Disease progression modeling of Alzheimer's disease according to education level

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Abstract

Background To develop a disease progression model of Alzheimer's disease (AD) that shows cognitive decline from subjective cognitive impairments (SCI) to dementia and to investigate the effect of education level on the whole disease spectrum. Methods We enrolled 565 patients who were followed up more than three times and had a clinical dementia rating sum of boxes (CDR-SB) score. Three cohorts, SCI (n=85), amnestic mild cognitive impairment (AMCI, n=240), and AD dementia (ADD, n=240), were overlapped in two consecutive cohorts (SCI and AMCI, AMCI and ADD) to construct a model of disease course, and a model with multiple single-cohorts was estimated using a mixed-effect model. To examine the effect of education level on disease progression, the disease progression model was developed with data from lower (≤12) and higher (>12) education groups. Results Disease progression takes 277.0 months (23.1 years) to advance from 0 to 18 points using the CDR-SB score. Based on our predictive equation, it takes 101.9 months to progress from SCI to AMCI and 71.1 months to progress from AMCI to ADD. The rate of CDR-SB progression was different according to education level. The lower-education group showed faster CDR-SB progression from SCI to AMCI compared to the higher-education group, and this trend disappeared from AMCI to ADD. Conclusion In the present study, we developed a disease progression model of AD spectrum from preclinical to the end stage of the disease. Our findings suggest that the contribution of education to cognitive decline varies depending on disease stage.

Background

Understanding Alzheimer's disease (AD) progression could be helpful in staging the current level of disease severity, establishing a management plan, predicting prognosis, and comparing the effects of treatment. However, there is limited knowledge about the temporal course of the AD spectrum, such as subjective cognitive impairments (SCI), amnestic mild cognitive impairment (AMCI), and AD dementia (ADD), because previous longitudinal studies have been conducted at a specific disease status.[1-3] Although a few studies have followed baseline cognitive participants to ADD, it is difficult because it can take several decades to develop dementia. In addition, representative ADD patients are limited because only a small number progress to actual dementia even if there are a large number of patients. Therefore, a statistical modeling study is required to understand the course of disease progression in AD.

Education level has been considered an important factor influencing the course of AD progression. However, evidence relating to the effect of education on cognitive trajectories across the whole disease spectrum is controversial. Previous studies have suggested that the impact of education tended to vary from early stage to late stage.[4-6] Thus, it remains uncertain whether education affects changes in the cognitive trajectory.

In the present study, we estimated a model of disease progression for the whole time span over a longer period using separate multiple cohorts. Each cohort was measured longitudinally from many individuals across the disease spectrum from the preclinical stage to the end stage of the disease. We therefore aimed to develop a disease progression model of AD that shows cognitive and functional performance

decline from the preclinical stage to the end stage. In addition, we investigated the effects of education level on progression across the whole disease spectrum

Methods

Participants

We enrolled 645 patients (129 SCI, 270 AMCI, and 246 ADD) who were followed up more than three times to obtain CDR-SB scores at the Samsung Medical Center from Jan. 2003 to Dec. 2015. Experienced neurologists evaluated the participants based on their clinical symptoms and reviews of medical/medication history, neuropsychological test results, magnetic resonance imaging (MRI), and laboratory tests. ADD patients met the criteria proposed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)[7]. The diagnosis of AMCI was based on the criteria proposed by Peterson and colleagues [8] with inclusion of the following modifications: (1) Subjective cognitive complaints by the patient or his/her caregiver, (2) normal activities of daily living, (3) objective memory decline assessment below the 16th percentile on neuropsychological tests, and (4) absence of dementia. The SCI group were individuals who had a self-reported persistent decline in cognitive/memory capacity but were not impaired on neuropsychological tests.[9]

In all three groups, we excluded participants with other structural lesions such as territorial infarction, intracranial hemorrhage, brain tumor, hydrocephalus, or severe white matter hyperintensities (WMH) observed on brain MRI. Severe WMH on MRI was defined as a cap or a band ≥10 mm as well as a deep white matter lesion ≥25 mm as modified from the Fazekas ischemia criteria.[10] We also excluded 79 patients whose CDR-SB score decreased or did not change during follow up. Finally, we included 85 SCI, 240 AMCI, and 240 ADD patients.

Education

We interviewed all subjects and caregivers to evaluate detailed information about their educational background, including whether or not they had completed each step of education (elementary school, middle school, high school, college, and graduate school). We divided subjects into two groups: those with more than 12 years of education and those with less. This cut-off was used because it corresponds to the duration of schooling that precedes the beginning of college in South Korea. Overall, 49 SCI, 144 AMCI, and 185 ADD patients were in the lower-education group (education ≤ 12 years) and 36 SCI, 96 AMCI, and 55 ADD patients were in the higher-education group (education > 12 years).

Neurophychological assessments

All patients underwent a standardized neuropsychological battery called the SNSB [11] and the CDR-SB. The SNSB, which is performed in most memory clinics in South Korea, consists of tests for verbal and visual memory, attention, language, praxis, four elements of the Gerstmann syndrome, visuoconstructive

function, frontal executive function, and the mini-mental state examination (MMSE). The CDR-SB is a three-point scale used to characterize six domains of cognitive and functional performance. CDR-SB scores from 0 to 18 were used.

To perform the SNSB in a memory clinic at a university hospital, the certificate of a 'Clinical Psychologist' authorized by the Korean Clinical Psychological Association is required. The qualifications required to obtain a certificate are: A graduate with a master's degree (clinical psychology major) who has completed three years of training under the guidance of a clinical psychologist or a graduate with a doctorate (clinical psychology major) who has completed two years of training under the guidance of a clinical psychologist. At least 3,000 hours of training is required for three years at the mandatory training institute.

Brain MRI scans

All patients underwent brain MRI including T2, FLAIR, T2* GRE, and three-dimensional (3D) T1 images at Samsung Medical Center using the same model of 3.0 T MRI scanner (Philips 3.0 T Achieva; Best, the Netherlands).

Statistical analysis

The descriptive statistics for continuous variables are presented by median and inter-quartile range (IQR, 1^{st} quartile, 3^{rd} quartile) due to the non-normality of variables (Table 1). The Shapiro Wilk test was used to test the normality. Categorical variables were summarized by frequencies and percentages. The pattern of CDR-SB scores was examined using a spaghetti plot (Figure 1A). CDR-SB with skewed distribution was transformed by the natural log after adding 0.5 to all scores because zero scores occur in CDR-SB. Locally weighted scatter plot smoothing (LOWESS) was used to fit a smooth line to a scatter plot (Figure 1B). A mixed-effect model with a random effect for the subject and a fixed effect for the time was applied to each set of disease cohort data. Time effect was fitted using a linear term or a quadratic term in the each model (Figure 1C). Studentized residuals were used to examine model assumptions and to detect outliers for each model. The observations with absolute studentized residuals greater than 3 were considered as outliers and excluded from the analysis. The improvements in the goodness of fits to the models were evaluated using Akaike information criterion (AIC), Bayesian information criterion (BIC), and AIC with a correction for finite sample sizes (AICC). From the predicted values and 95% confidence intervals for CDR-SB in all individuals for each cohort, overlapped intervals between two consecutive cohorts (SCI and AMCI, AMCI and ADD) and corresponding time periods were calculated (Figure 1D). These time periods were applied to overlap the two consecutive cohorts in constructing a disease progression model, and a model with multiple single-cohorts was estimated using a mixed-effect model. To examine the effect of education level on disease progression, another disease progression model of the entire ADD continuum was developed in lower and higher-education groups using mixed effect models. The time from SCI to AMCI and the time from AMCI to ADD were also calculated with this model. The change in the trend of CDR-SB over time between higher and lower-education groups was tested. For

all tests, a *p*-value < 0.05 was considered statistically significant. Statistical analysis was performed using SAS 9.4 (SAS Institute Inc, Cary, NC) and R 3.5.1 (Vienna, Austria) ggplot2 package.

Results

Clinical characteristics of participants

Table 1 summarizes the demographic characteristics of 565 patients. The number of subjects was 85, 240, and 240 in the SCI, AMCI, and ADD groups, respectively. Their median (IQR) age was 69 (64–75), 73 (65–77), and 74 (68–80) and median (IQR) years of education were 12 (6–16), 12 (6.5–16), and 9 (6–12), respectively.

Development of a disease progression model of AD

Combining SCI, AMCI, and ADD cohorts, we developed a disease progression model of AD. The predictive equation for the curve was as follows: $\ln(\text{CDR-SB} + 0.5) = -0.0885 + 0.006145 \times \text{time} + 0.000017 \times \text{time}^2$

Based on the predictive equation, it takes 277.0 months to increase the CDR-SB score from 0 to 18 points. The predicted CDR-SB score of measurements to convert from the SCI to the AMCI group was 1.21 (95% CI: 1.09–1.34) and the corresponding time was 101.9 months. The predicted CDR-SB value of measurements to convert from the AMCI to the ADD group was 4.02 (95% CI: 3.79–4.27) and the corresponding time was 71.1 months (Table 2).

Development of a disease progression model of AD according to education level

We also developed a disease progression model in lower and higher-education groups. The predictive equations for the curves were as follows (Figure 3):

Lower-education group: $\ln(\text{CDR-SB} + 0.5) = -0.01585 + 0.005247 \times \text{time} + 0.000021 \times \text{time}^2$

Higher-education group: $\ln(\text{CDR-SB} + 0.5) = -0.1377 + 0.00323 \times \text{time} + 0.000022 \times \text{time}^2$

Based on the predictive equations, the lower-education group takes 152.0 months to increase the CDR-SB score from 0 to 18 points. The predicted CDR-SB value for measurements to convert from the SCI to the AMCI group was 1.35 (95% CI: 1.19–1.52) and the corresponding time was 105.8 months. The predicted CDR-SB value for measurements to convert from the AMCI to the ADD group was 4.04 (95% CI: 3.78–4.31) and the corresponding time was 61.7 months.

The higher-education group takes 189.7 months to increase the CDR-SB value from 0 to 18 points. The predicted CDR-SB value for measurements to convert from the SCI to the AMCI group was 1.17 (95% CI: 1.01–1.36) and the corresponding time was 141.8 months. The predicted CDR-SB value for measurements to convert from the AMCI to the ADD group was 3.68 (95% CI: 3.31–4.09) and the corresponding time was 47.8 months.

We also observed the time it takes to increase the CDR-SB value in the model according to the level of education. In all sections, it takes less time to increase the CDR-SB value in the lower-education group (Table 3). The interaction effect (Time*Education group) was statistically significant ($p < .0001$). Consequently, the increase in the rate of CDR-SB is significantly faster in the lower-education group compared to that in the higher-education group.

Discussion

We estimated the entire disease progression of AD in a model using CDR-SB follow-up data from three relatively large-sized cohorts, SCI, AMCI, and ADD. Based on the predictive equation, it takes 277.0 months to increase the CDR-SB value from 0 to 18 points. We also found that it takes 101.9 months to progress from SCI to AMCI and 71.1 months to progress from AMCI to ADD. In particular, the CDR-SB progression from SCI to AMCI was faster in the lower-education group compared to the higher-education group, and this trend disappeared from AMCI to ADD. Taken together, our findings suggest that it might be helpful to stage the current level of disease severity and establish management plans by education level.

In the present study, we developed a disease progression model for the ADD spectrum. We found that the ADD process takes 277.0 months (23.1 years) to progress from 0 to 18 points in the CDR-SB value. Previous studies were limited in showing the entire disease progression from the preclinical stage to the end stage of the disease. Instead, previous modeling studies have reported different disease progression rates depending on disease severity,[12-14] the prediction of disease onset time,[15] and the impact of biomarkers on the disease course.[14, 16-18] In addition, our model is based on the CDR-SB, which is one of the most widely used dementia staging systems, and represents a validated, well-described, and reliable measure of disease progression.[19, 20] The CDR-SB has the advantage of being able to measure changes precisely over time from the preclinical stage to the end state of disease. Thus, our disease progression model represents the patients' functional ability across the whole disease spectrum.

Based on our predictive equation, it takes 101.9 months (8.4 years) to progress from SCI to AMCI and 71.1 months (6.0 years) to progress from AMCI to ADD. Similar to our results, one progression model study predicted that it took 7.9 years on average from cognitively normal to AMCI.[21] Another progression model study suggested that it took 4.3 years from AMCI to ADD,[1] and a previous study also showed that 60% of AMCI participants progress to ADD in 5 years.[17]

A noteworthy finding was that the lower-education group showed a faster CDR-SB progression from SCI to AMCI than the higher-education group, and this trend disappeared from AMCI to AD. Our findings were consistent with previous studies. That is, many previous studies have shown that high education in cognitively normal participants has a protective effect on cognitive decline or development of dementia, whereas in the dementia stage, these protective effects disappeared or higher educated dementia patients showed a steeper cognitive decline than lower educated patients with dementia. Furthermore, our previous study using CDR-SB showed that the protective effects in the higher-education group remain in

the early stage of AMCI, whereas it disappeared in the late stage of AMCI. This might be related to the pathophysiological burden to the brain over time that could not be compensated by cognitive reserve. Some studies suggest that a high education delayed the change point of accelerated cognitive decline, but was related to a steeper cognitive decline after the change point.[4, 6] Our previous MRI study of AD patients showed that the higher-education group is associated with greater brain cortical atrophy over time.[22] Inconsistent with our results, a recent study suggested that higher education was not associated with the onset or rate of accelerated cognitive decline, but the cut-off value of the lower-education group in this study was relatively high (14 years) compared to our study (12 years).[17]

Interestingly, the CDR-SB value at the conversion of SCI to AMCI or AMCI to ADD is lower in the higher-education group than in the lower-education group. Perhaps this is because the higher-education group are more likely to be involved in cognitive tasks or occupational roles where subtle cognitive decline could be easily detected before the CDR-SB value progressed further. Alternatively, considering that CDR reflects the activity of daily living (ADL) as well as cognition, it might be reasonable to expect that ADL is relatively conserved even after cognitive decline in the higher-education group.

The principal strength of this study is that the disease progression model for the whole time using multiple single-cohorts was estimated with a well-evaluated and large sample followed a maximum of 76 months. However, there are several limitations. First, we included patients based on clinical symptoms and reviews of medical/medication history, neuropsychological test results, MRI, and laboratory tests. Our patients were not confirmed by amyloid PET results, but only patients with a typical AD progression were included in our study. Second, we estimated that a model of the entire disease progression is built on CDR-SB, which is based on an interview with the patient and an informant that could be influenced by subjective aspects. To overcome this bias as much as possible, our CDR scores were evaluated by certified clinical psychologists. In addition, our model might have a limitation in the early stages of AMCI when the ADL is not impaired. Third, other variables that often overlap with education level were not excluded. For instance, better social-economic states are more supportive of accomplishing a higher education level, which may bring occupational attainment and good lifestyles.[23] However, our findings are noteworthy because our model allows an estimate of the time point of each individual patient in the disease trajectory using CDR-SB according to the level of education. The findings might have relevance in establishing public policies for AD.

Conclusion

The developed model is suitable for describing the progression of disease in AD, which takes 277.0 months to advance from 0 to 18 points in the CDR-SB value. The disease progression calculated by our equation showed that the progress based on CDR-SB was different according to the level of education.

List Of Abbreviations

AD: Alzheimer’s disease; ADD: Alzheimer’s disease dementia; AMCI: amnestic mild cognitive impairment; CDR-SB: clinical dementia rating sum of boxes; LOWESS: locally weighted scatter plot smoothing; MRI: magnetic resonance imaging; MMSE: mini-mental state examination; NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association; SCI: subjective cognitive impairment; WMH: white matter hyperintensities

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Samsung Medical Center. The requirement for participant’s consent was waived since we used retrospective de-identified data.

Consent for publication

Not applicable

Availability of data and materials

Anonymized and statistical information of all the participants were made available and shared only among qualified investigators.

Competing interests

The authors declare that they have no competing interest

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Not applicable

Authors’ contributions

K.W. Kim, D.L. Na, and S.W. Seo and contributed to the study concept and design. S.Y. Woo and S. Kim analysed and interpreted data. K.W. Kim and S.W. Seo drafted the manuscript. Y. Kim, H. Jang, S.H. Cho, Kim, S.E. Kim, S.J. Kim, and H.J. Kim and were involved data acquisition and manuscript revision.

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Not applicable

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Tables

Table 1. Demographics

	Low education (≤12)			High education (>12)			Total		
	SCI	AMCI	AD	SCI	AMCI	AD	SCI	AMCI	AD
N	49	144	185	36	96	55	85	240	240
Number of visits, median (IQR)	5 (3-6)	4 (3-5)	4 (3-5)	4 (3-5)	4 (3-6)	4 (3-5)	4 (3-5)	4 (3-5)	4 (3-5)
Follow up month, median (IQR)	80.1 (59.8-113.2)	46.2 (34.1-60.9)	40.1 (29.3-58.8)	78.8 (61.8-92.8)	48.0 (35.2-65.1)	40.1 (29.3-58.8)	79.3 (59.8-107.1)	47.1 (34.8-62.0)	42.7 (29.8-59.2)
Age (year), median (IQR)	70 (66-75)	73 (64-77)	75 (69-80)	68 (60-74)	73 (67-78)	72 (65-76)	69 (64-75)	73 (65-77)	74 (68-80)
Male, no. (%)	3 (6.1)	28 (19.4)	39 (21.1)	16 (44.4)	65 (67.7)	35 (63.6)	19 (22)	93 (39)	75 (31)
Education (year), median (IQR)	8 (5-12)	9 (6-12)	6 (3-11)	16 (16-16)	16 (16-16)	16 (15-16)	12 (6-16)	12 (6.5-16)	9 (6-12)
Baseline CDR-SB, median (IQR)	0.5 (0.5-1.0)	1.5 (1.0-2.0)	4.0 (3.0-5.0)	0.5 (0-0.5)	1.0 (1.0-1.5)	3.5 (2.5-4.5)	0.5 (0.0-1.0)	1.5 (1.0-2.0)	4.0 (3.0-5.0)
APOE 4 carries, no (%)†	10/31 (68)	50/120 (58)	54/110 (49)	13/26 (50)	35/84 (52)	19/31 (28)	23/57 (40)	85/204 (42)	73/141 (52)

AD: Alzheimer’s disease; AMCI: amnestic mild cognitive impairment; APOE 4: apolipoprotein E4; CDR-SB: clinical dementia rating sum of boxes; SCI: subjective cognitive impairment

IQR: Inter-Quartile Range

†APOE4 was analyzed in 402 patients. Participants with 1 or more copies of 4 allele (i.e. 2/4, 3/4,

4/4) are considered 4 carriers.

Table 2. Time to transition to disease status according to the level of education

	Number of subjects	Time to progression (months)	
		SCI → AMCI	AMCI → AD
Lower education group (≤ 12years)	378	105.8	61.7
Higher education group (> 12years)	187	141.8	47.8
Total	565	101.9	72.0

AD: Alzheimer's disease; AMCI: amnestic mild cognitive impairment; SCI: subjective cognitive impairment

Table 3. Time to CDR-SB increase according to level of education

	Number of subjects	Time to progression (months)			
		CDR-SB 0 → 2.5	CDR-SB 2.5 → 4.5	CDR-SB 4.5 → 9.5	CDR-SB 9.5 → 16
Lower education group (≤ 12years)	378	72.8	25.1	30.1	19.7
Higher education group (> 12years)	187	109.2	25.8	30.6	19.9
Total	565	139.4	43.9	52.2	34.0

AD: Alzheimer's disease; AMCI: amnestic mild cognitive impairment; CDR-SB: clinical dementia rating sum of boxes; SCI: subjective cognitive impairment

Figures

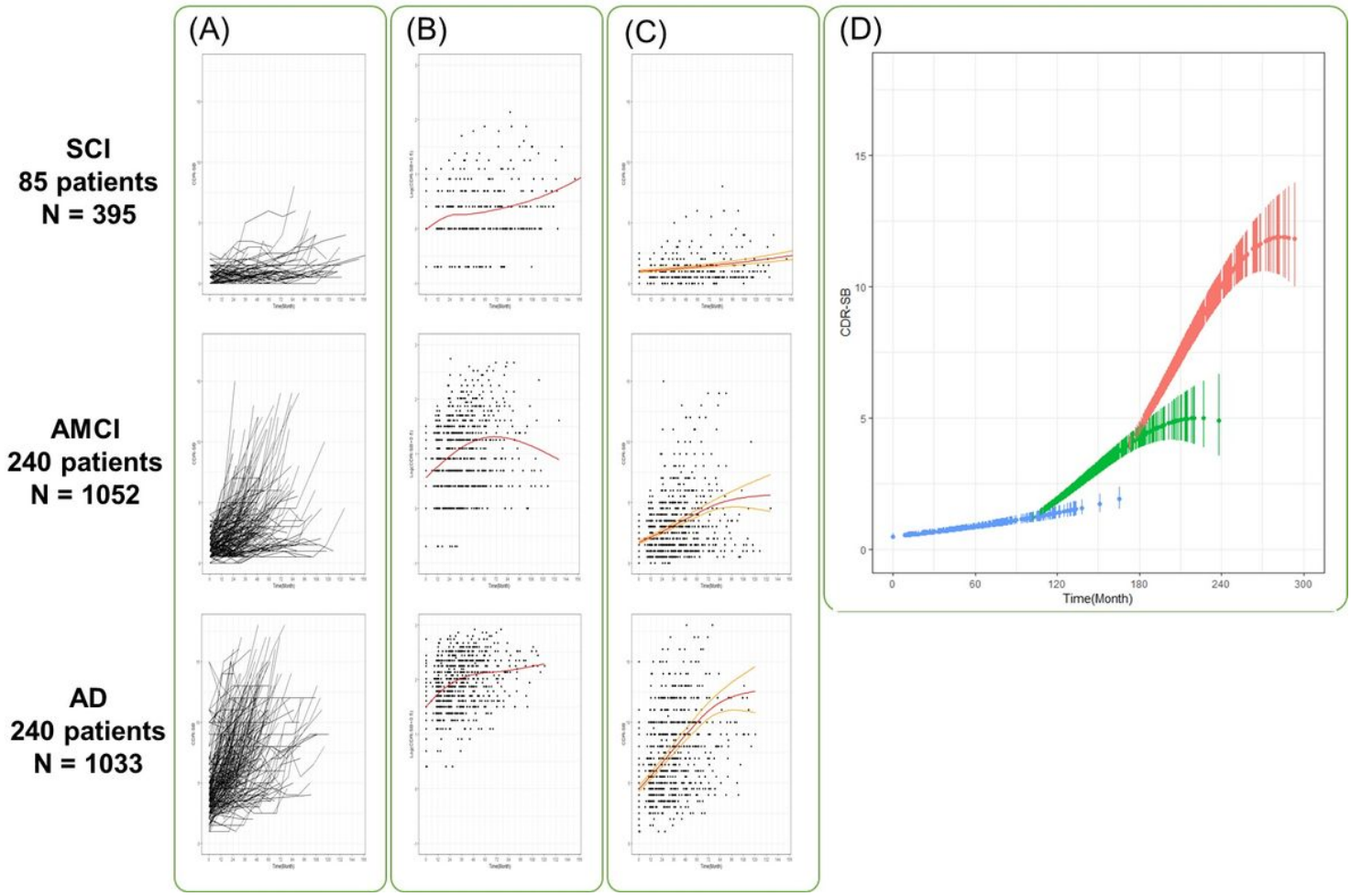

Figure 1

Disease progression modeling of CDR-SB in Alzheimer's disease (A) The pattern of CDR-SB values longitudinally observed in each of the three groups. (B) The smoothed line and the scatter plot with transformed CDR-SB using natural log in each of the three groups. (C) The scatter plot and the estimated model of CDR-SB over time for each cohort from a linear mixed model with time as a fixed effect and subjects as a random effect excluding outliers. (D) The predicted CDR-SB and 95% confidence interval of the two overlapping models of SCI (blue) and AMCI (green)24, and AMCI24 and AD (red). The predicted CDR-SB score of measurements to convert from the SCI to the AMCI group was 1.21 (95% CI: 1.09–1.34) and the corresponding time was 101.9 months. The predicted CDR-SB value of measurements to convert from the AMCI to the ADD group was 4.02 (95% CI: 3.79–4.27) and the corresponding time was 71.1 months. Abbreviations: AD, Alzheimer's disease; AMCI, amnestic mild cognitive impairment; CDR-SB, clinical dementia rating sum of boxes; SCI, subjective cognitive impairment.

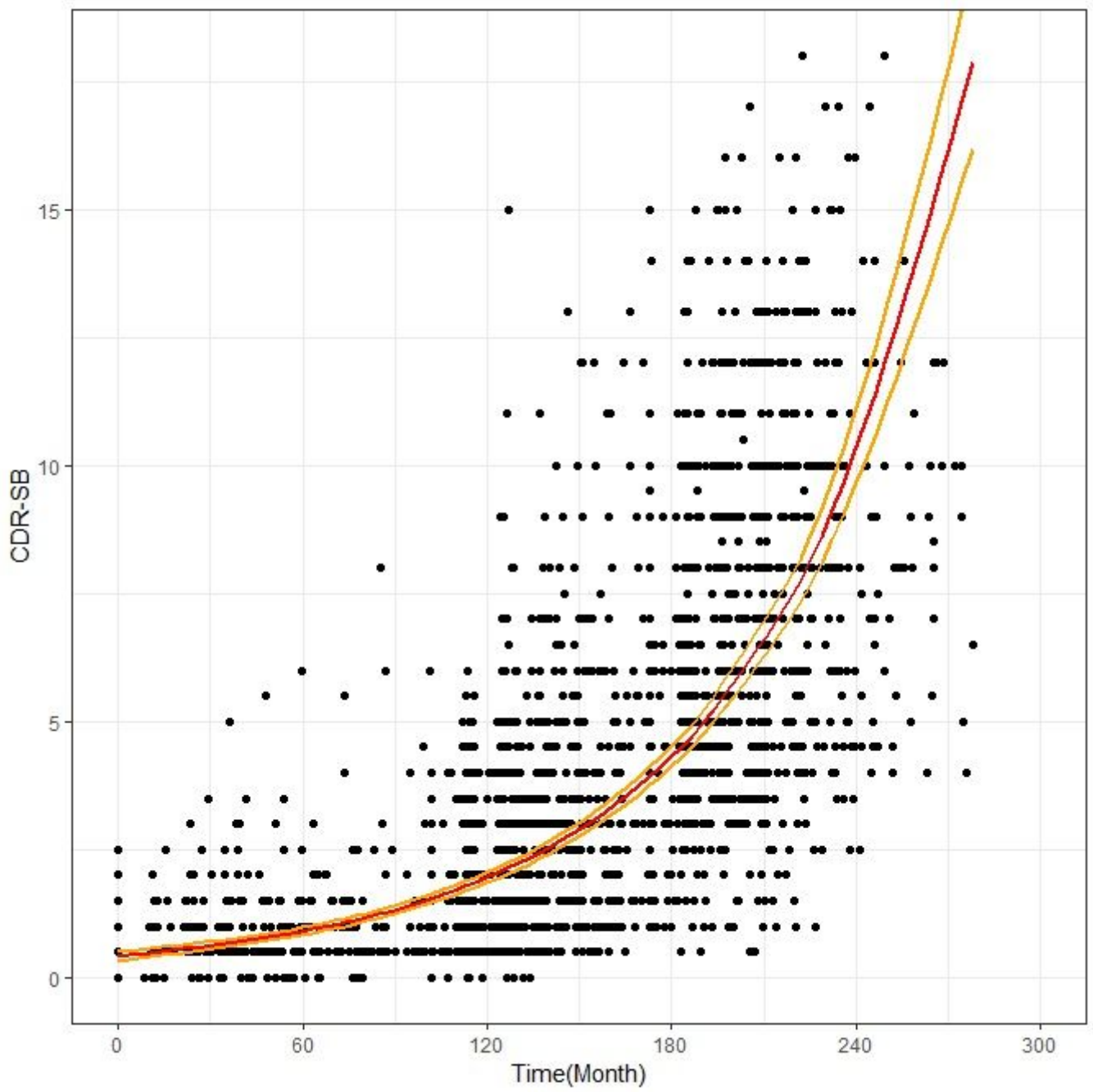

Figure 2

Disease progression model using CDR-SB The estimated model of CDR-SB from combined SCI, AMCI, and AD cohorts shows that it takes 277.0 months to increase the CDR-SB value from 0 to 18 points. The predictive equation for the curve is as follows: ln (CDR-SB+0.5) = −0.0885+0.006145×time+0.000017×time2. Abbreviations: AD, Alzheimer's disease; AMCI, amnestic mild cognitive impairment; CDR-SB, clinical dementia rating sum of boxes; SCI, subjective cognitive impairment.

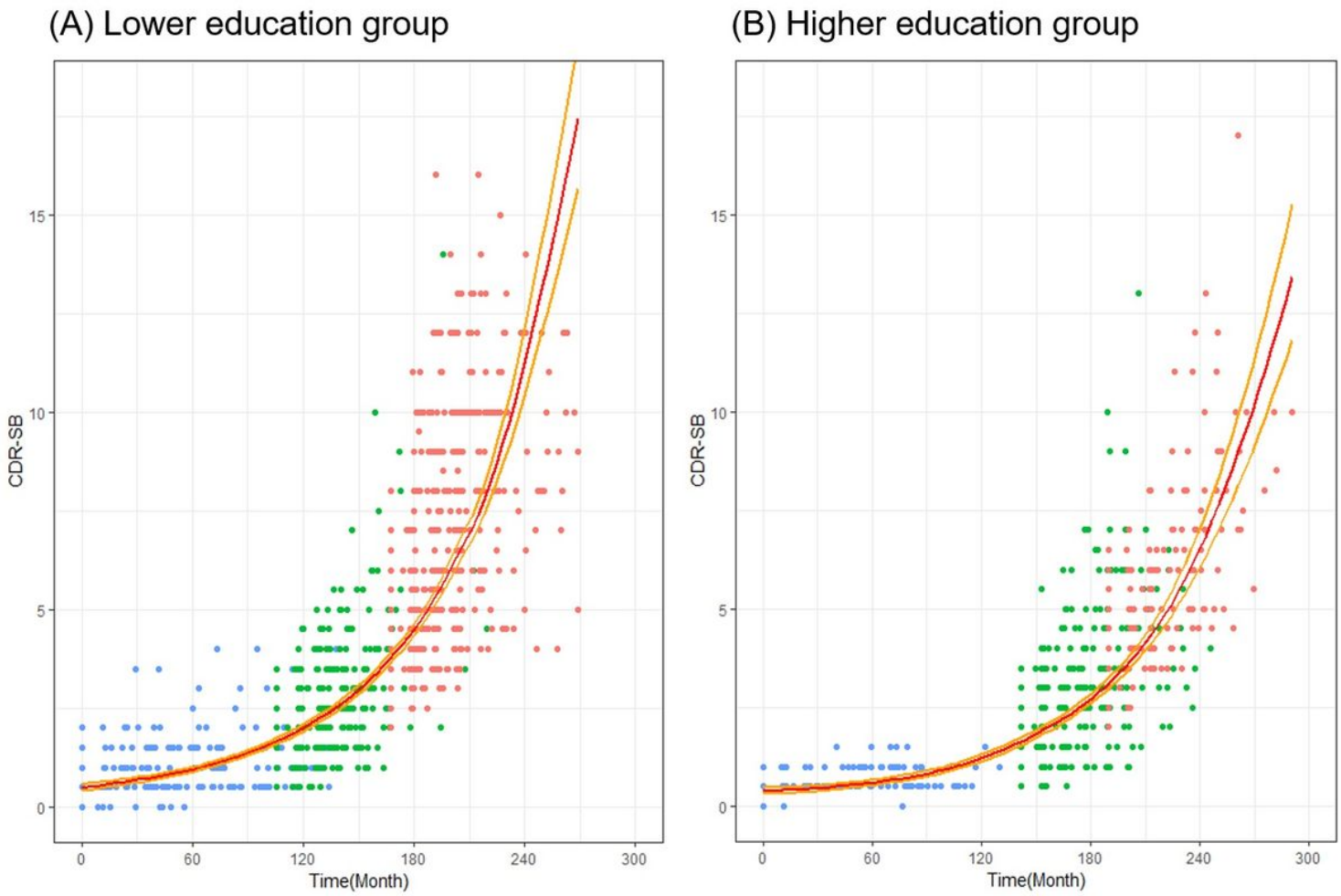

Figure 3

Disease progression model according to the level of education It takes less time to increase the CDR-SB value in lower education group in all sections. In the stages of SCI (blue) to AMCI24, the CDR-SB value increases faster in lower education group. From the stage of AMCI24 to AD (red), the CDR-SB value increases faster in higher education group. Abbreviations: AD, Alzheimer's disease; AMCI, amnestic mild cognitive impairment; CDR-SB, clinical dementia rating sum of boxes; SCI, subjective cognitive impairment.