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The complex interplay between cognitive reserve, age of diagnosis and cognitive decline in Alzheimer's disease: a retrospective study

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ABSTRACT

Objective: The present study examined the cognitive reserve (CR) theory at late stages of Alzheimer's disease (AD). The objective is to replicate previous studies and examine the complex role of education and family size as indicators of CR.

Participants and methods: This is a retrospective study included 642 patients diagnosed with AD after age 65, categorized into low education (LE, ≤ 8 years, $n = 141$) and medium-high education (MHE, ≥ 9 years, $n = 442$) groups. Participants were followed up longitudinally using the Mini Mental State Examination.

Results: Higher education in the MHE group, but not in the LE group, correlated with delayed diagnosis. In both groups, higher education correlated with accelerated cognitive decline. In the MHE group, country of origin was associated with cognitive decline, while in the LE group, it was linked to family size.

Conclusions: This study shows that in patients with MHE but not in LE, higher education resulted in delayed diagnosis. Conversely, in cases of LE, this measure may not fully reflect CR and abilities. Additionally, higher education was associated with faster deterioration, a finding that has not been replicated often in the literature. The study illustrates the complex impact of CR proxies on age of diagnosis and cognitive decline.

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Cognitive reserve; cognitive decline; Alzheimer's disease; education

Introduction

Alzheimer's disease (AD) is one of the most common causes of morbidity and mortality in the elderly, and its prevalence increases with age. The estimated prevalence of patients diagnosed with dementia worldwide is 55 million people, with the number expected to increase to 78 million by 2030 and to 139 million by 2050 (World Health Organization, 2022). AD is a neurodegenerative disease characterized by neuronal loss and brain atrophy that progress gradually. AD follows a prolonged, progressive course that begins with pathophysiological changes in the brains of affected individuals, years before any clinical manifestations are observed (Jack et al., 2013). Typically, the brain regions that are affected first are the medial-temporal lobe and neocortical structures (Breijyeh & Karaman, 2020). Most often, the first clinical manifestation is a deficit in short-term memory and new learning, reflected in rapid forgetting of newly learned information (Bradfield & Ames, 2020).

Studies have revealed discrepancies where postmortem analyses demonstrate significant AD-related brain pathologies in individuals who did not display corresponding cognitive deficits during their lifetime (Snowdon, 2003). The Cognitive Reserve (CR) and Brain Reserve (BR) theories have been proposed to elucidate this discrepancy between observed brain pathology and clinical manifestations (Stern, 2002). According to these theories, variations in premorbid brain structure (i.e., BR) and premorbid cognitive abilities (i.e., CR) may modulate the expression of pathological symptoms of AD and other neurological diseases (e.g., Traumatic Brain Injury, Parkinson's disease). The "nun study" led by Snowdon (2003) exemplifies this phenomenon by finding no direct relationship between the level of brain pathology and the clinical expressions of AD in the lives of more educated nuns.

The CR theory posits that certain life experiences, intelligence, and innate factors, and brain structure characteristics contribute to building resilience against cognitive decline by establishing a reserve of brain

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This article has been corrected with minor changes. These changes do not impact the academic content of the article.

resources capable of compensating for age or disease-related changes. A high level of CR may delay or reduce the clinical manifestations of the disease,[5] so that the age of diagnosis of AD is postponed (Scarmeas & Stern, 2003). Variables that are assumed to reflect CR are, for example, education, occupation, socioeconomic status (SES), leisure activities, and IQ level, indicating interpersonal differences in the way the brain deals with the pathology (Levi et al., 2013; Stern, 2002). Family size is considered to be a strong measure of SES (more children, lower SES) (Brosch & Peres, 2000; Newman, 2009). In patients with AD, it was found that education mediates the relationship between beta amyloid and the cognitive level (Ko et al., 2022) and that it is the variable that is suitable for evaluating CR in relatively advanced stages of AD (Montemurro et al., 2021). Typically, a composite index that considers multiple variables is employed to assess CR (Levi et al., 2013; Stern, 2012).

To evaluate cognitive decline and track the progression through different stages of AD, various standardized tests are utilized in clinics. One common assessment test is the Mini Mental Examination (MMSE) (Folstein et al., 1975), notable for its sensitivity to the patient's educational background. Consequently, it is typical to normalize the scores based on the estimated level of education or refer to subgroups of education level (Butler et al., 1996; Tombaugh et al., 1996).

While education is often used as a proxy for CR, it may not fully capture an individual's cognitive potential. Factors such as cultural background, access to resources, and individual motivations play significant roles in shaping intelligence, cognitive abilities and resilience. Intelligence encompasses a broad spectrum of cognitive abilities extending beyond academic knowledge, including problem-solving, adaptability, and creativity (Benedek et al., 2014; Burns et al., 2006; Sternberg, 1997). Acquiring higher education necessitates cognitive skills and abilities, leading to the common perception that advanced levels of education are associated with high cognitive abilities (Lee et al., 2003; Lövdén et al., 2020; Peng & Kievit, 2020). However, individuals with limited formal education can still possess considerable intelligence and cognitive capabilities, as their full cognitive potential might remain unattained due to various variables such as personality traits or life circumstances (Parisi et al., 2012). Immigrants, for instance, frequently encounter hurdles such as language barriers, cultural adaptation challenges, and socioeconomic inequalities, which limit their access to educational opportunities and hinder cognitive development (Baum & Flores, 2011; Berry, 1997; Jaimes Pérez, 2014). Similarly, individuals deeply engaged in religious practices may prioritize spiritual/religious studies over academic achievement (Horwitz, 2021; Moskovich & Liberman, 2018). Consequently, low levels of formal education may not fully reflect an individual's true cognitive abilities and reserve, considering the impact of external factors on educational opportunities and the attainment of cognitive potential.

The goals of the current study are to explore the multifaceted nature of CR and the limitations of common measures such as formal education. Recognizing the need for more comprehensive longitudinal research (Nelson et al., 2021), we conducted a retrospective study using a large dataset of patients with AD. Unlike previous research that primarily focused on cross-sectional comparisons (Stern, 2006, 2012) our study aimed to track patients from the time of AD diagnosis through the progression of the disease, starting from the point where patients presented with memory complaints and until the patient discontinued attending follow-up appointments at the clinic (not necessary passed away).

The current study explores the complex role of CR, measured by years of education and family size, as it is recommended to utilize a multi-factorial measurement that reflects CR (Levi et al., 2013), in predicting cognitive decline among patients with AD. Our first aim was to replicate previous findings (Scarmeas & Stern, 2003; Stern, 2002) and examine the relationship between CR levels and the age of diagnosis. Building on previous but limited research, we hypothesized that higher CR would be linked to a delayed AD diagnosis, particularly in groups with higher education levels.

While individuals with higher education likely attained their cognitive potential, it is plausible that various factors such as age and religion hindered those with less education from reaching their full potential. Consequently, years of schooling among the more educated individuals can be viewed as reflecting CR, whereas this may not hold true for those with lower education levels. Thus, we speculated that there will be a significant correlation between years of education and age of diagnosis in the more educated group, but not in the less educated group.

We also suggested that cognitive decline might progress faster in individuals with higher CR after an AD diagnosis, compared to those with lower CR (Scarmeas & Stern, 2003; Stern et al., 1999).

Methods

Participants and procedures

This is a retrospective study based on a clinical database of patients diagnosed with AD who were under long-

term follow-up at the Hadassah Mount Scopus Neuro-Geriatric and Memory Clinic. The clinic was established more than 20 years ago, and it serves as a center for the diagnosis, follow-up, and treatment of patients with AD in the Jerusalem area. The research was consistent with the relevant ethical guidelines and received approval from the institutional IRB.

The total database of the clinic included 2,040 patients diagnosed with dementia who were treated at the clinic between 1996 and 2020, but only 920 of them had at least one follow-up. Patients who came to the clinic only once were excluded from the sample. This exclusion was warranted because a single test may not sufficiently capture deterioration, leading to uncertain diagnoses. Since we did not collect causes for dropout from second follow-up, we aimed to ensure that CR or demographic differences did not explain the dropout. Therefore, we conducted t-tests on demographic variables (including age, family size, marital status, gender, education, country, and ethnicity). The t-test did not reveal significant differences between the groups for those who attended at least twice and those who did not.

Of 920 patients, 724 were diagnosed with AD and the rest with other types of dementia (e.g., Lewy body dementia and frontotemporal dementia), and therefore were excluded (Figure 1). The diagnosis of AD was performed by a neurologist at the clinic specializing in dementia. The diagnosis was based on a significant decline in cognitive abilities and daily function, as reported by the patient or a caregiver, and as manifest in cognitive tests (mainly the MMSE (Statsenko et al., 2023)), the NINCDS-ADRDA (McKhann et al., 1984), and the AA-NIA criteria (Montine et al., 2012). To rule out other diseases as the cause of dementia, all patients underwent brain imaging by MRI or CT and laboratory tests, including B12 and thyroid function. Patients were followed clinically up every 6–9 months, the cognitive decline was monitored and documented using the MMSE. The diagnosis usually relied on information from a primary caregiver to assess functioning. However, this data was not included in the study due to its collection through informal interviews.

Inclusion criteria were a diagnosis of possible or probable AD after the age of 65 (because there are

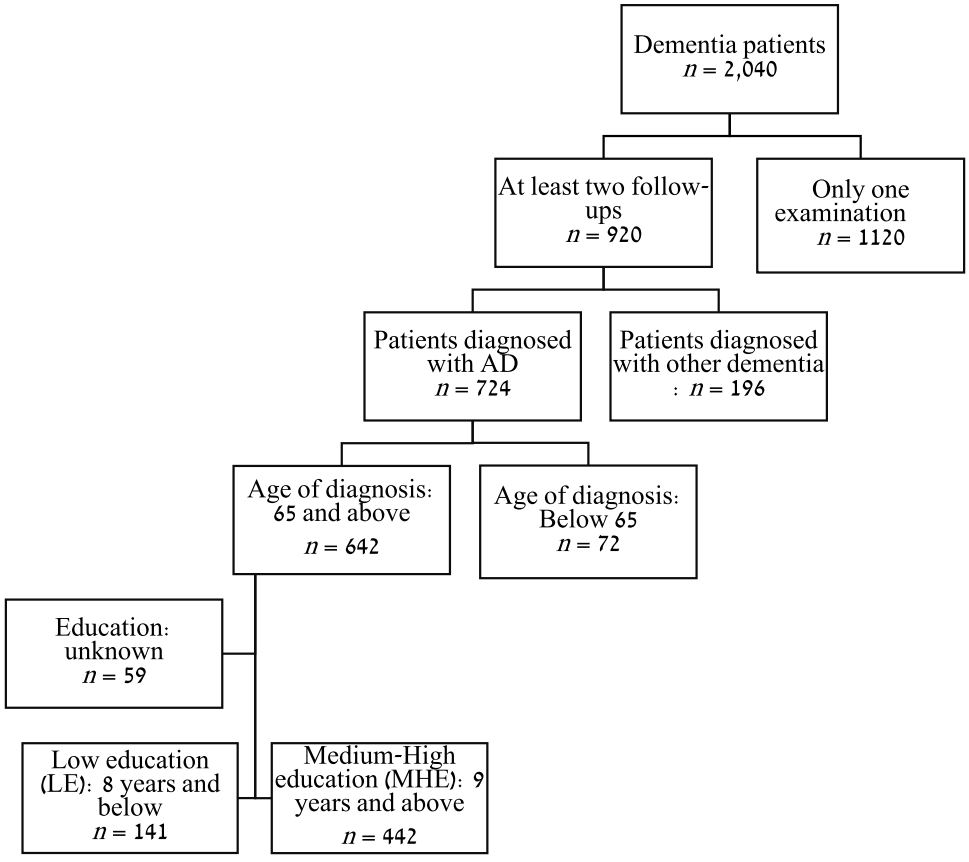

Figure 1. Distribution of the sample and filtering of participants.

many differences between the characteristics of AD above and below this age (Mendez, 2012)). Six hundred and forty-two patients (361 females, age range, 65–97 years) were diagnosed with AD after the age of 65 (Figure 1).

The participants were categorized into two education groups: those with basic education (8 years or less, $n = 141$, Low Education (LE)) and those with higher education (9 years or more, $n = 442$, Medium-High Education (MHE)). This division aligns with previous research on cognitive reserve (Stern et al., 1994; Zahodne et al., 2015) and is also based on the recommended cutoff point for the MMSE (Black et al., 1999; Folstein et al., 1975; Tombaugh et al., 1996). Individuals with an unknown number of years of education were excluded.

Measures

Demographic and clinical data were extracted from hospital records. Demographic data included age, gender, marital status, and country of origin (place of birth). These variables were collected to examine their impact on outcomes, given that research, such as a meta-analysis on immigration, suggests that migrants in Europe from Asia and Africa may face significantly increased dementia risk (Selten et al., 2021). Additionally, demographic factors like marital status have been linked to higher dementia odds (Liu et al., 2020), and gender differences in Alzheimer's prevalence are also well-documented (Castro-Aldrete et al., 2023). The epidemiological characteristics of AD include the year of diagnosis and the drug treatment (e.g., donepezil, rivastigmine, galantamine, memantine). CR variables included years of education and number of children (family size). The time between follow-ups was also recorded. MMSE is a 30-point screening tool that assesses multiple cognitive domains. It was administered at each follow-up by a neurologist. Only individuals who demonstrated sufficient proficiency in English or Hebrew to complete the MMSE were included in the study. Cognitive decline was assessed by measuring the difference in MMSE scores between the first and last follow-up, reflecting the progression of the disease. These two testing points were chosen in order to maximize the sensitivity of cognitive deterioration.

Statistical analyses

Data was entered into a Microsoft Excel file (Microsoft, Redmond, WA, U.S.A.), then transferred to a statistical analysis program (SPSS 26.0, Chicago, IL, U.S.A.). All statistical analyzes were done for each education group separately. We used Chi-squares and t-tests for independent samples were conducted to compare the groups of education level. We also used Pearson correlation coefficients between age of diagnosis and education to examine the relationship between the two. Next, we conducted stepwise regression analyses to predict the decline.

Results

Correlation between education and age of diagnosis

Table 1 presents the demographic variables of the participants of the two groups (and of the whole sample only as a reference point). The average age was similar in the two groups, and there were no significant differences between the groups in the time elapsed between the two follow-ups or in the score between the first MMSE and the last. But we found significant differences between the groups in the CR variables not only in years of education, which was expected as it defines the distinction between the groups, but also in the number of children, with the LE group showing a larger family size compared to the MHE group. In addition, as can be seen in Table 1, the groups differed significantly in the demographic variables of gender, marital status, and country of origin, as well as in the first and last MMSE scores. In the MHE group, over 70% of participants originated from western countries. In contrast, the LE group showed greater geographical diversity, with only 45% originating from western countries. The LE group started with a lower MMSE score, which indicates a lower cognitive level, than the MHE group, and correspondingly, the score at the last follow-up was significantly lower.

Correlations between CR variables and age of diagnosis in the MHE and LE groups

To examine the relationship between measures of CR and the age of diagnosis, we conducted separate Pearson's correlations between education and number of children and age of diagnosis for each group (the correlation between age of diagnosis and years of education was not significant in our whole sample). In the MHE group we found a significant correlation ($r(442) = 0.10$, $p = .045$) between education and the age of diagnosis, with higher education with later age of diagnosis. The correlation between

Table 1. Comparison of demographic and cognitive variables between the MHE and LE groups.

		Total Sample $n = 642$	MHE group $n = 442$	LE group $n = 141$	p (Between HE and LE)
Variables		Mean *(range)*	Mean *(range)*	Mean *(range)*	
Age at diagnosis		77.01 (65–97)	76.78 (65–97)	76.82 (65–88)	n.s.
Gender (men)		281 (43.8%)	206 (46.6%)	50 (35.5%)	0.02
Country of origin	Israel	217 (34.6%)	160 (36%)	45 (32.4%)	0.01
	Europe	165 (26.3%)	126 (28.5%)	12 (8.5%)	
	North Africa	74 (11.8%)	38 (8.6%)	32 (22.7%)	
	Former USSR	49 (7.8%)	42 (9.5%)	5 (3.6%)	
	Asia	45 (7.2%)	18 (4.1%)	22 (15.7%)	
Marital status	Married	419 (65.8%)	307 (69.5%)	81 (57.4%)	0.001
	Widowed	196 (30.8%)	116 (26.2%)	55 (39%)	
Education		11.82 (0–28)	13.93 (9–28)	5.21 (0–8)	0.01
Number of children		3.6 (0–16)	3.44 (0–16)	4.16 (0–12)	0.01
MMSE: first follow-up		21.51 (3–30)	22.26 (3–30)	19.52 (8–28)	0.01
MMSE: last follow-up		16.52 (0–30)	17.36 (0–30)	14.28 (0–28)	0.01
Difference between MMSE		5.01 (−9–30)	4.92 (−9–30)	5.22 (−5–23)	n.s.
Time difference between follow-ups (months)		33.05 (1–152)	32.27 (1–152)	34.89 (1–130)	n.s.

MMSE: Mini Mental Status Examination; values are mean ± *SD* or *n* (%) or Range; n.s. = non-significant.

the age of diagnosis and the number of children did not reach significant (MHE: $r(435) = -0.08$, $p = .07$). In the LE group, no significant correlations were found neither between education and the age of diagnosis ($r(141) = -0.04$, $p = .68$) nor between the age of diagnosis and the number of children (LE: $r(138) = 0.04$, $p = .67$).

Stepwise regressions to predict cognitive decline in the MHE and LE groups

To examine whether CR variables predict steeper cognitive deterioration, we performed stepwise regressions. The dependent variable was the cognitive decline between the first and last observation (MMSE difference). The predictors were the age of diagnosis and the CR measures (education and number of children). Because this was a retrospective study and the time difference between the two measurements was not constant, we entered this variable first as a predictor variable that enabled the isolation of the effect of the other variables beyond the obvious effect of the time difference. To reduce the effect of the variation in the severity of the current illness, as reflected in the last MMSE, we entered the last follow-up MMSE into the model. We observed that the difference between two follow-up measurements exhibited a stronger significant correlation with the last follow-up ($r(636) = -0.78$, $p < .01$) compared to the first ($r(636) = 0.21$, $p < .01$). Since our study did not account for reasons behind assessment discontinuation (such as death, technical issues, or health decline), incorporating the last MMSE ensures our predictive model remains adaptable and sensitive to ongoing cognitive changes. While there was notable variance also in the first follow-up ($SD = 4.49$), the variance in the final follow-up was higher ($SD = 6.97$), prompting its inclusion in the regression analysis. We also included all variables that exhibited differences among education groups in the regression analysis, including marital status, gender, country of origin, and ethnicity. This step was taken to verify that these factors were not the primary contributors to cognitive decline. Additionally, as a precautionary measure, we included the age of diagnosis in the analysis, even though no significant difference was observed between the education groups.

As shown in Table 2, In the MHE group, the stepwise regression analysis revealed that a combination of variables, including last follow-up MMSE, time difference between tests, education and country of origin, accounted for a substantial portion of the variance in the cognitive decline. The model demonstrated a significant overall fit, explaining approximately 71.8% of the variance ($R^2 = 0.718$, $p < 0.01$). The last MMSE alone explained a considerable portion of the variance, approximately 65%. Time difference between

Table 2. Age of diagnosis and the CR variables predicting cognitive decline: MHE group.

	R^2	*B*	*SE B*	*β*	*p*	*CI*
	0.718*					
MMSE last follow-up		−.692**	.026	−.74	.001	[−0.74, −0.64]
Time difference between follow-ups		.061**	.007	.25	.001	[0.05, 0.07]
Education		.232**	.058	.106	.001	[0.12, 0.35]
Country of origin		.126*	0.06	−0.05	0.03	[−0.24, −0.01]

**$p < 0.01$ *$p < 0.05$.

Table 3. Age of diagnosis and the CR variables predicting cognitive decline: LE group.

	R2	B	SE B	β	p	CI
	0.662*					
MMSE II: last follow-up		−.541**	.046	−.632	.001	[−0.63, −0.45]
Time difference between follow-ups		.066**	.01	.34	.001	[0.04, 0.09]
Education		.353**	.097	.2	.001	[0.16, 0.54]
Number of Children		−.293*	.147	−0.11	.048	[−0.58, −0.01]

**$p < 0.01$ *$p < 0.05$.

tests contributed to approximately 5.0% of the variance. While education explained a smaller portion of the variance individually, approximately 1%, and so as the country of origin, approximately 0.5%, its contribution remained significant beyond other variables. The stepwise regression removed marital status, gender, ethnicity, and age of diagnosis from the model because they did not significantly contribute to explaining the variance in the dependent variable.

We conducted the same stepwise regression for the LE group. As shown in Table 3, the model demonstrated a significant overall fit, explaining approximately 66.2% of the variance ($R^2 = 0.662$, $p < 0.01$). The last MMSE alone explained a considerable portion of the variance, approximately 50%. Time difference between tests contributed to approximately 8.0% of the variance. Education contributed approximately 5.0% of the variance and number of children contributed to approximately 1.0% of the variance. The CR variables 'contribution remained significant beyond other variables.

Discussion

The present study examined the effects of CR on the age of diagnosis and cognitive decline in patients diagnosed with AD. Unlike most previous studies, it focused on the late stages of the disease, which have been less studied (Li et al., 2021; Nelson et al., 2021). This research investigates how CR, measured by factors like education and family size, influences the age of AD diagnosis and subsequent cognitive decline. Using a retrospective approach and data from a large database spanning two decades, the study aims to replicate previous findings and assess the CR relationship across different life circumstances and cultural backgrounds. The study hypothesized that in patients with higher CR, the age of the disease diagnosis is delayed compared to patients with lower CR, and that higher CR predicts steeper cognitive decline. Based on research indicating that education can be influenced by factors such as immigration and religion (such as varying educational quality across countries, or differences between religious and secular educational frameworks (Avila et al., 2021; Baum & Flores, 2011; Berry, 1997; Jaimes Pérez, 2014; Jones et al., 2011)), and recognizing that family size can also be influenced by religious factors rather than solely reflecting socioeconomic status (Central Bureau of Statistics, 2024; Frejka & Westoff, 2008;), we hypothesized that standard variables used to reflect CR rates may not always be suitable due to diverse population characteristics. Specifically, we hypothesized that the impact of cognitive reserve might differ in groups with lower education levels, influenced by factors like immigration and religion, compared to those with higher education levels.

Because we hypothesized variations in characteristics between individuals with low and high reserves, we divided the sample by years of education into MHE and LE groups, similar to previous studies (Stern et al., 1994; Zahodne et al., 2015). Another reason for dividing the sample was the sensitivity of MMSE to education (Butler et al., 1996). The groups differed significantly in other demographic variables as well.

We found that in the MHE group age of diagnosis was associated with higher education, as predicted and consistent with previous studies (Scarmeas & Stern, 2003; Stern, 2002). We did not find a significant correlation between the age of diagnosis and family size. These correlations were not significant in the LE group. It is important to note that finding a correlation in the MHE group but not in the LE group does not imply that these groups are related to education in different ways or different extents. Rather, it indicates that the observed correlation between education and age of diagnosis is specific to the MHE group and not generalizable to the LE group. These findings, indicating that the relationship between years of education and age of diagnosis was not linear but valid only for those with more than basic education (9 years of schooling or more), is important and sheds light on factors that should be considered when choosing variables that may reflect CR. The finding can be explained by the fact that Israel is a country of immigrants and was especially so in the period following World War II, which was the generation of the study sample. Therefore, it is possible that in the LE group, education was not a reliable measure of CR because the population did not fulfill its educational potential owing to war and immigration. Another factor to consider is

that the LE group shows significant variability in countries of origin, which may suggest that years of education do not consistently reflect the type and quality of education received, given diverse educational systems. In contrast, the MHE group primarily comprises 70% of participants from Western countries, indicating a more uniform educational environment where years of education can reliably indicate levels of educational attainment. This finding is in line with demographic data on immigration to Israel during its establishment (Central Bureau of Statistics, 1973). Immigrants were commonly divided into two groups: those from Asia and Africa and those from Europe and America. The former group often had lower levels of education and larger family sizes. These explanations are also consistent with the finding that the average age of diagnosis did not differ between the groups.

We conducted stepwise regressions to examine the second hypothesis, which predicts a steeper decline in people with higher education, presumably because of a more severe neuropathology as a result of the late diagnosis. Our findings suggest that individuals with higher levels of education tend to experience a steeper decline over time (a positive correlation between years of education and the difference between measurements from the first to the last follow-up). Additionally, there appears to be an influence from the individual's country of origin, while in Western countries (for example, Israel, Europe and North America) the decline is more pronounced compared to Eastern countries, indicating a potential impact, such as differences in educational quality (Avila et al., 2021; Jones et al., 2011).

Even within the group with the lower education level, the finding is that more educated individuals experience faster deterioration compared to those with less education (similar to the MHE group with a larger effect). However, another explanatory factor here is the size of the family. Specifically, we find that a larger family size corresponds to a smaller difference between the first and last measurements. Therefore, it is plausible that within this group, higher education signifies a greater CR, leading to more pronounced deterioration, while the family size variable can also be influenced by religious factors rather than solely reflecting socioeconomic status (Central Bureau of Statistics, 2024; Frejka & Westoff, 2008; Lehrer, 2004). These conflicting findings suggest that demographic variables alone are insufficient for assessing CR within this group. This may also explain why no significant correlation was found between the CR variables and the age of diagnosis. An important theoretical insight is that two indices of CR predict opposite outcomes under certain conditions, which underscores the complexity of using different indices.

Taking into account life circumstances (e.g., immigration and religiosity) individuals who have accumulated more years of education deteriorated faster than those with lower education, probably because of severe neuronal loss in the brains of patients with higher CR (Amieva et al., 2014; Bigler, 2013; Mungas et al., 2018; Stern, 2006). The findings about steeper deterioration, is noteworthy and has not been widely replicated, but it does remain consistent with findings from studies conducted in the early stages of the disease (Amieva et al., 2014; Bigler, 2013; Scarmeas & Stern, 2003; Stern et al., 1999).

One of the main strengths of the present study is its sample, which consists of a less frequently studied population of individuals diagnosed with AD already in an advanced stage and receiving cholinesterase inhibitor treatment. The sample was also based on a wide clinical pool of patients who were monitored and treated for many years by the same medical team, resulting in relatively homogeneous treatment methods. The database charts the progress and treatment of AD in the advanced stages, under "real-life" conditions and not within the framework of clinical studies.

The present study, conducted within a memory clinic offers valuable insights with its inherent advantages in terms of ecological validity, yet also poses several limitations due to challenges in controlling for all the variables. Therefore, we had to control for intervening variables, such as the time difference between the follow-ups, the severity of the disease. It is important to note that this study exhibits considerable variability in both the initial and final MMSE scores, attributable to its ecological nature and the inherent diversity among individuals. Given the higher variance in the final MMSE scores, we included it as the first variable in our stepwise regression analysis to neutralize its effect and isolate the impact of CR.

It appears that the CR variables, in particular education, contributed to the variability of the cognitive decline. Furthermore, it would have been more informative to measure also other variables that reflect the decline, in addition to MMSE, and other measures of CR like leisure activities, but this was not available in the patients' medical records. It would have also been informative to examine the mortality of the patients; however, this information too was unavailable to us. It should be noted that the effect sizes in the Pearson correlations were small and given the limited range of years of education in the LE group, detecting statistically significant effects there may be challenging. The sample size reflects the study's ecological characteristics and adheres to established literature cutoffs. Nevertheless, future research could explore this further with a larger

sample of individuals with low educational backgrounds.

In conclusion, the present study expands our knowledge of factors determining CR, especially in the advanced stages of AD. The study shows that the effect of education on the age of diagnosis was not linear and remained valid for those with moderate to high but not necessarily for those with lower education, therefore, we were able to replicate previous studies only in the MHE education group. The study identifies additional factors that may influence CR, such as the attainment of cognitive potential, which may not be fully attained in the LE group. Thus, the study replicates findings (Scarmeas & Stern, 2003; Stern, 2002) about the delayed age of diagnosis in the MHE education group but also adds a new finding that, to the best of our knowledge, has not been reported in the literature before, that in the LE group, the consideration of cognitive potential is crucial since having a low level of education does not necessarily imply a lack of cognitive abilities, and thus reserves. The study sheds light on factors that should be considered when choosing CR variables.

Finally, the results of the study can also serve as a basis for diagnostic and therapeutic guidelines. For example, for patients with high CR, a different and more sensitive diagnosis is required because although the clinical expression appears later, the decline is faster. Therefore, it is important to refer such patients to a comprehensive neuropsychological diagnosis before the clinical deficits accumulate, as it is possible that their education and cognitive abilities mask cognitive deficits, as was found in other populations, such as those with ADHD (Milioni et al., 2017). Furthermore, the study highlights the importance of conducting tests and undertaking a more comprehensive investigation, even within the LE category. This is essential for gaining insights into the estimated level of intelligence, the life circumstances influencing low educational attainment, and the individual's socioeconomic status. Such an approach is necessary to ascertain the extent to which individuals have attained their cognitive potential and how this attainment affects their cognitive reserves.

The study has notable clinical and theoretical implications as it suggests that variables considered proxies of CR can significantly depend on context and circumstances. For instance, we found that the correlation between education and CR varies across different levels of education. Similarly, family size was observed to reflect CR only under specific circumstances, highlighting the the complexity of using the various indices that are supposed to reflect CR.

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