Transition from mild cognitive impairment to normal cognition: Determining predictors of reversion with Multi-State Markov Models

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ABSTRACT

Introduction: The theoretical framework of the AD continuum considers transition between stages in a unidirectional way. In the present work 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 community-dwelling Spanish individuals aged 70 years and over at baseline were followed-up for 5 years. During this time, 173 MCI and 36 dementia cases were identified. Multi-State Markov Models were performed to characterize transitions among 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 *APOE*) 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: Alzheimer´s disease, dementia, mild cognitive impairment, multi-state markov model, normal cognition, subjective cognitive decline.

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 in which a patient moves from the asymptomatic phase to an intermediate stage of mild cognitive impairment (MCI) and finally to dementia [2–4]. Under this conception, the progression through the stages always occurs in the same direction [5–9]. However, research has shown in recent years, a considerable percentage of individuals have been found to fluctuate over time between MCI and normal cognition (NC), resulting in a reversal of clinical status, known as the yo-yo effect [10].

Different 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.) 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 volumes in amygdala and hippocampi [16,17], with better vision and olfactory ability and with higher scores on the personality trait of openness to experience [17]. Some other modifiable variables such as smoking, obesity or hypertension are also associated with cognitive impairment and dementia [18].

Regarding neuropsychiatric symptoms, patients with fewer mixed anxious-depressive symptomatology 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. In other words, the reversion would be explained by a spurious first diagnosis. In relation to genetic factors, the absence of the *APOE* ε4 allele has been identified as a variable associated with reversion [15,16,20].

Regarding to variables that are related to a lower rate of reversion to NC, the following can be pointed out: presence of multidomain MCI or with 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 BNT) [15] as well as having been classified as amnestic MCI by at least two memory tests [13]. In some studies in which particularly low reversion rates have been found, it has been postulated that the data could be due to diagnostic errors arising from considering subjective memory complaints rather than objective scores obtained in neuropsychological batteries as an indicator of impairment [22].

In the present manuscript we analyze the data from an investigation framed in the Vallecas Project for the early detection of AD, an important longitudinal community-based investigation in older adults in Spain. The aims of our study are twofold. First, to examine the annual rate of reversion from MCI to NC in a sample of older adults who have been monitored longitudinally. Secondly, to detect the associations that may exist between a heterogeneous set of variables, some modifiable and others not, and reversion to NC. As this study focused 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 are able to accurately capture the transition of individuals in forward and backward directions 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 in continuous time.

METHODS

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 investigation for early detection of AD [24]. The participants were volunteers that 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 for six visits. The protocol included past medical history, neurological and neuropsychological examination, as well as biochemical and genetic blood test. The complete visit was usually carried out within four hours with convenient breaks. The neuropsychological battery included complete information about all cognitive domains that covered the whole spectrum of cognition.

Study Variables

a) Non-modifiable factors

The following non-modifiable variables were selected:

- Age: (1) 70-79 years old; and (2) 80-90 years old.
- Gender: (1) males; and (2) females.
- Individual socioeconomic status (ISES), operationally defined as a standardized composite score based on educational attainment, occupation and the highest level

of education reached by parents [25]: (1) quartile 1; (2) quartile 2; (3) quartile 3; and (4) quartile 4. Q1 represented the worst-off and Q4 the best-off.

- Neighborhood socioeconomic status (NSES), a standardized composite score based on average annual net income, % of resident with no formal qualifications, % of residents with higher education, % of residents with white-collar jobs, unemployment rate, and housing price (€/square meter) [25]: (1) quartile 1; (2) quartile 2; (3) quartile 3; and (4) quartile 4. Q1 represented the worst-off and Q4 the best-off.
- *APOE* genotype ascertained with total DNA isolated from peripheral blood following standard procedures and performed by Real-Time PCR [26]: (0) Non ε4 carriers; and (1) ε4 carriers.

b) *Modifiable factors*

The following variables were considered:

- Social engagement: (1) low (barely talks to friends or relatives); (2) medium (often talks to friends or relatives); and (3) high (talk to friends or relatives every day).
- Physical exercise: (0) sedentary (less than 60 minutes of aerobic physical activity a week); and (1) active (more than 60 minutes of aerobic physical activity a week).
- Diet: (0) unhealthy (predominance of the consumption of fats and carbohydrates); (1) balanced; (2) Mediterranean-based (predominance of the consumption of olive extra virgin oil, vegetables, fruits, legumes, and nuts).
- Cognitive training: (0) low (barely performs cognitive stimulation tasks); (1) medium (often performs cognitive stimulation tasks); and (2) high (performs cognitive stimulation tasks every day).
- Hypertension: (0) no; and (1) yes.

- Diabetes: (0) no; and (1) yes.
- Hypercholesterolemia: (0) no; and (1) yes.
- Depression: (0) no; and (1) yes.

c) *Clinical Diagnoses*

Cognitive status of every participant was diagnosed after each visit taking into account his/her age, gender, cognitive reserve, functional information, and cognitive scores. Cognitive diagnoses were agreed between neurologists and neuropsychologists at consensus meetings. MRIs were done to rule out the presence of macroscopic lesions or significant vascular damage which could interfere with cognitive performance. Criteria from the National Institute on Aging-Alzheimer´s Association (NIA-AA) were used to diagnose MCI and mild dementia [27]. All cognitively healthy subjects had a score = 0 in the global Clinical Dementia Rating (CDR) [28] while MCI and mild dementia cases scored 0.5 and 1 respectively.

Statistical analyses

Analyses were conducted using R version 3.1.1. [29], specifically packages *mice* [30] for multiple imputation and *msm* [31] for multi-state modeling. We used 2-sided significance tests for all analyses, with statistical significance set at p-value < 0.05.

We performed a preliminary analysis of data to find out 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). We therefore conducted a multiple imputation procedure under a fully conditional specification method in order to impute values as closer as possible to ideal predicted observations. Those imputed values were generated on the basis of existing variables through six different datasets, one for each study visit~~; a total of six imputation procedures were thereby conducted~~. In this sense it should be noted that those individuals who did not attend to any visit were excluded from the corresponding datasets. The imputation procedure replaced each missing observation with a set of plausible values representing uncertainty about the appropriate value to impute. The procedure was repeated five times and generated the corresponding five datasets whose coefficients varied from one set to another. The imputed datasets were analyzed using the usual procedure for complete data. Finally, the results of these analyses were combined to produce valid statistical inferences of data.

Multi-State Markov Model

We examined the stage-sequential dynamic 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 in the model. Thus, the transition matrix was calculated between any two unrounded ages and therefore accommodates variation in the time between participant visits [32]. We modeled therefore a MSMM with forward-backward algorithm to maximize likelihood estimation. Since we only observe states at a finite series of time and time interval between two consecutive visits in our longitudinal study varied across participants, a time-homogeneous model was preferred instead of a discrete one [33]. We then specified a multi-state model with three states (NC, MCI, and Dementia) as well as the initial values for the transition intensity matrix that corresponded to [(0,0.2,0.05), (0.1,0,0.3), (0,0,0)]. This matrix, which is really important because governs the whole model, represents the theoretical probabilities of transition from one state to another independently of the real data.

Then, we run several adjusted univariate MSMM for every non-modifiable and modifiable factors considered in this study in order to examine the effect of each single 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). After that, we carried out a multivariate analysis in which only those factors that were statistically significant in the univariate studies were included. Our models assumed that individuals could move or recover from consecutive states, as well as convert 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 membership over time conditional on previous status. The analysis of this matrix allowed us to better understand the temporal dynamics of AD continuum over time depending on a set of non-modifiable and modifiable factors. The R code for MSMM is available in Supplementary Material.

RESULTS

The sample was comprised of 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; high prevalence of vascular risk factors; and a moderate proportion of depressive symptoms.

INSERT TABLE 1

Participants were followed-up for a mean of 4.3 years (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 could assume that there is a high probability of AD dementia type, but there was no available biomarker confirmation. 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 any point of the follow-up, which represents approximately one in five cases. Of all these reversals, 70.6% remained stable within the NC and did not progress back to the MCI stage. On the other hand, of the 80.3% of cases that never reverted to cognitively healthy status, 76.3% maintained stability in the diagnosis of MCI, while the remaining 23.7% progressed to dementia during follow-up.

INSERT FIGURE 1

We performed a MSMM to understand the temporal dynamic of stages into the AD continuum (-2 log-likelihood=1,659.86; 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 membership in any specific the cognitive status. NC individuals at baseline had 96% of probabilities of remaining as NC during the five-year follow-up. In case of transition, they were most likely to transition to the MCI status, but not to dementia. Those with MCI status at baseline had 77% of probabilities of remaining there at follow-up and their most likely transition was similar between NC and dementia (11% vs. 12%, respectively). Dementia was the absorbing state and no reversions to MCI were observed during the follow-up.

INSERT TABLE 2

Then, to determine the impact of different non-modifiable and modifiable factors on the forwards and backwards transitions from NC to MCI, we performed a series of univariate MSMM (Table 3). The results showed that, 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 showed an increased risk of developing cognitive impairment. On the other hand, the analysis of the reversion from MCI to NC highlighted that beyond the age of 80 there were hardly any cases of reversion to the state of NC;

furthermore, those individuals with depressive symptoms were twice as likely to revert their cognitive state.

INSERT TABLE 3

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 for the development of 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.

INSERT TABLE 4

DISCUSSION

Our study aimed to examine the rate of annual spontaneous reversion from MCI to NC in a sample of longitudinally monitored individuals over 70 years of age and to identify the associations that may exist between a set of variables that have been found to be related to spontaneous reversion to NC. Overall, our results support the idea that there are some variables involved in a 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 the cases that did not revert, 70.6% remained stable in their diagnosis of MCI while the rest (23.7%) progressed to dementia. Interestingly, our five-year follow-up results also highlight 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, it is observed that individuals older than 80, with a lower individual socioeconomic status, *APOE* ε4 carriers and with a deficient daily activity, show a higher risk of experiencing cognitive impairment, which is consistent with previous research [15,16,20,34]. Leaving aside genetic aspects, and focusing on modifiable variables, these results can be explained by the fact that poorer socioeconomic levels have higher levels of physical disability and poorer general health [35], as well as higher levels of distress and poorer general mental health [36], which ultimately results in a greater acceleration of the aging process [37]. Similarly, higher socioeconomic status may improve motivation and conditions to engage in activities that enhance positive affect and general well-being, as well as facilitate access to a Mediterranean diet or better medical care, which may act as a preventive factor for MCI and AD [38].

Regarding to the reversion from MCI to NC, we observed that very few cases over the age of 80 reversed. As for modifiable variables, our results show that a higher ISES, cognitive training and the presence of affective symptoms (depression) are associated with reversion, the latter tripling the probability. There is a clear influence of negative affect on the outcome of cognitive examinations, because negative emotional states can chronic and increase symptoms of a neurological nature, which can lead to incorrect attributions in the assessment process [39]. When a diagnosis of MCI comorbid with depressive symptomatology is made, the results of the assessment are probably not representative of the individual's real cognitive potential, being well below his or her optimal performance. This would explain why, as the time passes, if their affective symptomatology improves, the results in the neuropsychological tests would correspond to a normal level of cognitive functioning, explaining the reversion process not by a spontaneous cognitive improvement but by a false positive diagnosis in a first assessment. From this fact derives the need at the applied level to take into consideration in detail the emotional variables in the clinical understanding of the individual and to increase caution in the diagnostic judgement in the different initial and follow-up examinations, focusing the conclusions of the evaluation on the solid evidence of MCI in at least two memory tests and, to a lesser extent, in the SCD.

In turn, and in line with previous research [11], it seems that there is a greater likelihood of reversion in those individuals with higher ISES and cognitive training, which is a fundamental variable in the aim of developing treatment programs aimed at both increasing the cases susceptible to reversion and avoiding those that could evolve from NC to MCI. It is important to note that, unlike what happens when classical models are used to study only the progression from NC to MCI, MSMM used here evaluate bidirectional transitions between the different states. This 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 do so only with the probability of reversion from MCI to NC. The unique variable that proved to be a predictor of conversion to MCI was, as would be expected due to its genetic association with AD, *APOE*.

As for the limitations of our study, it should be noted that, although the diagnosis of MCI is multifactorial, being 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 five-year follow-up time might not be long enough time to study the continuum of AD in perspective. Finally, it is possible that there were practice effects as improvements in cognitive test performance due to repeated evaluation [40-41]. However, our participants underwent the assessment protocol annually while practice effects studies repeat cognitive batteries after one week

[42]. In any case, practice effects remain a complex construct, worthy of continued investigation in the future with very long-term follow-up studies.

In conclusion, two are the most important contributions of our study. First, it seems that few cases reverted from MCI to NC above the age of 80 years. This outcome has a direct implication in clinical terms since intervention programs in this age group should aim to delay the progression to a state of dementia rather than trying to reverse the cognitive impairment. On the other hand, based on our results, it is important to note that the rate of progression from MCI to dementia is very similar to that of reversion from MCI to NC, which is somehow counter-intuitive to the pre-established idea of the disease continuum. Thus, as it has been above mentioned, reversion from MCI to NC could be due to an initial misdiagnosis but may also be conceptualized as a phenomenon that needs to be taken into account in clinical settings. Given that the reversion or progression through the various stages of the disease may be due to different variables, some modifiable, it is important to consider intervention programs both of preventive nature, with the aim of delaying the progression to a stage of dementia, and therapeutic to facilitate those cases that could revert to NC. In general terms, based on the available scientific data, public health strategies and programs should not only focus on promoting individual measures, such as lifestyle modification, but also have a global and more decisive impact on the reduction of social inequalities, increasing access to both physical and psychological health resources as a way of promoting healthy aging and reducing rates of cognitive impairment, which would ultimately result in more contained and efficient health spending.

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CONFLICTS OF INTEREST

The authors have no conflict of interest to report.

REFERENCES

[1] Niu H, Álvarez-Álvarez I, Guillén-Grima F, Aguinaga-Ontoso I. Prevalencia e incidencia de la enfermedad de Alzheimer en Europa: metaanálisis. Neurologia 2017;32:523–32. https://doi.org/10.1016/j.nrl.2016.02.016.

[2] Jack CR, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, et al. Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. Lancet Neurol 2013;12:207–16. https://doi.org/10.1016/S1474-4422(12)70291-0.

[3] Jack CR, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010;9:119–28. https://doi.org/10.1016/S1474-4422(09)70299-6.

[4] Villemagne VL, Burnham S, Bourgeat P, Brown B, Ellis KA, Salvado O, et al. Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: A prospective cohort study. Lancet Neurol 2013;12:357–67. https://doi.org/10.1016/S1474-4422(13)70044-9.

[5] Bruscoli M, Lovestone S. Is MCI really just early dementia? A systematic review of conversion studies. Int Psychogeriatrics 2004;16:129–40. https://doi.org/10.1017/S1041610204000092.

[6] Buratti L, Balestrini S, Altamura C, Viticchi G, Falsetti L, Luzzi S, et al. Markers for the Risk of Progression from Mild Cognitive Impairment to Alzheimer's Disease. J Alzheimer's Dis 2015;45:883–90. https://doi.org/10.3233/JAD-143135.

[7] Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303–8.

[8] Robertson K, Larson EB, Crane PK, Cholerton B, Craft S, McCormick WC, et al.

Using varying diagnostic criteria to examine mild cognitive impairment prevalence and predict dementia incidence in a community-based sample. J Alzheimer's Dis 2019;68:1439–51. https://doi.org/10.3233/JAD-180746.

[9] Wong CG, Thomas KR, Edmonds EC, Weigand AJ, Bangen KJ, Eppig JS, et al. Neuropsychological criteria for mild cognitive impairment in the framingham heart study's old-old. Dement Geriatr Cogn Disord 2019;46:253–65. https://doi.org/10.1159/000493541.

[10] Ellendt S, Voβ B, Kohn N, Wagels L, Goerlich KS, Drexler E, et al. Predicting Stability of Mild Cognitive Impairment (MCI): Findings of a Community Based Sample. Curr Alzheimer Res 2016;14:608–19. https://doi.org/10.2174/1567205014666161213120807.

[11] Shimada H, Doi T, Lee S, Makizako H. Reversible predictors of reversion from mild cognitive impairment to normal cognition: A 4-year longitudinal study. Alzheimer's Res Ther 2019;11. https://doi.org/10.1186/s13195-019-0480-5.

[12] Overton M, Pihlsgård M, Elmståhl S. Diagnostic Stability of Mild Cognitive Impairment, and Predictors of Reversion to Normal Cognitive Functioning. Dement Geriatr Cogn Disord 2020;48:317–29. https://doi.org/10.1159/000506255.

[13] Malek-Ahmadi M. Reversion from Mild Cognitive Impairment to Normal Cognition: A Meta-Analysis. Alzheimer Dis Assoc Disord 2016;30:324–30. https://doi.org/10.1097/WAD.0000000000000145.

[14] Olazarán J, Torrero P, Cruz I, Aparicio E, Sanz A, Mula N, et al. Mild cognitive impairment and dementia in primary care: The value of medical history. Fam Pract 2011;28:385–92. https://doi.org/10.1093/fampra/cmr005.

[15] Pandya SY, Lacritz LH, Weiner MF, Deschner M, Woon FL. Predictors of Reversion from Mild Cognitive Impairment to Normal Cognition. Dement Geriatr Cogn Disord 2017;43:204–14. https://doi.org/10.1159/000456070.

[16] Pandya SY, Clem MA, Silva LM, Woon FL. Does mild cognitive impairment always lead to dementia? A review. J Neurol Sci 2016;369:57–62. https://doi.org/10.1016/j.jns.2016.07.055.

[17] Sachdev PS, Lipnicki DM, Crawford J, Reppermund S, Kochan NA, Trollor JN, et al. Factors Predicting Reversion from Mild Cognitive Impairment to Normal Cognitive Functioning: A Population-Based Study. PLoS One 2013;8. https://doi.org/10.1371/journal.pone.0059649.

[18] Katayama O, Lee S, Bae S, Makino K, Shinkai Y, Chiba I, et al. Modifiable Risk Factor Possession Patterns of Dementia in Elderly with MCI: A 4-Year Repeated Measures Study. J Clin Med 2020;9:1076. https://doi.org/10.3390/jcm9041076.

[19] Sugarman MA, Alosco ML, Tripodis Y, Steinberg EG, Stern RA. Neuropsychiatric Symptoms and the Diagnostic Stability of Mild Cognitive Impairment. J Alzheimers Dis 2018;62:1841–55. https://doi.org/10.3233/JAD-170527.

[20] Roberts RO, Knopman DS, Mielke MM, Cha RH, Pankratz VS, Christianson TJH, et al. Higher risk of progression to dementia in mild cognitive impairment cases who revert to normal. Neurology 2014;82:317–25. https://doi.org/10.1212/WNL.0000000000000055.

[21] Shimada H, Makizako H, Doi T, Lee SC, Lee S. Conversion and Reversion Rates in Japanese Older People With Mild Cognitive Impairment. J Am Med Dir Assoc 2017;18:808.e1-808.e6. https://doi.org/10.1016/j.jamda.2017.05.017.

[22] Thomas KR, Eppig JS, Weigand AJ, Edmonds EC, Wong CG, Jak AJ, et al. Artificially low mild cognitive impairment to normal reversion rate in the Alzheimer's Disease Neuroimaging Initiative. Alzheimer's Dement 2019;15:561–9. https://doi.org/10.1016/j.jalz.2018.10.008.

[23] Jackson CH, Sharples LD, Thompson SG, Duffy SW, Couto E. Multistate Markov

Models for Disease Progression with Classification Error. J R Stat Soc Ser D (The Stat 2003;52:193–209. https://doi.org/10.2307/4128245.

[24] Olazarán J, Valentí M, Belén Frades, Zea-Sevilla MA, Ávila-Villanueva M, Fernández-Blázquez MÁ, et al. The Vallecas Project: A cohort to identify early markers and mechanisms of Alzheimer's disease. Front Aging Neurosci 2015;7. https://doi.org/10.3389/fnagi.2015.00181.

[25] Fernández-Blázquez MA, Noriega-Ruiz B, Ávila-Villanueva M, Valentí-Soler M, Frades-Payo B, Del Ser T, et al. Impact of individual and neighborhood dimensions of socioeconomic status on the prevalence of mild cognitive impairment over seven-year follow-up. Aging Ment Heal 2020. https://doi.org/10.1080/13607863.2020.1725803.

[26] Calero O, Hortigüela R, Bullido MJ, Calero M. Apolipoprotein E genotyping method by Real Time PCR, a fast and cost-effective alternative to the TaqMan® and FRET assays. J Neurosci Methods 2009;183:238–40. https://doi.org/10.1016/j.jneumeth.2009.06.033.

[27] Albert MS, Dekosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging and Alzheimer's Association workgroup. Alzheimer's Dement J Alzheimer's Assoc 2011;7:270–9. https://doi.org/S1552-5260(11)00104-X [pii]\n10.1016/j.jalz.2011.03.008.

[28] Hughes CP, Berg L, Danziger WL. A new clinical scale for the staging of dementia. Br J Psychiatry 1982;140:566–72. https://doi.org/10.1192/bjp.140.6.566.

[29] R Development Core Team. R: A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2012.

[30] van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate imputation by chained equations in R. J Stat Softw 2011;45:1–67. https://doi.org/10.18637/jss.v045.i03.

[31] Jackson CH. Multi-state models for panel data: The msm package for R. J Stat Softw 2011;38:1–28. https://doi.org/10.18637/jss.v038.i08.

[32] Jack CR, Therneau TM, Wiste HJ, Weigand SD, Knopman DS, Lowe VJ, et al. Transition rates between amyloid and neurodegeneration biomarker states and to dementia: A population-based, longitudinal cohort study. Lancet Neurol 2016;15:56–64. https://doi.org/10.1016/S1474-4422(15)00323-3.

[33] Wan L, Lou W, Abner E, Kryscio RJ. A comparison of time-homogeneous Markov chain and Markov process multi-state models. Commun Stat Case Stud Data Anal Appl 2016;2:92–100. https://doi.org/10.1080/23737484.2017.1361366.

[34] Kim GH, Lee HA, Park H, Lee DY, Jo I, Choi SH, et al. Effect of Individual and District-level Socioeconomic Disparities on Cognitive Decline in Community-dwelling Elderly in Seoul. J Korean Med Sci 2017;32:1508. https://doi.org/10.3346/jkms.2017.32.9.1508.

[35] Veenstra G. Social capital, SES and health: an individual-level analysis. Soc Sci Med 2000;50:619–29.

[36] Präg P, Mills MC, Wittek R. Subjective socioeconomic status and health in cross-national comparison. Soc Sci Med 2016;149:84–92. https://doi.org/10.1016/j.socscimed.2015.11.044.

[37] Kondo N. Socioeconomic disparities and health: impacts and pathways. J Epidemiol 2012;22:2–6.

[38] Sattler C, Toro P, Schönknecht P, Schröder J. Cognitive activity, education and socioeconomic status as preventive factors for mild cognitive impairment and Alzheimer's disease. Psychiatry Res 2012;196:90–5. https://doi.org/10.1016/j.psychres.2011.11.012.

[39] Greiffenstein MF, Baker WJ. Comparison of premorbid and postinjury MMPI-2 profiles in late postconcussion claimants. Clin Neuropsychol 2001;15:162–70.

https://doi.org/10.1076/clin.15.2.162.1895.

[40] Calamia M, Markon K, Tranel D. Scoring higher the second time around: meta-analyses of practice effects in neuropsychological assessment. Clin Neuropsychol. 2012;26(4):543-70. https://doi.org/10.1080/13854046.2012.680913.

[41] Duff K, Hammers DB. Practice effects in mild cognitive impairment: A validation of Calamia et al. (2012) [published online ahead of print, 2020 Jun 27]. Clin Neuropsychol. 2020;1-13. https://doi.org/10.1080/13854046.2020.1781933

[42] Duff K, Callister C, Dennett K, Tometich D. Practice effects: a unique cognitive variable. Clin Neuropsychol. 2012;26(7):1117-1127. https://doi.org/10.1080/13854046.2012.722685

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
Gender	
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

Table 2. Status 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
One-year follow-up	0.902	0.097	0.001
Two-year follow-up	0.874	0.116	0.010
Three-year follow-up	0.861	0.111	0.028
Four-year follow-up	0.854	0.104	0.043
Five-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

CI: Confidence interval; MCI: Mild Cognitive Impairment; NC: Normal cognition.

Table 3. Hazard Ratios (95% CI) for forwards and backwards 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)
Gender		
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)

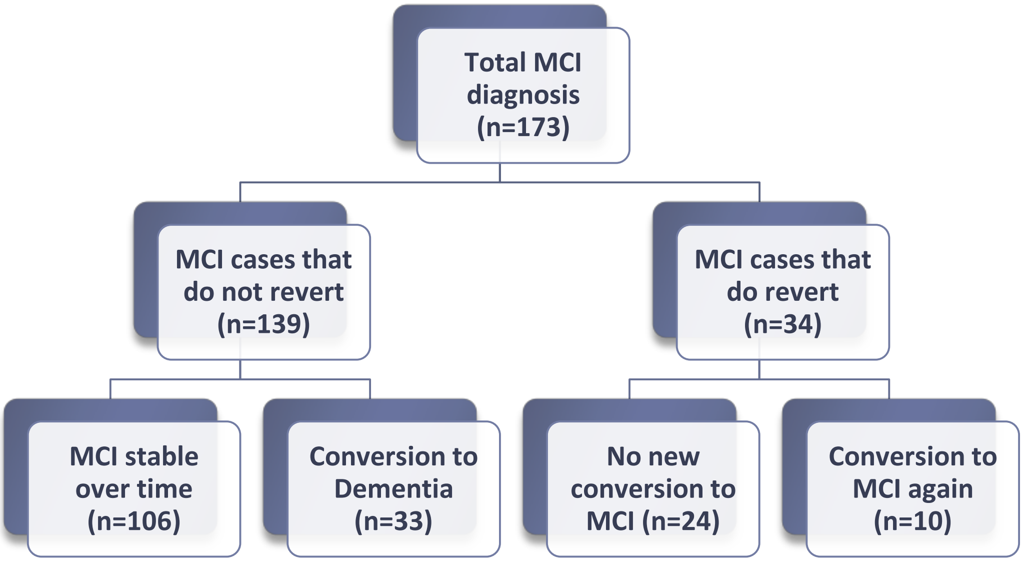
ISES: Individual socioeconomic status; MCI: Mild cognitive impairment; NC: Normal cognition; NSES: Neighborhood socioeconomic status.

Table 4. Hazard Ratios (95% CI) for forwards and backwards 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)

ISES: Individual socioeconomic status; MCI: Mild cognitive impairment; NC: Normal cognition.

Figure 1. Distribution of MCI diagnosis and progression during the follow-up.



MCI: Mild cognitive impairment; NC: Normal cognition.

Figure 2. Flow diagram and probability of transitions among cognitive states.