

Modeling functional loss in Alzheimer's Disease through cognitive reserve and cognitive state: A panel data longitudinal study

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ABSTRACT

Cognitive Reserve (CR) refers to the brain's ability, supported by active and modifiable forms of lifestyle compensation, to cope with neural changes due to age or disease, delaying the onset of cognitive deficits. In CR studies, neuropsychological performances and functional autonomy are considered alternative outcomes. While decreased functional independence gains importance in dementia diagnosis and monitoring, cognitive functioning may play a role in staging its severity. The main aim of the present study was to test a longitudinal model of Alzheimer's Disease (AD), in which CR (years of education) and current cognitive status (Mini-Mental State Examination, MMSE, score) would predict clinical progression in terms of loss of functional independence at a later time. From the ADNI database, we considered 308 AD participants, and for 180 of them, we could extract CSF Aβ1–42 baseline levels as an index of amyloid burden. Functional decline (one-year delta score at the Functional Activities of Daily Living Questionnaire) was explained by the CR and MMSE score interaction net of age; a trend was found also when controlling for amyloid burden. Functional decline at one year was increased for patients with high CR levels and low MMSE and with low CR and high cognitive state, compared to the opposite. The present investigation demonstrated the mutual role of past acquired CR and current cognitive status in predicting functional progression in AD. The study suggests a way to predictively interpret available demographic and clinical data, defining differential longitudinal trajectories that might be useful for clinical management.

1. Introduction

Some decades ago, several lines of evidence suggested that enriched life experiences, such as higher educational or occupational attainment, can be associated with a reduced risk of incident dementia (Evans et al., 1993; Stern et al., 1994). More specifically, early studies noted a discontinuity between the degree of brain pathology and the clinical manifestation of Alzheimer's Disease (AD) (Stern et al., 1999), suggesting that the observed severity is mediated through some form of lifestyle compensation. Since then, the concept of cognitive reserve (CR)

(Stern et al., 2020) as an active and modifiable protective factor has been extensively applied in studies on physiological and pathological ageing.

CR is defined as “the ability to optimize or maximize performance through differential recruitment of brain networks, which perhaps reflect the use of alternate cognitive strategies” (Stern, 2002). It refers to the brain's ability to cope with neural changes due to ageing or pathology, optimizing performance without showing cognitive impairment (neural reserve), and adapting to counteract cognitive decline (neural compensation) (Tucker and Stern, 2011; Pappalattera et al.,

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2024; Song et al., 2022). The CR construct is firmly grounded on modifiable lifestyle experiences (Song et al., 2022), and it has been estimated using proxies of different complexity and comprehensiveness, such as education level, occupational complexity and composite measures, including leisure activities, with years of education (as a continuous variable) being the most widely used proxy (see Harrison et al., 2015; Pinto et al., 2023, for umbrella reviews).

According to Stern's pivotal hypothesis (Stern et al., 1994), in individuals with high CR, the onset of cognitive loss and functional disability corresponds to more severe underlying neuropathology (Kadlec et al., 2018; Scarmeas and Stern, 2004; Stern et al., 1999). Hence, a higher CR would protect against the overt manifestation of AD, attenuating the clinical onset. However, by the time the CR becomes less effective, losing its protective role, the brain pathology is already quite advanced and this would be reflected in a rapidly increasing rate of clinical decline and deterioration of cognitive and functional abilities in people with high CR (Andel et al., 2006; Conde-Sala et al., 2013; Gialquinto et al., 2023; Scarmeas et al., 2006; Stern et al., 1994).

In CR studies, cognitive impairment and functional decline are typically considered different and alternative outcomes (Oliveira et al., 2016; Reed et al., 2010; Sobral and Paúl, 2013; Van Loenhoud et al., 2019), and the recently proposed models for CR use cognition as outcome (Song et al., 2022). This type of modelling of CR is adequate to resemble healthy functioning or disease stage characterized by a minimal functional impact on everyday activities, as in Mild Cognitive Impairment (Albert et al., 2011). However, the diagnosis of dementia is strongly grounded on the negative, functional impact of the progressive cognitive decline on daily life personal functioning (McKhann et al., 2011) rather than exclusively on performances on cognitive tests. In this vein, cognition may show a slight deterioration and fluctuations during some time without a significant impact on daily life activities. Furthermore, although inevitably related domains, cognitive and everyday functioning are clinically assessed and staged through different tools. Since in AD the correspondence between the levels of cognitive and brain impairment seems to depend on the amount of CR, instead of being used as an outcome in a CR model, a cognitive screening test score may be efficiently applied as an index of disease staging, indicating a time-point severity of the disorder.

1.1. Aim

The main aim of the present study was to develop a longitudinal model for the functional progression of AD dementia at one year, based on the mutual use of some readily available clinical information, namely CR and current cognitive functioning. In particular, we expected that, in patients affected by AD, the joint use of CR (years of education) and the current Mini-Mental State Examination (MMSE) score (Folstein et al., 1975) could predict functional decline at one year (Functional Activities of Daily Living Questionnaire, FAQ, delta score) (Pfeffer et al., 1982), net of age. According to the CR hypothesis, we foresaw that high CR and low MMSE would be associated with a greater functional decline after one year.

CR models are considered appropriate when they include three necessary components: lifestyle factors, cognition, and brain measures (Stern et al., 2023; <https://reserveandresilience.com/framework/>; see Song et al., 2022). Importantly, according to Stern and colleagues (2020), the association between lifestyle factors and cognition should be grounded on *in vivo* biomarker imaging (e.g., volume, white matter tract integrity, amyloid burden) or postmortem data confirming neuropathology. This is because unmeasured or unknown brain or pathological changes are likely to contribute to the interindividual variance in cognitive outcomes (Stern et al., 2023). Lesions typical of sporadic AD include intraneuronal inclusions of abnormally phosphorylated tau protein and extracellular deposits of amyloid-beta peptide, particularly the 42-amino acid isoform (A β 1–42). In AD patients, cerebrospinal fluid (CSF) biomarkers, namely A β 1–42, phosphorylated tau181 and total

tau, are shown to be altered, and decreased A β 1–42 is considered a good index of amyloid-beta deposition in plaques (Kurihara et al., 2024; Wang et al., 2023). Therefore, in a subsample of AD patients, for whom indexes of amyloid burden were available, we introduced CSF A β 1–42 values (see Jack et al., 2018, for AD biomarker characterization) as an additional covariate in the model (see Harris et al., 2015, for a similar approach). We expected that the predicted interaction between education and cognitive scores would be maintained, net of age and, more specifically for AD, net also of A β 1–42 levels.

2. Methods

2.1. Sample

Data used to prepare this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu) in November 2023. 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 (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

In the present study, we considered only patients with AD who completed the MMSE (Folstein et al., 1975) and the FAQ (Pfeffer et al., 1982) on the baseline evaluation (T0) and after twelve months (T1). The final sample for which all data were available consisted of 308 participants; 43.18 % were females. The mean age was 75.12 years (SD = 7.61), and the mean education was 15.28 (SD = 2.89). The mean MMSE score at baseline was 23.30 (SD = 2.11), suggesting a mild clinical stage of dementia. Of these 308 participants, only for a subsample, it was possible to extract beta-amyloid (A β 1–42) baseline levels in the cerebrospinal fluid (CSF). The subsample consisted of 180 participants; 42.86 % were females. The mean age was 75.01 years (standard deviation = 7.87), and the mean education was 15.52 (standard deviation = 2.83). The mean MMSE score at baseline was 23.37 (SD = 1.95). Table 1 shows the main sample and A β 1–42 subsample characteristics.

2.2. Measures

The MMSE (Folstein et al., 1975) is a screening test that evaluates orientation to place and time, immediate and delayed memory, attention, language, and visual construction. The MMSE is scored as the number of correctly completed items, with lower scores indicating poorer performance and greater cognitive impairment. The total score ranges from 0 to 30. We considered the MMSE raw score as an index of the subject's cognitive state at t0 (baseline assessment).

The FAQ (Pfeffer et al., 1982) is an interview with a caregiver who rates the patient on her/his ability to carry out ten complex activities of daily living (i.e., manage finances, complete forms, shop, perform games of skill or hobbies, prepare hot beverages, prepare a balanced meal, follow current events, attend to television programs, books or magazines, remember appointments, and travel out of the neighborhood). Each activity is rated as 0 (does without difficulty), 1 (has difficulty but does by self), 2 (needs frequent advice or assistance), or 3 (someone has taken over the activity). The sum across items provides a total disability score (higher scores = greater impairment; maximum score = 30). We computed the difference (deltaFAQ) between the FAQ score at t0 and t1 such that positive numbers indicate a worsened performance. We considered the deltaFAQ score indicating the increase or decrease of functional autonomy after twelve months. Since the study aimed to understand how the interaction between MMSE and CR influences the net change in functional abilities, a delta score has been defined, allowing to directly assess the impact of predictors on the dynamics of the variable over time.

We considered patients' years of education as a proxy of CR; baseline patient's MMSE score at the first visit (t0) as an index of disease severity,

Table 1

Samples characteristics. MMSE t0 = baseline MMSE total score; Education t0 = years of education; FAQ = FAQ total score; deltaFAQ = difference between the FAQ score at t0 (baseline) and t1; A β 1–42 = baseline levels of A β 1–42 in the CSF.

	Main sample					A β 1–42 levels sample				
	N	Mean	Std. Dev	Min	Max	N	Mean	Std. Dev	Min	Max
Gender	308	43.18 % females				180	42.86 % females			
MMSE t0	308	23.30	2.11	17	29	180	23.37	1.95	19	27
Education t0	308	15.28	2.89	6	20	180	15.52	2.83	8	20
Age t0	308	75.12	7.61	55.20	90.96	180	75.01	7.87	55.99	90.40
FAQ t0	308	13.08	7.02	0	30	180	13.06	7.10	0	28
FAQ t1	308	17.36	7.30	1	30	180	17.29	7.38	1	30
deltaFAQ	308	4.28	5.08	–12	24	180	4.23	4.67	–12	18
A β 1–42 t0						180	725.46	409.93	203	3427

patients' age at the baseline visit (t0) was considered as an index of ageing processes; baseline levels of A β 1–42 in the CSF were used as biomarkers for AD pathology (t0). ADNI CSF collection and analysis procedures have been previously described (Shaw et al., 2009). Each participant's A β 1–42 measurements were downloaded directly from the ADNI database.

The current study used de-identified archival data from ADNI, and for this reason, it was exempted from human subjects' review by our institutional ethics committee.

2.3. Statistical analysis

As a first-step analysis, we assessed in the main sample (308 participants) whether the baseline cognitive state (MMSE) interacts with baseline CR (years of education) to predict functional decrease after twelve months (deltaFAQ), net of the baseline age. To do so, we fitted a linear model with deltaFAQ as the dependent variable and MMSE, age and years of education as predictors. In particular, we looked for the interaction between MMSE and years of education, net of age.

In a subsequent analysis, we controlled for the level of AD pathology, as assessed by baseline A β 1–42 levels. In the subsample of 180 participants for whom these data were available, we assessed whether the baseline cognitive state (MMSE) interacts with CR (years of education) to predict functional decrease after twelve months (deltaFAQ), net of baseline age and baseline A β 1–42 levels. To do so, we added A β 1–42 levels as a predictor to the previous model and asked for the interaction between MMSE and years of education, net of the age and A β 1–42 levels.

We also tested the possibility that the interaction-based model provided more information than simpler models, excluding the interaction effects. Finally, Pearson's correlations were run between all variables and model assumptions were tested.

2.4. Changes Scores additional check

Assessing longitudinal effects with change scores (i.e., delta) guarantees easiness in the interpretation of the results. However, change scores have been widely criticized for their sensitivity to regression toward the mean. We controlled whether it was appropriate to use the change score in this situation. One key problem is the non-equivalence between groups at baseline (Van Breukelen, 2013). A second potential issue is that if any variable is correlated with the baseline score, it will tend to have a spurious relationship with the change score (Allison, 1990). For this study, we retrospectively and randomly drew a sample of participants, avoiding any comparison between groups. When this is the case, there is no need to control for the presence of positive or negative effects at t0, because the effects should average out over the population (Liker, et al., 1985). Nonetheless, to control for any correlation with the baseline score, we ran the same models of the main analyses using the FAQ t0 score as a dependent variable. We assessed if the effect of interest (i.e., the interaction between MMSE at t0 and Education at t0) predicted the FAQ score at the baseline. Results showed non-significant results both in the main sample ($t = 1.781$, $p = 0.076$) and in the sub-sample

($t = 0.964$, $p = 0.336$). Given the lack of effect on FAQ t0, the effect observed with delta scores as the dependent variable is likely unbiased. However, cautious considerations should always be kept when using change scores.

3. Results

Table 2 (main analysis) shows the results (data on model assumptions were reported in supplementary materials). The model is significant ($F(4,303) = 2.56$, $p = 0.038$). Crucially, we found a significant interaction between MMSE and years of education, net of age ($t = -2.29$; $p = 0.023$). The interaction shows that patients with low CR have a more considerable functional decrease when they still have a high, compared to a low, cognitive state. The opposite is true for higher CR levels (i.e., education), where lower cognitive states predict greater functional decreases, compared to higher cognitive states. The interaction can be interpreted through Figure 1, panel A.

Table 2 (A β 1–42 levels analysis) shows the results. Although the general model was not significant ($F(5,174) = 1.51$, $p = 0.189$), we found significant main effects of MMSE ($t = 2.09$; $p = 0.038$) and years of education ($t = 2.00$; $p = 0.047$). Crucially, the interaction between MMSE and years of education, net of age and A β 1–42 levels was at the limit of significance testing ($t = -1.94$; $p = 0.054$). The interaction, which can be interpreted through Figure 1, panel B, sustains the results of the main analysis.

Table 3 shows the comparison between models with or without the interaction level. Results support the importance of the interaction effect.

Finally, Table 4 shows the correlations between all variables: no significant correlations were found.

4. Discussion

In this paper, we proposed a model for the functional progression of mild-stage AD dementia at one year, using longitudinal cognitive assessments from the ADNI database (adni.loni.usc.edu) and applying a linear model approach. Previous longitudinal studies investigating the impact of CR on disease progression used alternatively cognitive or functional scores, as outcome measures (e.g., diagnostic conversion from MCI to AD and memory and executive function changes, namely ADNI-MEM and ADNI-EF scores respectively, in Van Loenhoud et al., 2019; Clinical Dementia Rating – CDR – scale and MMSE changes in Oliveira et al., 2016; Barthel Index and MMSE in Sobral and Paül (2013)). While this may be adequate for healthy or minimally functionally impaired populations as MCI, decreased functional autonomy in daily living gains critical importance in the diagnostic and longitudinal monitoring of diagnosed dementia.

In the present study, disease progression was operationalized as a clinical change in functional independence (McKhann et al., 2011), measured as the difference between FAQ scores at baseline and after one year (deltaFAQ), where the FAQ score was shown to have a high degree of concordance with the CDR-Sum of Boxes (Mouchet et al., 2021). The

Table 2

Linear model results. The table shows the results from the linear models with deltaFAQ as the dependent variable. In the left part of the table, we tested MMSE, age and years of education as predictors; in the right part of the table, we added Aβ1–42 levels as a predictor. Significance code: * ≤ 0.05. df = degrees of freedom.

Predictors	Main analysis			Aβ1–42 levels analysis				
	Estimate	Std. Error	t value	Pr(> t)	Estimate	Std. Error	t value	Pr(> t)
(Intercept)	−33.26	17.90	−1.86	0.064	−41.38	23.55	−1.757	0.081
MMSE t0	1.74	0.76	2.23	0.022 *	2.05	0.98	2.09	0.038 *
Education t0	2.74	1.15	2.39	0.017 *	2.91	1.45	2.00	0.047 *
Age t0	−0.07	0.04	−1.82	0.070	−0.05	−0.05	−1.08	0.281
Aβ1–42					−0.00	0.00	−0.57	0.567
MMSE t0:Education t0	−0.11	0.05	−2.29	0.023 *	−0.12	0.06	−1.94	0.054
R ² / adjusted R ²	0.03 / 0.02				0.04 / 0.01			
F(df)	2.56 (4,303)			0.038 *	1.51 (5,174)			0.189

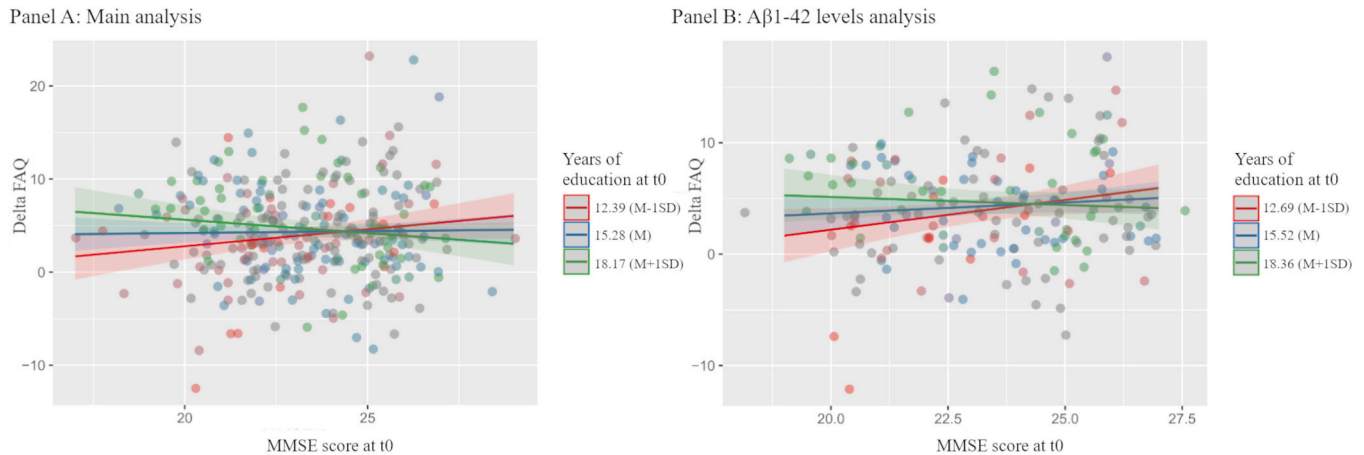


Fig. 1. The figure shows the functional decrease (deltaFAQ) predicted by the interaction between cognitive state (MMSE) and cognitive reserve (years of education) net of age (left panel) or age and Aβ1–42 levels (right panel). Low levels (1 SD below the mean) of CR are depicted in red; high levels (1 SD above the mean) are depicted in green (mean levels in blue).

Table 3

Model comparison. The table shows the comparison between our models and simpler models that do not include the interaction.

		AIC	BIC	adjusted R2	LogLik	Df	Chisq	Pr(>Chisq)
Main analysis	Model with interaction	1876	1898	0.020	−931.83			
	Model without interaction	1879	1898	0.006	−934.46	−1	5.264	0.022 *
Aβ1–42 levels analysis	Model with interaction	1071	1093	0.042	−528.36			
	Model without interaction	1073	1092	0.021	−530.29	−1	3.849	0.050 *

Table 4

Correlation matrix. The table shows the correlations between all variables. The upper triangle shows the sample included in the main analysis; the lower triangle shows the sample included in the Aβ1–42 levels analysis.

	deltaFAQ	MMSE t0	Education t0	Age t0
deltaFAQ		0.024	0.077	−0.100
MMSE t0	0.078		0.088	−0.012
Education t0	0.070	0.073		−0.007
Age t0	−0.104	−0.041	−0.094	
Aβ1–42	−0.045	0.093	0.055	0.183

baseline level of cognitive functioning, measured as the score at the widely used MMSE screening test (a measure of global cognitive functioning) (Folstein et al., 1975), was considered a current index of disease staging (Kennedy et al., 2015).

Results showed that, in patients affected by AD, years of education as CR proxy, and MMSE score at first visit interacted in explaining functional disease progression at one year. Change scores have often been criticized for their sensitivity to regression toward the mean (Allison, 1990). Although our study did not involve comparisons between groups,

we accounted for any correlation with the baseline score. Given the absence of an effect on FAQ at t0, the effect observed using delta scores as the dependent variable is likely unbiased. Nevertheless, caution is always warranted when interpreting results based on change scores. The present study demonstrated that controlling for age and amyloid burden (decreased Aβ1–42 in CSF), patients with higher CR levels and low cognitive status had a more considerable functional decrease at one year. On the contrary, AD patients with lower CR showed greater deterioration when they still had a high cognitive state (higher MMSE score).

One possible interpretation is that functional independence may have already reached a plateau in low CR patients with lower cognitive status, and functional changes are most evident when cognitive functioning is still at least partially preserved.

Among the most widely used proxies of CR (see Harrison et al., 2015, and Pinto et al., 2023, for umbrella reviews), higher education has been linked to a lower risk of developing MCI or AD across studies (Dekhtyar et al., 2015, 2016; Evans et al., 1997; Karp et al., 2004; Singh-Manoux et al., 2011; Soldan et al., 2017; Stern et al., 1994), and to predictors of cognitive functioning and decline in healthy ageing (Le Carret et al., 2003; Pipoly et al., 2024; Vonk et al., 2022; see Wu et al., 2020, for

systematic review), although not all researchers support this view (Bauer et al., 2020; McKenzie et al., 2023; Nyberg et al., 2021; see Pappalettera et al., 2024, for review). The lack of consent might be traced back to the fact that education alone might have a partial impact (explaining only a piece of variance) and that the conjunct use of more proxies or of standardized questionnaires (e.g., Cognitive Reserve Scale, León et al., 2011; or Cognitive Reserve Index questionnaire, CRI-q, Nucci et al., 2012), which consider several modifiable lifestyle factors, can fill better the CR construct (Devita et al., 2020). Indeed, education is considered a static part of CR, because it generally concerns, at a maximum level, early-life experiences (Lamballais et al., 2020), although associated with other proxies, such as occupation and ANART scores (Lo and Jagust, 2013). Notwithstanding this, education alone has been demonstrated to possibly have a protective role on AD progression (Garibotto et al., 2008; Tokuchi et al., 2014; Whalley et al., 2004; Xu et al., 2019), proving to be a readily available and useful CR proxy. The present data support this line of evidence, with (past) years of education assigning specific significance to MMSE cognitive functioning – and, by extension, to disease severity – in predicting one-year changes in functional autonomy. Nevertheless, at present, it cannot be ruled out that other variables related to education might contribute to the observed effects.

Within a CR framework (Stern, 2002), the predictive power of education modulated by disease severity in AD is in line with what was shown by Serra et al. (2015) in a limited group of MCI patients. In this population, high CR showed a significantly reduced risk of developing AD over months. According with our results, patients with high CR and higher cognitive efficiency at baseline (as measured by MMSE) survived longer, likely without developing AD, as compared with those with high CR and low general cognitive efficiency at baseline.

While most studies have focused on the relationship between CR and the risk of dementia in nondemented older adults or MCI patients, there is more limited literature on the relationship between CR and clinical progression in individuals with AD. In this population, higher CR, measured through the CRI-q (Nucci et al., 2012), was associated with slower AD progression on the Clinical Dementia Rating scale (Garba et al., 2021). Van Loenhoud et al. (2019) applied a “residual” approach to measuring CR (Reed et al., 2010), modelling demographic and brain predictors of cognition and treating the variance in cognition that is not explained by these predictors as a measure of current CR (Stern et al., 2020). In this study, “residual” CR, which was shown to correlate with years of education, has a protective role in healthy and MCI individuals, and an opposite, exacerbating effect in the clinical progression of AD patients (Cadar et al., 2015). This paradoxical result may represent an inflection from mitigation to exacerbation, which might take place around the onset of dementia, in line with the CR hypothesis (Kadlec et al., 2018; Scarmeas and Stern, 2004; Stern et al., 1999).

As previously discussed, in high CR people, the onset of cognitive loss and functional disability corresponds to more severe underlying neuropathology. In this regard, the interaction model proposed in the present study, with the joint use of two separate predictive indices, can consider both CR and disease severity and allow for the delineation of individualized trajectories, in which past CR assumes a different meaning according to the current level of disease severity in the mild stage AD population (Robitaille et al., 2018). These results support the literature demonstrating that higher CR may postpone clinical onset of AD but also accelerate cognitive decline after diagnosis (Andel et al., 2006; Scarmeas et al., 2006; Yoon et al., 2021). In fact, higher CR has been shown to be associated with slower decline when cognitive functioning is well-preserved, reflecting mild disease staging, and more rapid change when cognition becomes more severely impaired.

In the present study, the protective effect of CR, still evident in the early stages of AD, is likely attributable to the way the outcome is defined and measured (loss of functional autonomy and not cognitive performance), which possibly occurs temporally after cognitive status deteriorates. In this vein, a low MMSE score associated with high CR

might suggest a forthcoming deterioration, delineating a time window in which, as some functional autonomy is still preserved, prognostic decisions can be taken, or interventions planned. A different picture prevails in cases of low CR, with AD patients deteriorating more at one year when they still have high cognitive status (higher MMSE score). Without arguing against the CR hypothesis, this result may be due to the flattening of daily functioning autonomy in patients with more severe deterioration, which beyond a certain threshold, may be less detectable at a clinical assessment. Accordingly, the present results can also have implications in implementing clinical trials, since matching patients according to their level of CR and cognitive state can improve the ability to identify the effects of pharmacological interventions.

With the deepening of the subsample analysis, the present AD longitudinal model includes all the three components considered to be necessary for a CR-based study, namely lifestyle factors, cognition, and brain measures (Stern et al., 2023; see Song et al., 2022, for a systematic review). Introducing a biomarker imaging variable as CSF A β 1–42 levels in the model (see Harris et al., 2015, for a similar methodological approach) allows to control for the contribution of brain pathology on defined clinical outcomes (Xu et al., 2019), supporting the CR construct. Differently from CR designs proposed for healthy or minimally impaired individuals, the present study suggests the importance of modelling AD progression on functional outcome measures, on which clinical diagnosis is primarily based.

4.1. Limitations

Our study has several limitations. Firstly, although longitudinal investigations are relatively rare, especially in the progression of AD, the present study is mainly concerned with the mild phase of the disease (mean MMSE t0 = 23.33; mean FAQ t0 = 13.09), including a follow-up of one year, which could be a rather short duration for AD. One possible speculation is that the relationship between CR and MMSE score may attenuate in later stages, most likely due to the flattening of cognitive and functional performances in severe dementia.

Furthermore, only for a limited subsample of patients was an amyloid burden index available. The reduced power affected the analysis including the biomarker: the results are less strong, but in line with previous findings, corroborating their potential significance in the context of CR.

Another limitation is that the present study is based on ADNI data, collected from different centers, and necessarily relies on the use of the available proxies, such as years of education for CR or MMSE score for global functioning index. We might speculate that the relatively low percentage of variance explained by the model may be due to the application of these proxies. Future studies, possibly prospective, may verify whether the use of multidimensional proxies can lead to a better fitting model, which might be more relevant from a clinical perspective. Although based on suboptimal proxies, the model significantly explains some of the variance and changes in functional autonomy as assessed through the one-year deltaFAQ. A secondary yet important aspect of the proposed model is highlighted by the ease with which education and MMSE scores can be retrieved in the clinical setting. Thus, although they are based on suboptimal proxies, our results are likely of interest to the many centers where only data collected for clinical purposes are available.

Finally, a further limitation of the study concerns the number of follow-ups included. It has been recently suggested that three time-points achieve more robust longitudinal modelling addressing individual differences (Parsons and McCormick, 2024). A third wave of data was available in the ADNI database for an insufficient number of participants for the scope of this study; therefore, we limited our analysis, and consequently our conclusions, to one year.

5. Conclusions

In summary, the present CR-based model shows the mutual role of past acquired CR and current cognitive status (disease severity) in predicting AD progression. The longitudinal study highlights a way to interpret, net of age and amyloid burden, demographic and clinical data readily available at the first visit. The combined use of information on years of education and MMSE score might help clinicians predict the individual's course, providing suggestions for clinical management and interventions. Future studies could investigate whether the interaction between CR and performance on specific neuropsychological tests (e.g., measuring mnemonic, linguistic, visuospatial or executive functions) may be a better predictor of disease progression in patients with typical (mnemonic) and atypical AD.

Ethics declarations

The studies involving human participants were reviewed and approved by the Ethical approval was obtained by the ADNI investigators. The patients/participants provided their written informed consent to participate in this study.

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CRediT authorship contribution statement

Daniele Romano: Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization. **Giorgia Tosi:** Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization. **Laura Veronelli:** Writing – original draft, Methodology, Conceptualization.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.neurobiolaging.2024.12.002](https://doi.org/10.1016/j.neurobiolaging.2024.12.002).

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