly for female APOE ε4 carriers and most slowly for male APOE ε4 non-carriers ($p < 0.001$). Using the median ADAS-cog13 values for participants with MCI due to AD who progressed to AD dementia, we calculated the time to progress from preclinical AD to AD dementia for four combinations of sex and APOE ε4 status (Table 2). We estimated that female APOE ε4 carriers with a median ADAS-cog 13 score (29 points) at the time of progression would take 11.5 (95% CI, 10.0-11.9) years to progress to AD dementia. When estimated in the same way, male APOE ε4 carriers took 12.7 (10.5–14.0) years to progress from preclinical AD to AD dementia, while female APOE ε4 non-carriers took 20.2 (13.5–23.7) years and male APOE ε4 non-carriers took 24.0 (17.7–30.9) years.

Table 2
Estimated time to reach AD dementia depending on APOE ε4 status by sex

Group	Participants (N)	ADAS-cog 13[a] Median (IQR)	Estimated years[b] (95% CI)
Female APOE ε4 carriers	44	29 (23.5–33.0)	11.5 (10.0, 11.9)
Male APOE ε4 carriers	57	25 (20.0–31.0)	12.7 (10.5, 14.0)
Female APOE ε4 non-carriers	14	31 (23.0–34.0)	20.2 (13.5, 23.7)
Male APOE ε4 non-carriers	19	25 (20.0–31.0)	24.0 (17.7, 30.9)

[a]ADAS-cog 13 median (IQR) at the point of conversion from MCI due to AD to AD dementia

[b]Estimated years from preclinical AD to AD dementia

We assigned the median ADAS-cog 13 score at the point of conversion from MCI due to AD to AD dementia to the equation for each sex and APOE ε4 combination to obtain the estimated converting year to AD dementia.

Abbreviations: ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale; APOE = Apolipoprotein E; IQR = interquartile range

Correction for learning effects

We performed a sensitivity analysis to investigate the robustness of LEs. LEs were significant and were estimated to affect a given ADAS-cog 13 score by -0.52 for preclinical AD and by -0.54 for MCI due to AD in all models (Additional file 1: Table S1). After correcting for LEs and repeating the analyses, we estimated the disease progression course from preclinical AD to AD dementia according to ADAS-cog 13 scores. The estimated times for preclinical AD to progress to MCI due to AD and to AD dementia were 6.7 (95% CI, 5.0–9.0) and 14.2 (13.1–14.9) years based on median ADAS-cog 13 scores (Additional file 1: Figure S1). When we analysed differences in the rate of cognitive decline based on a combination of sex and APOE ε4 status after correcting for LEs (Additional file 1: Figure S2), the progression order and significant differences among groups did not change compared to the analysis of data uncorrected for LE.

Discussion

In the present study, using two separate cohorts, we modelled disease progression from preclinical AD to AD dementia and determined whether APOE ε4 status and sex affected progression across the entire AD spectrum. Our main findings were as follows. Our novel disease progression model indicated that it would take 7.8 years for preclinical AD to progress to MCI due to AD and 15.2 years to progress to AD dementia based on median ADAS-cog 13 scores. APOE ε4 carriers and women had worse cognitive trajectories across the entire AD spectrum. Across all sex and APOE ε4 combinations, female APOE ε4 carriers had the fastest cognitive decline. Taken together, our findings provide a further understanding of AD progression across the disease spectrum, and they will help to design individualized therapeutic and preventive strategies to ameliorate cognitive decline.

We modelled the AD disease progression course using two different cohorts and estimated that it took almost 15 years for preclinical AD to progress to AD dementia. In a recent article [15], 14.5% of individuals with preclinical AD developed incident MCI due to AD within a 3.7 year (mean) follow-up period, and 3.2% developed AD dementia within 4.2 years of follow-up [15]. Additionally, studies have found that 32.7% [15] and 70.0% [16] of individuals with MCI due to AD developed AD dementia within 3.2 and 3.6 years of follow-up, respectively [15, 16]. However, 2–4 years of follow-up may not be sufficient to estimate the entire course of disease progression. These previous findings, thus, mainly characterize fast decliners in each disease stage. However, our estimated course is consistent with indirect evidence provided in previous studies [6, 17], according to which the temporal lag between Aβ deposition and the clinical syndrome of AD dementia was a decade [6]. In a meta-analysis, age-related increases in amyloid positivity on PET in participants with normal cognition paralleled age-specific, AD-type dementia prevalence estimates with an intervening period of about 20 years [17, 18]. Another study estimated that it took 19.2 years for ^{11}C-PiB levels observed in healthy controls with a 1.5 SUVR threshold to reach the mean SUVR of AD (2.3) [19]. Our finding that it would take more than 15 years for preclinical AD to progress to AD dementia suggests that appropriate interventions are needed to prevent preclinical AD from progressing to AD dementia.

In the present study, the estimated time from the preclinical to prodromal stage (7.8 years) was similar to that from the prodromal to dementia stage (7.4 years). Initially, we expected that the preclinical phase might be longer than the prodromal phase. Our finding might have been related to our definition of the prodromal phase using the early stage of MCI. If we define MCI due to AD as LMCI, the estimated time from preclinical AD to LMCI (8.9 years) would be longer than that from MCI due to AD to AD dementia (6.3 years). Alternatively, the study design—in particular, whether a study includes volunteer or clinic-based participants—might affect time-to-event estimates. For example, studies may overestimate the progression rate in the presymptomatic phase because the included participants might have more concerns about their cognition. Our disease progression model could therefore be used to estimate the current and future state of preclinical AD patients in a prevention trial.

Another main finding is that APOE ε4 and sex had distinct effects on the progression course across the AD continuum. Our finding that APOE ε4 aggravated cognitive decline across the entire AD spectrum regardless of sex is partially consistent with previous studies. While APOE ε4 is a well-known risk factor for AD dementia in the preclinical or prodromal stage [20], it has been debated whether APOE ε4 predicts a worse prognosis [21, 22]. A previous study by our group revealed that APOE ε4 predicted more rapid hippocampal and cortical atrophy in dementia with AD [21]. However, other studies have suggested that AD patients with APOE ε4 had a lower global amyloid burden than matched APOE ε4 non-carriers [22–24]. This discrepancy might be due to differences in the study populations (patients who progressed to AD dementia over time in the current study sample compared to patients who had already progressed to AD dementia in previous studies).

A more noteworthy finding that female APOE ε4 carriers showed more prominent cognitive decline than did male APOE ε4 carriers across the AD spectrum [25, 26]. Our findings are consistent with a previous study [25], which showed that women with higher Aβ levels had a faster cognitive decline than men and that women with preclinical AD who were APOE ε4 carriers declined faster than their men counterparts. However, the previous findings were not statistically significant after correction for multiple comparisons [25]. Our findings further suggest that female APOE ε4 carriers had a steeper cognitive decline than did male APOE ε4 carriers throughout the entire AD spectrum. Therefore, developing a progression model stratified by these factors will help to select cohorts for AD clinical trials.

Several possible explanations may account for the combined effects of sex and APOE [27–30]. A potential mechanism could be that oestradiol promotes synaptic sprouting in response to injury through an APOE-dependent mechanism [27]. Additionally, oestrogen might promote neural function under normal conditions, but exacerbate dysfunction when network activity is disrupted [28]. Alternatively, a previous study showed that the APOE ε4-by-sex interaction on cerebrospinal fluid (CSF) tau levels was significant, suggesting that the increased APOE-related risk in women may be associated with tau pathology [29]. In a recent multicohort study [30], women showed a stronger association between APOE and CSF tau levels than did men, particularly among amyloid-positive individuals, suggesting that APOE may modulate the risk of downstream neurodegeneration in a sex-specific manner, particularly in the presence of amyloidosis.

The ADNI is a well-organized, longitudinal cohort that serves as an excellent resource to investigate the disease course of AD. This study, however, has several limitations. We only included participants who were amyloid-positive by PET. This leaves open the possibility that some patients had another primary pathological diagnosis. Although participants clinically diagnosed with frontotemporal dementia or dementia with Lewy bodies and who had moderate to severe white matter hyperintensity were excluded from the ADNI dataset, we did not consider the effects of other neurodegenerative pathologies, including cerebrovascular disease, α-synuclein, transactive response DNA-binding protein, argyrophilic grain pathology, and hippocampal sclerosis, on the progression model. Importantly, amyloid positivity might only be a contributing or incidental factor in some patients with dementia. This argument is mitigated to some degree by the fact that we included participants who progressed from MCI due to AD to AD dementia. Additionally, we found that the ADAS-cog 13 scores in some participants with CN and MCI improved over time. Although we controlled for LEs, we did not completely exclude the possibility that LEs might affect the disease progression to some degree.

Nevertheless, ADAS-cog 13 is the standard tool used in many clinical trials to assess AD, which makes our results more interpretable across studies than if we had used another instrument. Finally, our progression rate from NC to MCI (29.1%) was higher than has been observed in community-recruited older adults. For example, a greater risk of progression from NC to MCI was observed in clinically-recruited older adults (30% per year) than in community-recruited older adults (5% per year) [31]. The ADNI used identical recruitment mechanisms to those of typical trials, including advertising and recruitment from memory clinics. Although our data might not be representative of the general population, the recruitment and subject baseline characteristics were similar to those of a typical AD clinical trial.

Conclusions

In the current study, we found that our model of the progression to disease may help clinicians to predict where patients are in the disease course. In addition, it will help to predict how the disease course could vary by sex and APOE ε4 status when consulting with patients and predicting treatment effects. Understanding the natural history of AD and the rates of change of clinical phenotypes and biomarkers will facilitate specific appropriate interventions.

Abbreviations

Aß: amyloid-β; AD: Alzheimer’s disease; ADD: AD dementia; ADAS-cog 13: Alzheimer’s Disease Assessment Scale–Cognitive Subscale 13; ADNI, Alzheimer’s Disease Neuroimaging Initiative; APOE: Apolipoprotein E; CN: cognitively normal; LE: learning effects; MCI: mild cognitive impairment; SMC: subjective memory concerns

Declarations

Acknowledgements

Not applicable

Funding

This research was supported by a National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIP) (No. NRF-2017R1A2B2005081), Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea **(HI18C0335)** and Research of Korea Centers for Disease Control and Prevention (No. 2018-ER6203-01).

Availability of data and materials

All raw data are available on the ADNI website. Anonymized and statistical information of all the participants are available, upon reasonable request only among qualified investigators.

Authors' contributions

SHC, SYW, SK and SWS contributed to the study conception, design of the study, data analysis, data interpretation and drafting. HJK, HMJ, BCK, SEK, SJK, JPK, YHJ and DLN contributed to data interpretation. SL, RO, SL and MW drafted the manuscript.

Ethics approval and consent to participate

The Institutional Review Boards approved this study at all participating centers. Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

References

1. Donohue MC, Sperling RA, Petersen R, Sun CK, Weiner MW, Aisen PS, et al. Association Between Elevated Brain Amyloid and Subsequent Cognitive Decline Among Cognitively Normal Persons. JAMA. 2017;317:2305-16.
2. Ward A, Tardiff S, Dye C, Arrighi HM. Rate of conversion from prodromal Alzheimer's disease to Alzheimer's dementia: a systematic review of the literature. Dement Geriatr Cogn Dis Extra. 2013;3:320-32.
3. Cho H, Jeon S, Kang SJ, Lee JM, Lee JH, Kim GH, et al. Longitudinal changes of cortical thickness in early- versus late-onset Alzheimer's disease. Neurobiol Aging. 2013;34:1921 e9-1921 e15.
4. Snowdon DA, Nun S. Healthy aging and dementia: findings from the Nun Study. Ann Intern Med. 2003;139:450-4.
5. Wolf PA. Contributions of the Framingham Heart Study to stroke and dementia epidemiologic research at 60 years. Arch Neurol. 2012;69:567-71.
6. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7:280-92.
7. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7:270-9.
8. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Jr., Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7:263-9.
9. Aisen PS, Petersen RC, Donohue M, Weiner MW, Alzheimer's Disease Neuroimaging I. Alzheimer's Disease Neuroimaging Initiative 2 Clinical Core: Progress and plans. Alzheimers Dement. 2015;11:734-9.
10. Skinner J, Carvalho JO, Potter GG, Thames A, Zelinski E, Crane PK, et al. The Alzheimer's Disease Assessment Scale-Cognitive-Plus (ADAS-Cog-Plus): an expansion of the ADAS-Cog to improve responsiveness in MCI. Brain Imaging Behav. 2012;6:489-501.
11. Mohs RC, Knopman D, Petersen RC, Ferris SH, Ernesto C, Grundman M, et al. Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's Disease Assessment Scale that broaden its scope. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord. 1997;11 Suppl 2:S13-21.
12. Landau SM, Mintun MA, Joshi AD, Koeppe RA, Petersen RC, Aisen PS, et al. Amyloid deposition, hypometabolism, and longitudinal cognitive decline. Ann Neurol. 2012;72:578-86.

13. Elman JA, Jak AJ, Panizzon MS, Tu XM, Chen T, Reynolds CA, et al. Underdiagnosis of mild cognitive impairment: A consequence of ignoring practice effects. Alzheimers Dement (Amst). 2018;10:372-81.
14. Vivot A, Power MC, Glymour MM, Mayeda ER, Benitez A, Spiro A, 3rd, et al. Jump, Hop, or Skip: Modeling Practice Effects in Studies of Determinants of Cognitive Change in Older Adults. Am J Epidemiol. 2016;183:302-14.
15. Roberts RO, Aakre JA, Kremers WK, Vassilaki M, Knopman DS, Mielke MM, et al. Prevalence and Outcomes of Amyloid Positivity Among Persons Without Dementia in a Longitudinal, Population-Based Setting. JAMA Neurol. 2018;75:970-9.
16. Ye BS, Kim HJ, Kim YJ, Jung NY, Lee JS, Lee J, et al. Longitudinal outcomes of amyloid positive versus negative amnestic mild cognitive impairments: a three-year longitudinal study. Sci Rep. 2018;8:5557.
17. Jansen WJ, Ossenkoppele R, Knol DL, Tijms BM, Scheltens P, Verhey FR, et al. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. JAMA. 2015;313:1924-38.
18. Jansen WJ, Ossenkoppele R, Tijms BM, Fagan AM, Hansson O, Klunk WE, et al. Association of Cerebral Amyloid-beta Aggregation With Cognitive Functioning in Persons Without Dementia. JAMA Psychiatry. 2018;75:84-95.
19. Villemagne VL, Burnham S, Bourgeat P, Brown B, Ellis KA, Salvado O, et al. Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. Lancet Neurol. 2013;12:357-67.
20. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA. 1997;278:1349-56.
21. Kim YJ, Cho H, Kim YJ, Ki CS, Chung SJ, Ye BS, et al. Apolipoprotein e4 affects topographical changes in hippocampal and cortical atrophy in Alzheimer's disease dementia: a five-year longitudinal study. J Alzheimers Dis. 2015;44:1075-85.
22. Lehmann M, Ghosh PM, Madison C, Karydas A, Coppola G, O'Neil JP, et al. Greater medial temporal hypometabolism and lower cortical amyloid burden in ApoE4-positive AD patients. J Neurol Neurosurg Psychiatry. 2014;85:266-73.
23. Rowe CC, Ellis KA, Rimajova M, Bourgeat P, Pike KE, Jones G, et al. Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. Neurobiol Aging. 2010;31:1275-83.
24. Ossenkoppele R, van der Flier WM, Zwan MD, Adriaanse SF, Boellaard R, Windhorst AD, et al. Differential effect of APOE genotype on amyloid load and glucose metabolism in AD dementia. Neurology. 2013;80:359-65.
25. Buckley RF, Mormino EC, Amariglio RE, Properzi MJ, Rabin JS, Lim YY, et al. Sex, amyloid, and APOE epsilon4 and risk of cognitive decline in preclinical Alzheimer's disease: Findings from three well-characterized cohorts. Alzheimers Dement. 2018;14:1193-203.

26. 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.
27. Stone DJ, Rozovsky I, Morgan TE, Anderson CP, Finch CE. Increased synaptic sprouting in response to estrogen via an apolipoprotein E-dependent mechanism: implications for Alzheimer's disease. J Neurosci. 1998;18:3180-5.
28. Broestl L, Worden K, Moreno AJ, Davis EJ, Wang D, Garay B, et al. Ovarian Cycle Stages Modulate Alzheimer-Related Cognitive and Brain Network Alterations in Female Mice. eNeuro. 2018;5:ENEURO.0132-17.2018.
29. Altmann A, Tian L, Henderson VW, Greicius MD. Sex modifies the APOE-related risk of developing Alzheimer disease. Ann Neurol. 2014;75:563-73.
30. Hohman TJ, Dumitrescu L, Barnes LL, Thambisetty M, Beecham G, Kunkle B, et al. Sex-Specific Association of Apolipoprotein E With Cerebrospinal Fluid Levels of Tau. JAMA Neurol. 2018;75:989-98.
31. Chen Y, Denny KG, Harvey D, Farias ST, Mungas D, DeCarli C, et al. Progression from normal cognition to mild cognitive impairment in a diverse clinic-based and community-based elderly cohort. Alzheimers Dement. 2017;13:399-405.

Figures

Figure 1

Flow Diagram for Selection of the Study Participants We excluded the following participants: 1) 54 participants whose amyloid PET result changed from positive to negative; 2) 40 participants in whom ADAS-cog13 scores were obtained only once; 3) 445 participants with amyloid-negative PET results, because if amyloid-negative CN could become amyloid-positive, it would be difficult to create a disease progression model with amyloid-negative MCI; and 4) 116 participants with dementia at baseline, because their follow-up was short and the ADAS-cog 13 scores of AD dementia participants were in the range of the ADAS-cog 13 scores of participants who progressed from MCI due to AD to AD dementia. Abbreviations: AD = Alzheimer's Disease; ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale

Figure 2

Modelling the course of Alzheimer’s disease with ADAS-cog 13 scores (a) The pattern of individual ADAS-cog 13 scores in individuals with preclinical AD and MCI due to AD. (b) The estimated model of ADAS-cog 13 scores over time for each cohort, obtained from a linear mixed model with time as a fixed effect and

subjects as a random effect (excluding outliers). (c) The estimated ADAS-cog 13 score and 95% confidence interval were examined for all follow-up times for all subjects. The estimated ADAS-cog 13 was 15.8 points at the point where the 95% CI for the estimated ADAS-cog 13 score of the two cohorts began to overlap. Y axis: subject ID, X axis: Estimated value of ADAS-cog 13. (d) Scatter plot of the combined preclinical AD and MCI due to AD cohorts shifted by the time of 93.9 months, corresponding to an ADAS-cog 13 score of 15.8 points. Abbreviations: AD = Alzheimer's Disease; ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale; MCI = mild cognitive impairment

Figure 3

Disease progression model from preclinical AD to AD dementia The curves present the estimated model—ADAS-cog 13=(2.8492+0.0130*month)2-0.5 and its 95% CI—and the plots show preclinical AD (green dots), progression to MCI due to AD (yellow dots), MCI due to AD (blue dots), and progression to AD dementia (red dots). Using the median ADAS-cog 13 scores at the time of progression for individuals who progressed from preclinical AD to MCI due to AD (16.0 points) and from MCI due to AD to AD dementia (26.8 points), we estimated the time for preclinical AD to progress to MCI due to AD (7.8 years) and to AD dementia (15.2 years). When using the median ADAS-cog 13 scores for late MCI (19.0 points) to estimate time to progression, it took 8.9 years for preclinical AD to progress to late MCI. Abbreviations: AD = Alzheimer's Disease; ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale; MCI = mild cognitive impairment

Figure 4

APOE ε4 and sex effects on disease progression We analysed differences in cognitive decline by sex and APOE ε4 status. Different-coloured lines indicate female APOE ε4 carriers (red), female APOE ε4 non-carriers (pink), male APOE ε4 carriers (dark blue) or male APOE ε4 non-carriers (light blue). The estimated equation for each APOE ε4 and sex combination is as follows: ADAS Cog-13=(2.6131+0.0203*month)2-0.5 for female APOE ε4 carriers =(2.6842+0.0121*month)2-0.5 for female APOE ε4 non-carriers = (3.1198+0.0127*month)2-0.5 for male APOE ε4 carriers =(3.0806+0.0068*month)2-0.5 for male APOE ε4 non-carriers Abbreviations: ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale; APOE = Apolipoprotein E

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile.docx
- SFigure2.tif
- SFigure1.tif