Journal of Alzheimer's Disease 70 (2019) 361–370
DOI 10.3233/JAD-190370
IOS Press

Impact of Resilience on the Association Between Amyloid-β and Longitudinal Cognitive Decline in Cognitively Healthy Older Adults

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Accepted 6 May 2019

Abstract. The present study aims at investigating if the association between amyloid-β and longitudinal cognitive decline in cognitively healthy elderly is modulated by resilience capacity. Resilience capacity was quantified by education, which is a common proxy of resilience and has been shown to be related to a wide range of behaviors promoting resilience. Analyses were conducted with longitudinal cognitive data from the Alzheimer's Disease Neuroimaging Initiative (ADNI). 276 cognitively healthy older individuals (≥56 years) were included in the study. Baseline amyloid pathology was quantified using CSF amyloid-β 1–42 measurements. Longitudinal cognitive decline was assessed using ADAS13, Clinical Dementia Rating – Sum of Boxes, and ADNI-Memory composite scores. Duration of follow-up was 10 years (mean follow-up: 2.6 years). Linear mixed effects models demonstrated stronger cognitive decline over time with increasing baseline amyloid. Subsequent mixed-effects analyses showed that this amyloid-related cognitive decline is stronger in individuals with lower resilience capacity (i.e., lower levels of education). Of note, this effect was not an artifact of differences in neurodegeneration patterns between individuals with lower and higher resilience. Results suggest that resilience capacity has high potential to counteract early amyloid pathology and to significantly slow cognitive decline.

Keywords: Amyloid-β, cognitive decline, healthy older adults, preclinical Alzheimer's disease, resilience

INTRODUCTION

Amyloid-β deposition in the brain is a central pathological marker of Alzheimer's disease (AD) [1, 2]. Elevated brain amyloid is also present in approximately one-third of cognitively normal individuals aged 65 years and older, suggesting that amyloid pathology precedes dementia symptoms by years [3–5]. This early phase of amyloid accumulation in the absence of cognitive symptoms has been termed as preclinical stage of AD [5].

Research on the impact of amyloid deposition on cognition in cognitively normal older individuals is inconsistent. Several studies reported a lack

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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of associations with cognition for both memory [3, 4, 6–10] and non-memory domains [6–8, 10, 11], while others found modest correlations primarily with memory scores [4, 11–18]. In line with these outcomes, conflicting results on the association between elevated amyloid in cognitively normal older adults and subsequent conversion to dementia have been reported [15, 19–23]. A recent natural history biomarker study aimed at increasing the understanding of this somewhat unclear risk for AD-related cognitive decline among cognitively normal individuals with elevated brain amyloid, using longitudinal data of a large study cohort [24]. The study showed that cognitive decline over a period of 10 years was considerably stronger in individuals with elevated baseline brain amyloid than in those with normal baseline amyloid. This result highlights the relevance of brain amyloid for subsequent cognitive decline. However, marked interindividual variability in cognitive decline and conversion rates in individuals with elevated amyloid has also been observed in this study [24].

The variation in the extent of cognitive decline in the face of amyloid deposition might be explained by differences in resilience capacity, a concept postulating that individual differences in the cognitive process or neural networks underlying task performance allow some individuals to cope better with brain damage than others [25]. Resilience can be seen as a general term that refers to the variance in clinical/cognitive outcomes which is not explained by the level of brain aging or the amount of pathology. There are many potential structural and functional brain mechanisms underlying and determining the manifestation of resilience. These mechanisms have been subsumed under the terms cognitive reserve (efficiency, capacity, flexibility of cognitive processes), brain reserve (neurobiological capital, such as numbers of neurons, synapses etc.), and brain maintenance (reduced development over time of age-related brain changes and pathology) [26]. One of the most commonly used proxies for resilience capacity is educational attainment. On the one hand, education has been suggested to directly influence neuronal mechanisms underlying brain resilience [27, 28]. On the other hand, education has been shown to be related to a wide range of lifestyle factors promoting resilience, such as cognitive, physical, and social activity as well as socioeconomic status [29–31]. Some studies showed that the association between amyloid load and cognitive decline is stronger among individuals with low education [32–34], suggesting that high resilience capacity may compensate the negative effects of amyloid on cognition. This compensation may be of particular importance in cognitively normal individuals with elevated amyloid load, i.e., in individuals with preclinical AD, as it may prevent or postpone AD-related cognitive decline and conversion to symptomatic disease stages. First longitudinal analyses in this specific group support this assumption [33]. Nevertheless, the impact of resilience on amyloid-related cognitive decline in cognitively healthy older individuals has not yet been well characterized. Thus, the purpose of this study was to investigate to what extent resilience capacity, as measured by educational attainment, modifies amyloid-related cognitive changes among older participants with normal cognition. Data were taken from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database.

MATERIALS AND METHODS

Study population

Data were obtained from the ADNI database (http://adni.loni.usc.edu). The ADNI has observed individuals diagnosed as cognitively normal or with varying degrees of cognitive impairments since 2005, including serial evaluations through neuroimaging, cerebrospinal fluid (CSF), and other biomarkers as well as through clinical and neuropsychological assessments [35]. The primary goal of ADNI has been to test whether these assessments can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. ADNI was approved by the institutional review boards of each participating institution and written informed consent was obtained from all participants.

All participants from ADNI with normal cognition and a CSF amyloid-β peptide measurement at baseline assessment have been selected, resulting in a total of 276 subjects that were included in the study. Data were collected at 83 ADNI sites in the United States and Canada from September, 2005 to July, 2017.

Selection criteria

CSF amyloid-β

CSF measures of amyloid-β have been chosen since several studies indicated that this measure is the most sensitive amyloid marker for the detection of early amyloid pathology [36, 37]. CSF amyloid-β was measured using the multiplex xMAP Luminex

platform (Lumnix Corp., Austin, TX). CSF biomarkers collected at different centers were stored and analyzed at the Penn ADNI Biomarker Core Laboratory at the University of Pennsylvania, Philadelphia. More details on the acquisition and processing steps of the CSF- and PET amyloid data can be found on the ADNI website (http://adni.loni.usc.edu/methods).

Normal cognition

Normal baseline cognition was defined by Mini-Mental State Examination (MMSE) [38] scores of ≥24 and Clinical Dementia Rating (CDR) [39] Global and Memory Box scores of 0. Logical Memory Delayed Recall [40] scores are based on educational attainment and had to be at least 9 for 16 years of education, at least 5 for 8 to 15 years of education, and at least 3 for 0 to 7 years of education. This definition was in accordance to the group specific inclusion criteria for normal controls in ADNI.

Outcomes

Cognitive outcome variables included longitudinal measures of Alzheimer Disease Assessment Scale - 13-item cognitive subscale (ADAS13) [41], Clinical Dementia Rating - Sum of Boxes (CDR-SB) [42], and the ADNI-memory composite score (ADNI-Mem) [43]. While ADAS13 and CDR-SB assess a broader range of cognitive domains that are typically affected in AD, ADNI-Mem specifically reflects memory performance by incorporating all of the memory information available from the neuropsychological battery administered in ADNI. Neurodegeneration and AD-markers included CSF total-tau (t-tau) and hyperphosphorylated-tau (p-tau) [44], fluorodeoxyglucose (FDG)-PET, and ventricular volume (as measured with Freesurfer [45]). All data were obtained from the ADNI database.

Statistics

The data were investigated using linear mixed effects models [46]. Initially, cognitive decline over time was investigated. Cognitive outcomes (ADAS13, CDR-SB, ADNI-Mem) were set as dependent variables. The models included individual specific random intercepts and fixed effects for age, gender, APOE4 status, education, and time. The effect of time on the progression of cognition was tested using likelihood ratio tests that compared the full model to a reduced model with no parameters for time. Subsequently, the effect of the baseline amyloid-β level on longitudinal cognitive decline was tested. The models included individual specific random intercepts and fixed effects for age, gender, APOE4 status, education, time, amyloid-β and for the interaction time × amyloid-β. The effect of amyloid-β on longitudinal cognitive decline was tested using likelihood ration tests comparing the full model to a reduced model with no parameters for the interaction term.

In a second step, the effect of resilience (as measured by education) on amyloid-β-related longitudinal cognitive decline was investigated. Cognitive outcomes (ADAS13, CDR-SB, ADNI-Mem) were set as dependent variables. Individual-specific intercepts were set as random effects. Time, age, gender, APOE4 status, education, and the interaction terms time × education, time × amyloid-β, education × amyloid-β, and time × education × amyloid-β were set as fixed effects. The effect of resilience on amyloid-β-related cognitive decline was tested using likelihood ratio tests that compared the full model to a reduced model with no parameters for the interaction education × time × amyloid-β. Additional analyses were applied to test if potential effects of education on amyloid-β-related longitudinal cognitive decline might be an artifact of differences in neurodegeneration patterns between lower and higher educated individuals. Therefore, baseline neurodegeneration- and AD-markers (t-tau, p-tau, FDG-PET, ventricular volume) were included as control variables in the above described mixed-effects models.

A conservative Bonferroni correction was applied to control for type I error (total number of applied tests: N = 12). Accordingly, the threshold for statistical significance was set at $p < 0.004$ (2-sided) (initial threshold for statistical significance, $p < 0.05$, divided by the number of applied tests, N = 12). Models were fit and plotted using R (version 3.4.3, https://www.R-project.org/). All data used in this study are available in the ADNI public data repository. Anonymized patient identification numbers from the ADNI cohort used in this article are available by request from any qualified investigator.

RESULTS

Descriptive characteristics

Descriptive characteristics of the study group are summarized in Table 1. At baseline, mean age of the study group was 74.40 (SD, 6.0) years and mean education was 16.28 (SD, 2.7) years. 70 individuals

Table 1
Descriptive and clinical characteristics

	Study Group ($n = 276$)
Baseline characteristics	
Age, mean (SD), y	74.40 (6.0)
Age range, y	56–89
Woman (%)	139 (50.4)
Education, mean (SD), y	16.28 (2.7)
≥1 APOE4 allele (%)	70 (25.4)
CSF $A\beta_{42}$ mean (SD), pg/ml	199.90 (51.76)
ADAS13, mean (SD)	9.36 (4.4)
CDR-SB, mean (SD)	0.03 (0.1)
ADNI-Mem, mean (SD)	1.03 (0.6)
CSF t-tau, mean (SD), pg/ml	68.52 (32.4)
CSF p-tau, mean (SD), pg/ml	30.54 (17.5)
FDG-PET, SUVR	1.31 (0.1)
Ventricular volume, mean (SD), % ICV	2.17 (1.0)
Follow-up characteristics	
Follow-up, mean (SD), y	2.62 (2.4)
Follow-up, min/max, y	0.25/10
Progression to MCI (%)	42 (15.2)
Progression to dementia (%)	15 (5.4)

APOE4, Apolipoprotein E; CSF $A\beta_{42}$, cerebrospinal fluid amyloid-β; ADAS13, Alzheimer Disease Assessment Scale 13-item cognitive subscale; CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes; ADNI-Mem, ADNI-memory composite score; CSF t-tau, cerebrospinal fluid total-tau; CSF p-tau, cerebrospinal fluid phospho-tau; FDG-PET, Fluorodeoxyglucose - positron emission tomography; SUVR, standardized uptake value ratio; ICV, intracranial volume; MCI, mild cognitive impairment.

(25.4%) had at least one APOE4 allele, 139 individuals (50.4%) were female. Mean CSF amyloid-β level of the participants was 199.90 (SD, 51.76).

Mean follow-up period was 2.6 (SD, 2.4) years. Minimum follow-up was three months; maximum follow-up was 10 years. 42 participants (15.2%) converted to MCI and 15 participants (5.4%) converted to dementia within the follow-up period.

Effect of time and amyloid-β on the progression of cognition

Likelihood ratio tests for the overall effect of time on cognition were significant for all cognitive measures (ADAS13: $\chi^2 = 152.88$, $p < 0.001$; CDR-SB: $\chi^2 = 229.26$, $p < 0.001$; ADNI-Mem: $\chi^2 = 84.116$, $p < 0.001$), indicating worse cognition with increasing time. Subsequent analyses investigating the effect of baseline amyloid-β levels on longitudinal cognitive decline demonstrated stronger decline with increasing amyloid-β levels for all cognitive outcomes (ADAS13: $\chi^2 = 123.63$, $p < 0.001$; CDR-SB: $\chi^2 = 204.66$, $p < 0.001$; ADNI-Mem: $\chi^2 = 95.02$, $p < 0.001$) (see Fig. 1).

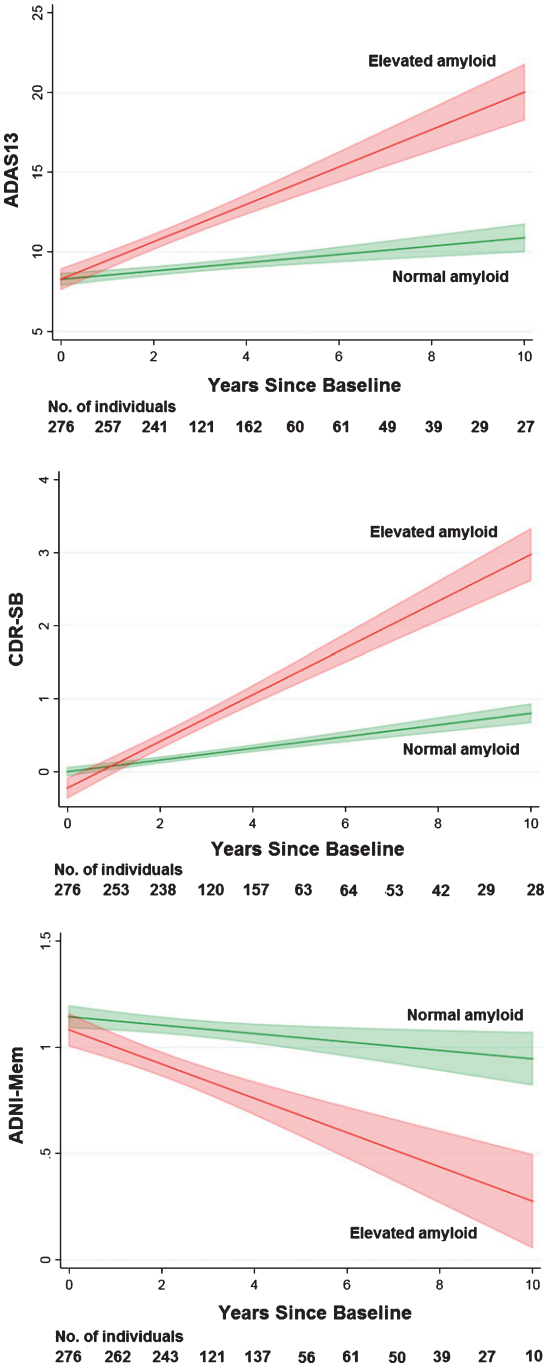

Fig. 1. Impact of baseline amyloid-β on longitudinal cognitive decline in cognitively healthy older adults (linear prediction plots with 95% confidence interval bands). For illustration purposes, individuals have been categorized in groups with normal and elevated baseline amyloid. Elevated amyloid was defined by CSF amyloid-β less than 192 pg/mL (a proposed cutoff for amyloid positivity based on CSF measurement [44]. ADAS13, Alzheimer Disease Assessment Scale 13-item cognitive subscale; ADNI-Mem composite, ADNI-memory composite score; CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes.

Effect of resilience (as measured by education) on amyloid-β-related longitudinal cognitive decline

Likelihood ratio tests investigating the effect of education on the association between baseline amyloid-β and subsequent cognitive decline showed significant effects of the interaction time × education × amyloid-β on all cognitive measures (ADAS13: $\chi^2 = 28.34$, $p < 0.001$; CDR-SB: $\chi^2 = 10.12$, $p = 0.001$; ADNI-Mem: $\chi^2 = 9.31$, $p = 0.002$), indicating stronger amyloid-β related cognitive decline in lower educated participants (see Fig. 2).

Additional analyses showed that the above described effects of the interaction time × education × amyloid-β on cognitive measures survived after controlling for neurodegeneration- and AD markers (t-tau, p-tau, FDG-PET, ventricular volume) (ADAS13: $\chi^2 = 16.58$, $p < 0.001$; CDR-SB: $\chi^2 = 17.95$, $p < 0.001$; ADNI-Mem: $\chi^2 = 13.68$, $p < 0.001$), indicating that the effect of education on the association between baseline amyloid-β and subsequent cognitive decline is not an artifact of differences in neurodegeneration patterns between lower and higher educated individuals.

DISCUSSION

The present study aimed at investigating to what extent resilience capacity, as measured by educational attainment, modifies amyloid-related cognitive decline among older adults with normal cognition (aged 56 years and older). Results demonstrated that amyloid-related cognitive decline over a period of 10 years was considerably stronger in participants with lower resilience capacity than in participants with higher resilience capacity in a variety of cognitive measures (ADAS13, CDR-SB, and ADNI-Mem).

A recently published large longitudinal natural history biomarker study of cognitively normal older individuals highlighted the clinical relevance of elevated brain amyloid by showing stronger cognitive decline over a period of ten years in a variety of cognitive tests in older adults with elevated cerebral amyloid compared to older adults without elevated cerebral amyloid [24]. In line with this result, stronger longitudinal cognitive decline in individuals with higher amyloid pathology could also be observed in the present study. However, marked interindividual variability in cognitive decline in individuals with elevated amyloid as well as heterogeneous results on the association between cerebral amyloid load and cognition in previous studies challenge the assumption that amyloid pathology inevitably leads to cognitive decline [6–11, 24, 47]. The differences in study results may be the result of different study designs and differences in the quantification of amyloid-β. It has also been hypothesized that differences in resilience capacity may account for the observed variance in amyloid-related cognitive decline [18, 48]. Our finding of a strong association between educational attainment, as a common proxy of resilience, and amyloid-related cognitive decline supports this hypothesis.

Supplementary analyses indicated that the effect of resilience on the association between baseline amyloid-β and subsequent cognitive decline is not an artifact of differences in AD-markers and neurodegeneration patterns (t-tau, p-tau, FDG-PET, ventricular volume) between individuals with lower and higher resilience capacity. This result is in line with previous reports [49, 50]. The mechanisms underlying the compensatory effects against amyloid pathology are largely unknown. The concept of resilience as a complex construct referring to multiple reserve-related processes can roughly be classified into passive and active models. Passive models define resilience as the amount of damage that can be sustained before reaching a threshold for clinical expression, for instance larger brains that might simply tolerate more pathology. Such models have been subsumed under the term brain reserve [26]. Active models define resilience as an active attempt to compensate for brain damage, e.g., by using alternative and/or additional brain structures or networks [48, 51]. Active models have been subsumed under the term cognitive reserve [26]. Previous studies indicate that resilience against AD-related cognitive decline might be based on both passive and active mechanisms. On the one hand, studies repeatedly indicated that the premorbid brain size protects against AD-related cognitive decline in the sense of a passive reserve factor [52–54]. On the other hand, studies using resting-state and task-related fMRI demonstrated that higher capacity or flexibility of brain networks as well as higher connectivity within networks attenuates AD-related cognitive decline in the sense of an active reserve factor [55–59]. Further research is necessary to determine the specific mechanisms underlying resilience against amyloid-pathology.

In this study, only participants with normal cognition at baseline were included. Against that

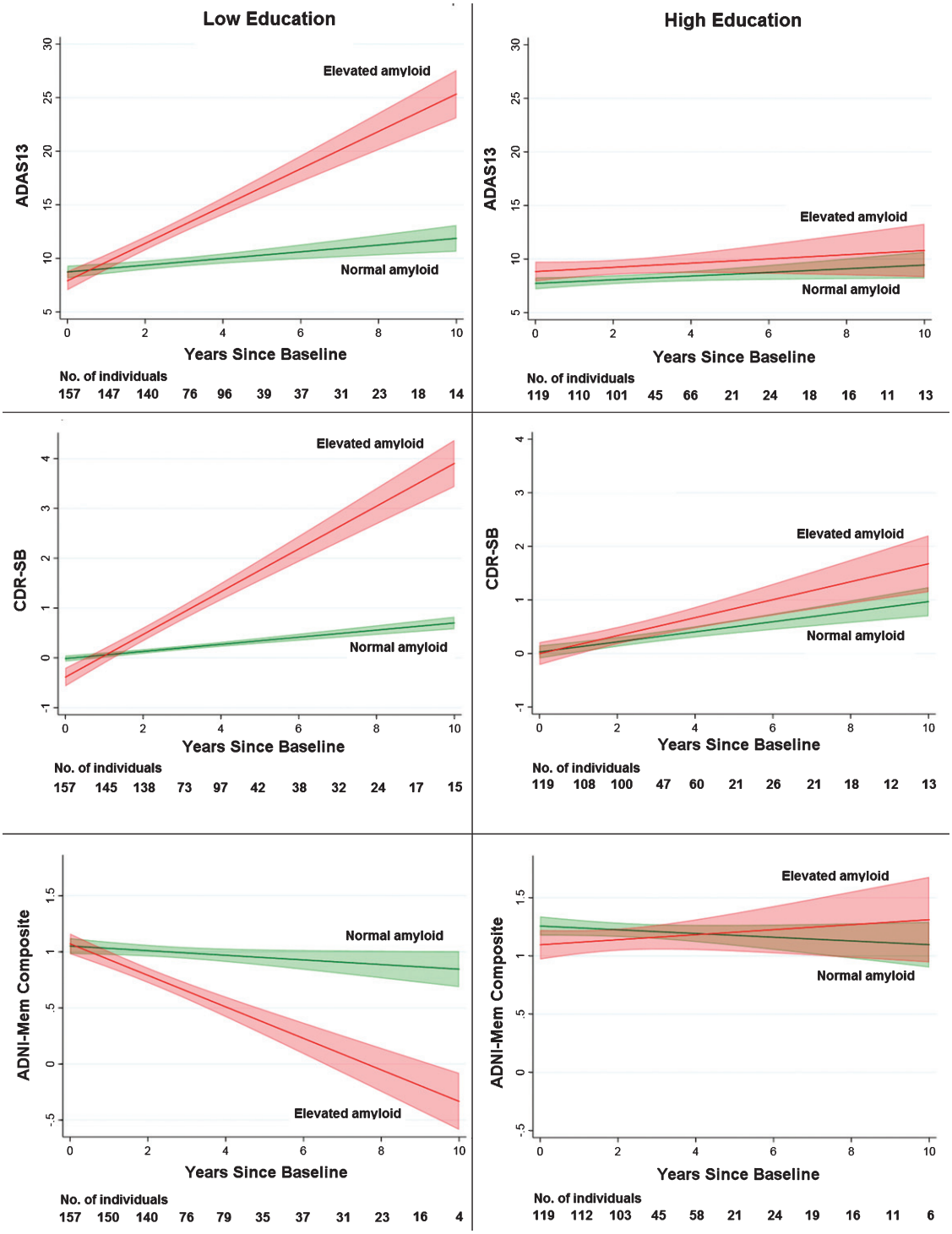

Fig. 2. Impact of educational attainment on amyloid-β related longitudinal cognitive decline in cognitively healthy older adults (linear prediction plots with 95% confidence interval bands). For illustration purposes, individuals have been categorized in groups with low/high education as well as in groups with normal and elevated baseline amyloid. Low/high education was defined by a median split. Elevated amyloid was defined by CSF amyloid-β less than 192 pg/mL (a proposed cutoff for amyloid positivity [44]). ADAS13, Alzheimer Disease Assessment Scale 13-item cognitive subscale; ADNI-Mem composite, ADNI-memory composite score; CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes.

background, the present results are of particular importance as they highlight the significance of resilience capacity in preventing or postponing AD-related cognitive decline in individuals at early stages of AD. Given the increase in educational attainment in the last decades, increases in resilience capacity might also explain the declining trend in dementia prevalence and incidence that has been observed in recent years despite simultaneously increasing life expectancy [60, 61].

Based on the observed effects of resilience on amyloid-related cognitive decline, future studies are needed to develop intervention strategies aiming at increasing resilience capacity in the face of amyloid pathology, especially in preclinical phases of AD. Education, which is a common proxy for resilience and which has been used to quantify resilience in the present study, is related to a wide range of lifestyle factors promoting resilience, such as sustained cognitive and physical activity, active participation in social networks, and socioeconomic status. Thus, it is likely that the observed positive effects of resilience on amyloid-related cognitive decline are at least in part mediated, or moderated, by these lifestyle factors. This assumption is supported by the fact that the formal education period is a static measure that is normally defined sometime in the past in early adulthood while the described lifestyle factors are state markers, which may, from a chronological perspective, have a more direct influence on resilience in elderly. The development of intervention strategies requires the disentanglement of potential compensating effects of educational attainment itself and related lifestyle factors in future studies. Moreover, it has been shown that tau deposition in the brain, which is a further central pathological marker of AD, is associated with cognitive performance and clinical outcome measures in normal older adults and early symptomatic AD patients, independent of associated amyloid deposition [62]. Thus, future studies should also investigate the effect of resilience on tau-related cognitive decline in cognitively normal individuals.

Limitations

The study has some limitations. First, due to the limited number of observations of cognitive performance at the latest time points, conclusions made about these time points might be imprecise. Future studies should replicate the findings of this study based on a higher number of follow-up data, especially after a follow-up interval of six/seven years. Second, changes on continuous measures are of uncertain clinical importance. Third, because analyses were not specified prior to the beginning of data collection analyses should be considered as exploratory.

Conclusions

Our results showed that higher resilience in older individuals, as assessed by educational attainment, was associated with less amyloid-related longitudinal cognitive decline in cognitively normal older individuals. This effect was not an artifact of differences in AD markers or neurodegeneration patterns between individuals with lower and higher resilience. Results suggest that resilience capacity has high potential to counteract early amyloid pathology and to significantly slow cognitive decline. Against the background of the increasing educational attainment in the last decades, increases in resilience capacity might explain the declining trend in dementia prevalence and incidence that has been observed in recent years despite simultaneously increasing life expectancy. Further research is needed to investigate the mechanisms underlying the compensatory effects against amyloid pathology and to develop intervention strategies aiming at increasing resilience capacity in the face of amyloid pathology.

ACKNOWLEDGMENTS

Data used in preparation of this article were obtained from the Alzheimer's disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: https://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: Alzheimer's Association; Alzheimer's Drug Discovery Foundation; BioClinica, Inc.; Biogen Idec Inc.; Bristol-Myers Squibb Company; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; GE Healthcare; Innogenetics, N.V.; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Develop-

ment, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Medpace, Inc.; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Synarc Inc.; and Takeda Pharmaceutical Company. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (http://www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/19-0370).

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