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FEATURED ARTICLE

Transition from mild cognitive impairment to normal cognition: Determining the predictors of reversion with multi-state Markov models

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Abstract

Introduction: The theoretical framework of the Alzheimer's disease continuum considers transition between stages in a unidirectional manner. Here we examine the rate of reversion from mild cognitive impairment (MCI) to normal cognition (NC) and explore a set of potential variables associated with this phenomenon.

Methods: A total of 985 Spanish community-dwelling individuals aged 70 years and over at baseline were monitored for 5 years. During this time, 173 MCI and 36 dementia cases were identified. Multi-state Markov models were performed to characterize transitions between states through the dementia continuum.

Results: The rate of reversion from MCI to NC was 11%. There were significant non-modifiable (age, socioeconomic status, or apolipoprotein E) and modifiable factors (cognitive training or absence of affective symptoms) associated with reversion.

Discussion: Overall, our results highlight that the likelihood of progression from MCI to dementia is very similar to that of reversion from MCI to NC.

KEYWORDS
Alzheimert's disease, dementia, mild cognitive impairment, multi-state Markov model, normal cognition, subjective cognitive decline

1 | INTRODUCTION

Alzheimer's disease (AD) is the most common type of dementia.[1] It is characterized by a progressive and irreversible decline of cognitive status that leads to an increase in functional dependency. The course of the disease is understood as a continuum from the asymptomatic phase to an intermediate stage of mild cognitive impairment (MCI) and finally to dementia.[2–4] Under this continuum, progression through the stages always occurs in the same direction, from asymptomatic to symptomatic and pathological.[5–9] However, research in recent years has shown that a considerable percentage of individuals fluctuate over time between MCI and normal cognition (NC), resulting in a reversal of clinical status, known as the yo-yo effect.[10]

Various studies have indicated that lifestyle may play a crucial role in the reversion phenomenon. Thus, individuals with a high level of cognitive and social activity (e.g., driving, reading, attending cultural classes, etc.) might revert more easily than those with a less stimulating lifestyle.[11] In turn, reversion is also more likely in younger patients,[12–15] as well as in those with better scores on general cognitive assessments and with higher amygdala and hippocampus volumes,[16,17]

with better vision and olfactory ability, and with higher scores on the personality trait of openness to experience.[17] Other modifiable variables such as smoking, obesity, and hypertension are also associated with cognitive impairment and dementia and their progression.[18]

Regarding neuropsychiatric symptoms, patients with fewer mixed anxious–depressive symptoms seem to revert more easily than those with higher scores in anxiety, apathy, or depression.[15,19] Paradoxically, affective symptoms have also been found to be a predictor for reversion.[13,14] Emotional variables are known to have a decisive influence on cognitive performance. The attenuation of depressive and anxiety symptoms between baseline and follow-up visits may allow for individuals to perform better on cognitive tests, which can lead to reversion from MCI. Thus, under this scenario, the diagnosed reversion could be explained by a spurious first diagnosis. Regarding genetic factors, the absence of the apolipoprotein E (*APOE*) ε4 allele has been identified as a variable associated with reversion.[15,16,20]

Several studies have also identified factors that are related to a lower rate of reversion to NC. Examples of these include the presence of multidomain MCI or a highly impaired cognitive domain, as well as the presence of arthritis,[17,20] amnestic MCI,[16,20] amnestic multidomain and non-amnestic multidomain MCI,[21] lower scores on language and memory assessment instruments (namely logical memory, verbal fluency, digit symbol, and Boston Naming Test),[15] and also having been classified as amnestic MCI by at least two memory tests.[13] Nevertheless, particularly low reversion rates could also be due to diagnostic errors arising from the consideration of subjective memory complaints rather than objective scores obtained in neuropsychological batteries as an indicator of impairment.[22]

Here we analyzed the data from an ambitious longitudinal community-based study addressing the early detection of AD in Spain. The objectives of our study were twofold. First, we sought to examine the annual rate of reversion from MCI to NC in a sample of older adults who have been monitored longitudinally. Second, we aimed to detect possible associations between a heterogeneous set of variables (some modifiable and others not) and reversion to NC. As this study focuses on the temporal dynamics of the dementia continuum, we performed a multi-state Markov model (MSMM) in continuous time to better characterize transitions among the following states: NC, MCI, and dementia. Analyses based on this approach are appropriate for modeling the course of health processes in continuous time because they can accurately capture the state transitions, including both forward and backward directions, of individuals across discrete stages.[23] Then, considering the assumption of the AD continuum, MSMM enables us to describe the process in which individuals move through the AD stages over time.

HIGHLIGHTS

- Multi-state Markov models help to examine transitions through the Alzheimer's disease continuum.
- Likelihood of progression from mild cognitive impairment (MCI) to dementia is similar to reversion to normal cognition (NC).
- Very few cases over the age of 80 reversed from MCI to NC.
- Modifiable lifestyle factors are associated with the reversion phenomenon.

RESEARCH IN CONTEXT

1. **Systematic Review**: The conceptual framework of the Alzheimer's disease continuum considers mild cognitive impairment (MCI) as a prodromal stage that increases the risk of future dementia. Although the transition between stages is usually conceived in a unidirectional manner, cases of reversion from MCI to normal cognition (NC) has been described.
2. **Interpretation**: Using multi-state Markov models, our results in older adults indicate that the probability of progressing from MCI to dementia is similar to that of reverting from MCI to NC. Thus, the transition through the stages appears to be bidirectional. Younger age, individual socioeconomic status, cognitive training, and depression may influence in reversion.
3. **Future directions**: The onset of MCI does not lead inexorably to dementia, but a return to a state of NC is possible. Future work should experimentally examine the implication of modifiable lifestyle factors in the reversion phenomenon to improve individualized intervention programs.

2 | METHODS

2.1 | Participants

The participants of this study comprised 985 community-dwelling individuals aged 70 years old and over at baseline. All of them were part of the Vallecas Project cohort, a community-based longitudinal study addressing the early detection of AD.[24] The participants were volunteers who were recruited through radio and TV campaigns, leaflet distribution, and visits of the research team to social centers for the elderly. The study was approved by the Research Ethics Committee of the Carlos III Institute of Health, Madrid, Spain. Informed written consent was obtained from all participants enrolled in this study.

The participants underwent a detailed assessment protocol annually over six visits. The protocol included past medical history, neurological and neuropsychological examination, as well as a biochemical and genetic blood test. A full visit was usually carried out within 4 hours, with convenient breaks. The neuropsychological battery included tests measuring a wide range of cognition.

2.2 | Study variables

Two large groups of variables were considered in our study. First, we addressed non-modifiable risk factors for MCI, which included age, sex, *APOE* genotype, individual socioeconomic status (ISES), and neighborhood socioeconomic status (NSES). These last two variables have been used by our research group in other studies.[25] ISES was operationally defined as a standardized composite score based on educational attainment, occupation, and the highest level of education reached by parents. NSES, on the other hand, was a standardized composite score based on average annual net income, percent of residents with no formal qualifications, percent of residents with higher education, percent of residents with white-collar jobs, unemployment rate, and housing price (€/square meter). Second, we included a modifiable risk factor for MCI that covered social engagement, physical exercise, diet, cognitive training, hypertension, diabetes, hypercholesterolemia, and depression. For further details about the definition and levels of the non-modifiable and modifiable factors, see the supporting information.

2.3 | Neuropsychological assessment

The neuropsychological protocol of the Vallecas Project was designed to comprehensively assess the cognitive function of the participants, as well as their progression during follow-up. Neuropsychologists with broad experience in cognitive aging and dementias were in charge of applying the neuropsychological testing battery following the standard test instructions.

Although this battery had a special focus on the evaluation of memory, attention, and executive functions as potential early markers of AD, the neuropsychological profile was also completed by obtaining information related to other cognitive domains such as language, visuospatial ability, and visuoconstruction. All these data allowed us to identify the strengths and weaknesses of the cognitive profile and to characterize, where appropriate, the type of cognitive impairment exhibited by each subject.

The following main cognitive tests made up the neuropsychological battery in this study: Mini-Mental State Examination (MMSE); Clock Drawing Test; Free and Cued Selective Reminding Test (FCSRT); Rey-Osterrieth Complex Figure Test (ROCF); Lexical Fluency Test (P, M, R); Semantic Fluency Test (Animals, Fruits, and Vegetables, Tools); Digits Forward and Backward and Digit Symbol (Weschler Adult Intelligence Scale [WAIS-III]); Symbolic gesture and Imitation of bilateral postures test barcelona revisado (TBR); Rule shift cards (Behavioural Assessment of the Dysexecutive Syndrome [BADS]); and Boston Naming Test (BNT-15 version). Additionally, the battery was completed with scales for the evaluation of subjective cognitive decline (Everyday Memory Questionnaire [EMQ]), mood (State-Trait Anxiety Inventory [STAI] and Geriatric Depression Scale [GDS-15]) and activities of daily living (Functional Assessment Questionnaire [FAQ]). Finally, all subjects underwent a detailed survey and assessment protocol to gather information on demographics (age, sex, level of education, marital status, living situation, socioeconomic status, occupation, etc.), lifestyle (physical activity, social support, eating and sleeping habits, etc.), quality of life (well-being, perceived health, etc.), and medical history (vital signs, physical symptoms, clinical anamnesis, medication, neurological examination, depressive episodes, etc.).

2.4 | Cognitive diagnoses

The operational definition adopted in the present study for the diagnosis of MCI was that published by the National Institue on Aging–Alzheimer's Association working group.[26] Specifically, we used the core clinical criteria for the diagnosis of MCI in which clinical judgment plays an essential role. The specific criteria used included the following: (1) concern regarding a change in cognition compared to the person's previous level, (2) impairment in one or more cognitive domains, (3) preservation of independence in functional abilities, and (4) not demented.

Clinical diagnoses were agreed between neurologists and neuropsychologists at consensus meetings. Each individual was independently diagnosed according to age; sex; estimated cognitive reserve from educational attainment, occupation, and socioeconomic status; level of functional dependence to perform activities of daily living; and cognitive scores. A magnetic resonance imaging (MRI_ scan of the brain was also performed to rule out the presence of macroscopic lesions or significant vascular damage that could interfere with cognitive performance. Cognitive test scores 1.5 standard deviations below the mean according to appropriate normative data were taken into account as an estimate of impairment. Nevertheless, rather than psychometrically invariable cut-off points, diagnoses were based on clinical impression. All cases of MCI were classified as single- or multiple-domain amnestic MCI because no pure non-amnestic MCI cases were identified in our sample.

2.5 | Statistical analyses

Analyses were conducted using R version 3.1.1,[27] specifically packages mice[28] for multiple imputation and msm[29] for multi-state modeling. We used two-sided significance tests for all analyses, with statistical significance set at $P < .05$.

We performed a preliminary analysis of data to determine their distribution and explore the nature and distribution of missing values. Nearly 10% of data were missed, but no profiles of missingness were identified (i.e., the missingness spread over many individuals, variables, and study visits). Therefore, we conducted a multiple imputation procedure under a fully conditional specification method to impute values as close as possible to ideal predicted observations. These imputed values were generated on the basis of existing variables through six distinct datasets, one for each visit. In this regard, it should be noted that those individuals who did not attend any visit were excluded from the corresponding datasets. The imputation procedure replaced each missing observation with valid statistical inferences of data.

2.5.1 | Multi-state Markov model

We examined the stage-sequential dynamics of AD using MSMM in continuous time. The Markov assumption claims that the rate of transition from one state to another depends only on the current state. Although this assumption seems to be restrictive, it is necessary to compute the likelihood for intermittently observed data like ours by introducing age into the model. Thus, the transition matrix was calculated between any two unrounded ages, thereby accommodating variation in the time between visits.[30] Therefore, we modeled an MSMM with a forward-backward algorithm to maximize likelihood estimation. Because we only observe states at a finite series of time, a time-homogeneous model was preferred instead of a discrete one.[31] Therefore, we specified a multi-state model with three states (NC, MCI, and dementia), as well as the initial values for the transition intensity matrix, which corresponded to ([0,0.2,0.05], [0.1,0,0.3], [0,0,0]). This matrix represents the theoretical probabilities of transition from one state to another independently of the real data.

We then ran several adjusted univariate MSMMs for each non-modifiable and modifiable factor considered in this study to examine the effect of each feature on the transition between cognitive states (for all factors, those levels related to a lower probability of developing MCI were adopted as reference categories). Next, we carried out a multivariate analysis that included only those factors that were statistically significant in the univariate studies. Our models assumed that individuals could move or recover from consecutive states, as well as move from any state to dementia, which was conceived as the absorbing state. All transitions were interval-censored because we could not know the exact time in which individuals had transitioned. MSMM provided the estimated transition probability matrix and its 95% confidence intervals to evaluate the probability of a change of MCI status over time conditional on previous status. The analysis of this matrix allowed us to better understand the temporal dynamics of the AD continuum over time in function of a set of non-modifiable and modifiable factors. The R code for MSMM is available in supporting information.

3 | RESULTS

The sample comprised 985 individuals whose demographic and clinical characteristics at baseline are shown in Table 1. The individuals were mostly in their seventies; predominantly female; with a relatively high educational attainment; low risk of dementia according to the proportion of *APOE* ε4 carriers; relatively active in social, physical, and cognitive dimensions; with a high prevalence of vascular risk factors; and with a moderate proportion of depressive symptoms.

Participants were followed up for a mean of 4.3 years (standard deviation [SD] 1.5; median 4.9; range 1.0–6.8). During this time, a total of 173 MCI and 36 dementia cases were identified. Based on the cognitive trajectories of these 36 dementia cases (marked memory impairment as a primary symptom during follow-up and MRIs excluding significant vascular damage), we assumed that there was a high probability of AD dementia type, but no biomarker was available to confirm this. Figure 1 shows the distribution of MCI cases in the sample through the follow-up. As can be appreciated, 19.7% of MCI diagnoses reverted to NC at some point during the follow-up, which represents approximately one in five cases. Of these reversals, 70.6% remained stable

TABLE 1 Baseline demographic and clinical characteristics of the sample

Baseline characteristic	Summary
Age (mean ± SD)	74.7 ± 3.9
Years of education (mean ± SD)	10.7 ± 5.8
Age groups	
70–79 years old (%)	87.2
80–90 years old (%)	12.8
Sex	
Female (%)	62.3
Male (%)	37.7
APOE	
Non-carrier ε4 (%)	81.2
Carrier ε4 (%)	18.8
Social engagement	
High (%)	61.5
Medium (%)	35.1
Low (%)	3.4
Physical exercise	
Active (%)	66.8
Sedentary (%)	33.2
Diet	
Mediterranean-based (%)	28.1
Balanced (%)	63.7
Unhealthy (%)	8.2
Cognitive training	
High (%)	11.4
Medium (%)	69.4
Low (%)	19.2
Hypertension	
No (%)	48.2
Yes (%)	51.8
Diabetes	
No (%)	89.0
Yes (%)	11.0
Hypercholesterolemia	
No (%)	45.6
Yes (%)	54.4
Depression	
No (%)	67.5
Yes (%)	32.5

Abbreviations: *APOE*, apolipoprotein E; SD, standard deviation

TABLE 2 Prevalence of cognitive status by visit and transition probability matrix for AD continuum

Status prevalence by visit…	NC	MCI	Dementia
Baseline	0.945	0.055	0.000
1-year follow-up	0.902	0.097	0.001
2-year follow-up	0.874	0.116	0.010
3-year follow-up	0.861	0.111	0.028
4-year follow-up	0.854	0.104	0.043
5-year follow-up	0.823	0.128	0.049
Probability of transitioning to…conditional on…	**NC**	**MCI**	**Dementia**
NC (95% CI)	0.96 (0.95-0.97)	0.03 (0.02-0.04)	0.01 (< 0.01–0.02)
MCI (95% CI)	0.11 (0.07-0.14)	0.77 (0.74-0.81)	0.12 (0.09–0.15)
Dementia	0.00	0.00	1.000

Abbreviations: CI, confidence interval; MCI, mild cognitive impairment; NC, normal cognition.

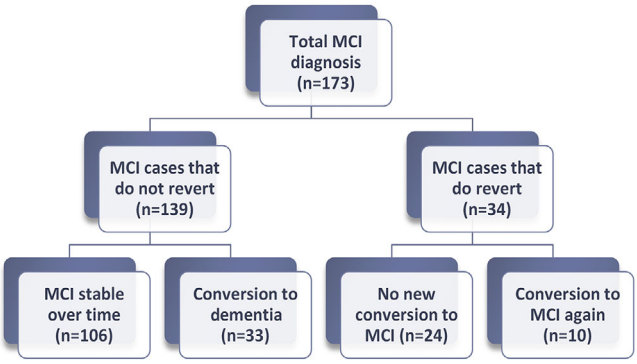

FIGURE 1 Distribution of MCI diagnosis and progression during the follow-up. MCI, mild cognitive impairment

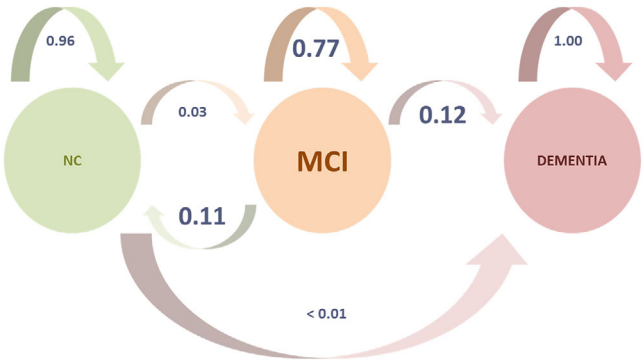

FIGURE 2 Flow diagram and probability of transitions between cognitive states, MCI, mild cognitive impairment; NC, normal cognition

within NC and did not revert to the MCI stage. On the other hand, of the 80.3% of cases that never reverted to a healthy cognitive status, 76.3% maintained stability in the diagnosis of MCI, while the remaining 23.7% progressed to dementia during follow-up.

We performed an MSMM to understand the temporal dynamics of stages along the AD continuum (-2 log-likelihood = 1,659.86; Aikake information criterion [AIC] = 1,667.86). Table 2 shows the transition probability matrix across cognitive statuses. These transition probabilities express the incidence of transitioning during the follow-up conditional on earlier classification in any specific cognitive status. NC individuals at baseline had a 96% probability of remaining as NC during the 5-year follow-up. In the event of transition, they were most likely to progress to the MCI status, but not to dementia. Those with MCI status at baseline had a 77% probability of remaining there at follow-up and the likelihood of transition to NC and dementia was similar (11% vs. 12%, respectively). Dementia was the absorbing state and no reversions to MCI were observed during the follow-up.

To determine the impact of different non-modifiable and modifiable factors on the forward and backward transitions from NC to MCI, we performed a series of univariate MSMMs (Table 3). Regarding the progression from NC to MCI, individuals over 80 years old, who had a lower ISES, were *APOE* ε4 carriers, and showed poor daily cognitive activity had an increased risk of developing cognitive impairment. On the other hand, analysis of the reversion from MCI to NC highlighted that beyond the age of 80 there were hardly any cases. Furthermore, those individuals with depressive symptoms were twice as likely to revert their cognitive state.

Finally, a multivariate analysis was carried out to include the variables that had been significant in the univariate models. Table 4 shows that a lower level of ISES, as well as being a carrier of the ε4 allele, both non-modifiable factors, increased the risk of developing MCI. Interestingly, a higher level of cognitive training and depressive symptoms, both potentially modifiable factors, were associated with reversion from MCI to NC. Of particular importance was the effect of depression, which tripled the probability of reversion.

4 | DISCUSSION

Our study aimed to examine the rate of annual spontaneous reversion from MCI to NC in a sample of longitudinally monitored individuals

TABLE 3 Hazard ratios (95% CI) for forward and backward transitions between NC and MCI by non-modifiable and modifiable factors: univariate models

Non-modifiable factors	Progression from NC to MCI	Reversion from MCI to NC
Age		
70–79 years old	[Reference]	[Reference]
80–90 years old	1.34 (1.13–2.02)	0.13 (0.09–0.18)
Sex		
Female	[Reference]	[Reference]
Male	1.03 (0.73–1.46)	1.00 (0.51–1.95)
ISES		
Q4	[Reference]	[Reference]
Q3	1.33 (0.80–2.21)	0.41 (0.13–1.31)
Q2	1.79 (1.07–3.01)	0.66 (0.26–1.69)
Q1	1.95 (1.18–3.21)	0.46 (0.18–1.19)
NSES		
Q4	[Reference]	[Reference]
Q3	1.19 (0.72–1.95)	0.67 (0.23–1.92)
Q2	1.66 (1.04–2.67)	1.18 (0.48–2.92)
Q1	1.21 (0.73–2.01)	0.42 (0.18–1.21)
APOE		
Non-carrier ε4	[Reference]	[Reference]
Carrier ε4	1.77 (1.21–2.59)	0.51 (0.21–1.22)
Modifiable factors	**Progression from NC to MCI**	**Reversion from MCI to NC**
Social engagement		
High	[Reference]	[Reference]
Medium	0.63 (0.28–1.42)	0.36 (0.10–1.34)
Low	0.49 (0.22–1.08)	0.52 (0.15–1.77)
Physical exercise		
Active	[Reference]	[Reference]
Sedentary	1.04 (0.72–1.49)	0.78 (0.39–1.53)
Diet		
Mediterranean-based	[Reference]	[Reference]
Balanced	0.99 (0.68–1.46)	1.23 (0.53–2.86)
Unhealthy	0.92 (0.45–1.86)	2.17 (0.69–6.89)
Cognitive training		
High	[Reference]	[Reference]
Medium	1.88 (0.89–3.99)	0.38 (0.09–1.67)
Low	2.95 (1.33–6.55)	0.57 (0.12–2.59)
Hypertension		
No	[Reference]	[Reference]
Yes	1.10 (0.78–1.55)	0.91 (0.47–1.76)
Diabetes		
No	[Reference]	[Reference]
Yes	1.36 (0.82–2.24)	0.86 (0.33–2.22)
Hypercholesterolemia		
No	[Reference]	[Reference]
Yes	1.07 (0.76–1.51)	1.34 (0.71–2.74)
Depression		
No	[Reference]	[Reference]
Yes	1.37 (0.97–1.95)	1.99 (1.03–3.84)

(Continues)

TABLE 3 (Continued)

Abbreviations: *APOE*, apolipoprotein E; CI, confidence interval; ISES, individual socioeconomic status; MC, mild cognitive impairment; NC, normal cognition; NSES, neighborhood socioeconomic status.

TABLE 4 Hazard ratios (95% CI) for forward and backward transitions between NC and MCI by non-modifiable and modifiable factors: Multivariate model

	Progression from NC to MCI	Reversion from MCI to NC
ISES		
Q4	[Reference]	[Reference]
Q3	1.10 (0.63–1.92)	0.13 (0.03–0.50)
Q2	1.45 (0.82–2.58)	0.37 (0.14–0.99)
Q1	1.37 (0.77–2.43)	0.16 (0.05–0.47)
APOE		
Non-carrier ε4	[Reference]	[Reference]
Carrier ε4	1.77 (1.18–2.66)	0.49 (0.20–1.20)
Cognitive training		
High	[Reference]	[Reference]
Medium	1.20 (0.43–3.33)	0.09 (0.02–0.43)
Low	1.74 (0.59–5.11)	0.17 (0.03–0.81)
Depression		
No	[Reference]	[Reference]
Yes	1.39 (0.95–2.02)	3.25 (1.55–6.80)

Abbreviations: *APOE*, apolipoprotein E; CI, confidence interval; MC, mild cognitive impairment; NC, normal cognition.

over 70 years of age and to identify the associations between a set of variables that have been found to be related to spontaneous reversion to NC. Overall, our results support the notion that several variables are involved in reversion from MCI to NC.

In our sample, approximately one in five cases of MCI (19.7%) reverted to NC, with 70.6% of these showing diagnostic stability. Of the 80.3% of cases that did not revert, 70.6% remained stable in their diagnosis of MCI while the rest (23.7%) progressed to dementia. Interestingly, our 5-year follow-up results also highlighted that the probability of progression from MCI to dementia was similar to the likelihood of reversion from MCI to NC. To the best of our knowledge, this is the first time that this finding has been obtained by simultaneously studying the transition between the different states of the AD continuum (NC, MCI, and dementia) using MSMM.

In relation to the progression from NC to MCI, individuals over 80 years of age who had a lower socioeconomic status, were *APOE* ε4 carriers, and had a deficient daily activity showed a higher risk of experiencing cognitive impairment, which is consistent with the findings of previous research.[15,16,20,32] Leaving aside genetic aspects and focusing on modifiable variables, these results can be explained by the higher levels of physical disability and poorer general health of lower socioeconomic levels,[33] as well as higher levels of distress and poorer general mental health,[34] which ultimately results in a greater acceleration of the aging process.[35] Similarly, higher socioeconomic status may improve motivation and conditions to engage in activities that enhance positive affect and general well-being, as well as facilitating access to a Mediterranean diet or better medical care, which may contribute to preventing MCI and AD.[36]

Regarding the reversion from MCI to NC, very few cases over the age of 80 years experienced this transition. As for modifiable variables, our results demonstrate that a higher ISES, cognitive training, and the presence of affective symptoms (depression) are associated with reversion, the latter tripling the probability. We observed a clear influence of negative affect on the outcome of cognitive examinations. Indeed, negative emotional states can exacerbate neurological symptoms, which can lead to incorrect attributions during the assessment.[37] When a diagnosis of MCI comorbid with depressive symptomatology is made, the results of the assessment are probably not representative of the individual's true cognitive potential, being well below his/her optimal performance. In this regard as time passes, if their affective symptomatology improves, the results in the neuropsychological tests would correspond to a normal level of cognitive functioning, thus explaining the reversion not by spontaneous cognitive improvement but by a false-positive diagnosis in the first assessment. Accordingly, clinical diagnosis should take into full consideration variables that relate to the emotional status of the patient. Furthermore, care should be taken regarding the diagnosis made in initial and follow-up examinations, and the conclusions of the evaluation should be underpinned by evidence of MCI in at least two memory tests.

In turn, and in line with previous research,[11] it seems that there is a greater likelihood of reversion in individuals with higher ISES and cognitive training. Those variables are fundamental for developing treatment programs aimed at both increasing the cases susceptible to reversion and avoiding those that could evolve from NC to MCI. The cognitive training considered in our study was not an intervention but it was the participants' reported engagement in standard cognitive activities such as reading, crosswords, card games, puzzles, etc. These tasks are low-cost, easy to implement, and can be performed without any professional supervision. These features have a clear implication from the perspective of prevention, as standard cognitive activity routinely recommended in clinical settings may have real therapeutic value. If this is the case, individual cognitive intervention guided by an expert therapist can be expected to lead to an exponential increase in the effect of cognitive stimulation. This hypothesis, which is beyond the scope of this study, should be addressed further in future studies.

Of note, unlike models dealing only with the progression from NC to MCI, the MSMM used here evaluated bidirectional transitions between the different states. This novel analysis approach could explain why variables that are traditionally associated with an increased risk of progression to MCI (i.e., ISES, cognitive stimulation, and depression) in our multivariate study are only associated with the probability of reversion from MCI to NC. The only variable that proved to be a predictor of transition to MCI was *APOE*, as would be expected due to its genetic association with AD. On the other hand, we found no effect of variables such as social network, physical exercise, diet, or vascular risk factors, which, according to the literature, could be associated with MCI. The lack of effect observed could be explained by the fact that these variables do not have a significant effect in a 5-year follow-up period such as that used in the present study. Rather these variables could have an effect in the longer term, beginning in adulthood or middle age, which would require a very long follow-up of 30 or 40 years.

Regarding the limitations of our study, it should be noted that, although the diagnosis of MCI is multifactorial and explained by reversible and non-reversible variables, the absence of information about some biomarkers makes it difficult to determine the etiology of each particular case of MCI and, consequently, the explanatory conclusions about the diagnostic modifications of reversion. Likewise, the 5-year follow-up might not be long enough to properly characterize the continuum of AD. Finally, practice effects may have manifested as improvements in cognitive test performance due to repeated evaluation.[38,39] However, our participants underwent the assessment protocol annually while practice effect studies repeat cognitive batteries after 1 week.[40] In any case, practice effects remain a complex phenomenom worthy of further research using very long-term follow-up studies.

In conclusion, our study makes two key contributions to the field. First, we found that only a few cases of subjects above the age of 80 reverted from MCI to NC. This outcome has a direct implication in clinical terms because intervention programs in this age group should aim to delay progression to dementia rather than reverse cognitive impairment. On the other hand, it is important to note that the rate of progression from MCI to dementia was very similar to that of reversion from MCI to NC—a result somewhat counter-intuitive to the pre-established idea of the disease continuum. Thus, as mentioned above, reversion from MCI to NC could be due to an initial misdiagnosis but could also be conceptualized as a phenomenon that needs to be considered in clinical settings. Given that the reversion or progression through the various stages of the disease may be due to various variables, some modifiable, it is important to consider intervention programs that are both preventive, to delay progression to dementia, and therapeutic, to identify those cases that could revert to NC. In general terms, based on the scientific data available, we propose that public health strategies and programs should not only focus on promoting individual measures, such as changes in lifestyle, but also have a global and more decisive impact on the reduction of social inequalities. To facilitate the access to both physical and psychological health resources could be an approach to promote healthy aging and to reduce the rates of cognitive impairment.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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