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Estimating Bidirectional Transitions and Identifying Predictors of Mild Cognitive Impairment

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Abstract

Background and Objectives

Various resources exist for treating mild cognitive impairment (MCI) or dementia separately as terminal events or for focusing solely on a 1-way path from MCI to dementia without taking into account heterogeneous transitions. Little is known about the trajectory of reversion from MCI to normal cognition (NC) or near-NC and patterns of postreversion, which refers to cognitive trajectories of patients who have reversed from MCI to NC. Our objectives were to (1) quantitatively predict bidirectional transitions of MCI (reversion and progression), (2) explore patterns of future cognitive trajectories for postreversion, and (3) estimate the effects of demographic characteristics, *APOE*, cognition, daily activity ability, depression, and neuropsychiatric symptoms on transition probabilities.

Methods

We constructed a retrospective cohort by reviewing patients with an MCI diagnosis at study entry and at least 2 follow-up visits between June 2005 and February 2021. Defining NC or near-NC and MCI as transient states and dementia as an absorbing state, we used continuous-time multistate Markov models to estimate instantaneous transition intensity between states, transition probabilities from one state to another at any given time during follow-up, and hazard ratios of reversion-related variables.

Results

Among 24,220 observations from 6,651 participants, there were 2,729 transitions to dementia and 1,785 reversions. As for postreversion, there were 630 and 73 transitions of progression to MCI and dementia, respectively. The transition intensity of progression to MCI for postreversion was 0.317 (2.48-fold greater than that for MCI progression or reversion). For postreversion participants, the probability of progressing to dementia increased by 2% yearly. Participants who progressed to MCI were likely to reverse again (probability of 40% over 15 years). Age, independence level, *APOE*, cognition, daily activity ability, depression, and neuropsychiatric symptoms were significant predictors of bidirectional transitions.

Discussion

The nature of bidirectional transitions cannot be ignored in multidimensional MCI research. We found that postreversion participants remained at an increased risk of progression to MCI or dementia over the longer term and experienced recurrent reversions. Our findings may serve as a valuable reference for future research and enable health care professionals to better develop proactive management plans and targeted interventions.

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Glossary

ADC = Alzheimer's Disease Center; **aMCI** = amnestic MCI; **BMI** = body mass index; **CDR** = Clinical Dementia Rating; **FAQ** = Functional Activities Questionnaire; **GDS-15** = 15-item Geriatric Depression Scale; **HR** = hazard ratio; **IQR** = interquartile range; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **NACC** = National Alzheimer's Coordinating Center; **naMCI** = nonamnestic MCI; **NC** = normal cognition; **NPI-Q** = Neuropsychiatric Inventory Questionnaire.

With the rapid aging of the world population, dementia constitutes a substantial psychological and social burden. The natural evolution of dementia is a dynamic and chronic process underscored by different states throughout its evolutionary trajectory. Mild cognitive impairment (MCI), generally considered an intermediate state between normal cognition (NC) and dementia, is of considerable public health interest due to its transient nature and heterogeneous transitions that may be persistent, worsen, or even reverse back to NC.[1]

Various resources exist for treating MCI or dementia separately as terminal events or for focusing solely on a 1-way path from MCI to dementia without taking into account heterogeneous transitions.[2,3] Available longitudinal studies have reported highly heterogeneous estimates of reversion from MCI to NC in older adults, ranging from 2.1% to 53%.[4,5] Treating MCI exclusively as the prelude to unavoidable future dementia may result in an unbalanced assessment of MCI.[6] A set of potential variables associated with reversion from MCI to NC have been explored,[7] and the effects of education and other indicators of cognitive reserve on the reversion have been estimated.[8] However, an outstanding question is whether MCI should be considered a benign entity with a high chance of reversion to NC, a malignant entity with a high risk of progression to dementia, or both.[9] The majority of studies provided simple frequencies, and only a few studies were specifically designed to investigate reversion. There is a paucity of literature on the evolutionary trajectory of reversion, let alone patterns of postreversion.[10] In this context, postreversion refers to cognitive trajectories of patients who have reversed from MCI to NC. Further long-term outcomes for postreversion remain largely unaddressed. Indeed, it remains unclear how soon the reversion or progression occurs following an MCI diagnosis and whether patients who have reversed to NC can maintain this state over the long term or show progress to dementia at a faster rate if followed up for a sufficient period. Investigation of these issues ideally requires qualified assessments with larger sample sizes and longer follow-ups. In this regard, further accurate measurement of the evolutionary trajectory from clinical studies and public health investigations is critical for early detection and preventive interventions for dementia.

The research questions of this study are as follows: (1) How can the bidirectional transitions of MCI (reversion and progression) be quantitatively predicted? (2) What patterns of future cognitive trajectories underscore postreversion? and (3) Which of the selected covariates affect transition probabilities in the natural history of MCI? To address these questions, we used a multistate Markov model to estimate the fate of MCI and explore the evolution of postreversion.

Methods

Samples

The data analyzed in this study were part of the National Alzheimer's Coordinating Center Uniform Data Set (NACC) (naccdata.org). All Alzheimer's Disease Centers (ADCs) enroll and follow patients annually with a standardized protocol and provide pooled data for research through the NACC.[11] We constructed a retrospective cohort by reviewing patients with an MCI diagnosis at study entry between June 2005 and February 2021. Patients were included if they were (1) diagnosed with MCI at baseline and (2) observed for at least 2 visits during the study period until they received a diagnosis of dementia or until February 2021, whichever came first. We excluded observations after the dementia diagnosis to render the data compatible with subsequent multistate Markov models.[12]

Standard Protocol Approvals, Registrations, and Patient Consents

Written informed consent was obtained from all participants and their study partners. The study was approved by the Institutional Review Board of the University of Washington.

Measures

Cognitive States

Cognitive status was reassessed by multidisciplinary protocols and consensus groups approximately yearly during subsequent follow-ups, based on the neuropsychological performance, neurologic examinations, and medical records, and was categorized as any of the following states: NC, impaired but not MCI, MCI, or dementia. All ADCs followed the guidelines set forth by an expert panel, consisting of physicians and neuropsychologists for the diagnosis of MCI.[13] Specifically, the standard criteria for AD and other types of dementia were used to determine whether a participant had NC or dementia and, if not, to determine whether a participant met the MCI core clinical criteria. Participants who met the criteria were diagnosed with MCI, whereas those who did not receive the diagnosis impaired but not MCI. Based on clinical judgment and cognitive test scores, cognitive status at

study entry was further stratified into amnestic MCI (aMCI) and nonamnestic MCI (naMCI) for subsequent comparative analyses, with the former referring to memory impairments in one or more domains and the latter referring to impairments in language, attention, executive function, or visuospatial ability. We were unable to reliably distinguish between NC and impaired but not MCI due to the inconsistent use of the latter term at ADCs. Some ADCs frequently use the term, whereas others do not use it at all.[11] The raincloud plot in eFigure 1 (supplementary material, http://links.lww.com/WNL/C425) shows the clinical assessments of these 4 cognitive states, including scores for the Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR), Functional Activities Questionnaire (FAQ), 15-item Geriatric Depression Scale (GDS), and Neuropsychiatric Inventory Questionnaire (NPI-Q). Subpanels (A-C) depict participants with baseline diagnosis of MCI, aMCI, and naMCI, respectively. The figure shows that the cognitive patterns we observed for NC and impaired but not MCI were similar. Accordingly, these 2 cognitive states were pooled into a single <MCI state representing no impairment or any impairment falling below the MCI criteria threshold applied in this study.[14] Also, we performed sensitivity analyses to assess the robustness of the pooling, adding 2 scenarios in which impaired but not MCI was either treated as an independent transient state or excluded.

Predictors

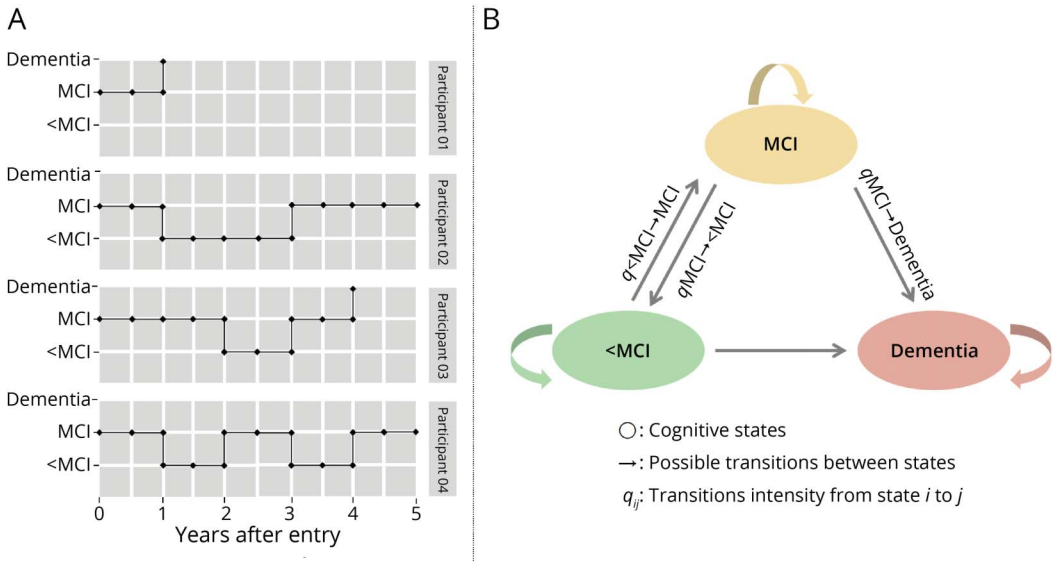
Demographic characteristics included sex (male/female), age (years), educational attainment (years), marital status (married/single), living situation (living alone/living with others), independence level (able to live independently/requiring some assistance with complex activities/requiring some assistance with basic activities/completely dependent), handedness (left-handed/right-handed/ambidextrous), body mass index (BMI), corrected vision (normal/abnormal), and corrected hearing (normal/abnormal). Genetic information included *APOE* ε4 allele status (presence/absence of at least 1 epsilon 4 allele). Cognitive function was assessed using the MMSE and CDR. Ability to perform daily activities was measured using the FAQ. The GDS and NPI-Q served as global measures of depression and neuropsychiatric symptoms, respectively.

Statistical Analysis

A multistate model is a continuous-time stochastic process model in which participants may experience finite clinical states during follow-up. The model provides a comprehensive view of the disease process and facilitates potential factors analyses and long-term predictions.[15] A time-homogeneous Markov chain, assuming a Markov process with constant transition intensity, is time independent but dependent on subject-related variables.[16] The model allows the transition probability to vary over time while the rate remains constant.

In this study, the multistate Markov model considered the transient and bidirectional nature of a participant's cognitive status who underwent cognitive measurements at each visit. Figure 1A presents the transitions of typical samples in this study, illustrating different patterns of disease reversion or

Figure 1 Possible Transition Paths for the Selected Participants (A) and Transitions Numbers Between Transient States (<MCI, MCI) and Absorbing State (Dementia) (B)



(A) Possible transition paths for 3 selected participants. We truncated observations after the diagnosis of dementia. The filled circles indicate actual observations. The solid line is a possible transition path during the follow-up period. The possible transition paths were randomly selected on the basis of the observed states. (B) Schema of the Markov model specified in this study. The arrows in the figure specify possible transitions between these states. Each transition parameter q indicates the transition intensity; that is, q_{ij} is interpreted as an instantaneous risk of transition from state i to j. MCI = mild cognitive impairment; <MCI = no impairment or any impairment falling below the MCI criteria threshold; MMSE = Mini-Mental State Examination.

progression among participants. We viewed cognitive status (including < MCI, MCI, and dementia) as state space and treated time on study (time of participant visits) as the time scale for transitions of the Markov chain from one state to another. Figure 1B specifies the state structure, with circles representing cognitive states and arrows indicating possible transitions between states. <MCI and MCI were defined as transient states and dementia as the absorbing state. Transition intensity q_{ij} reflected the overall speed of transition, that is, an instantaneous risk of transition from state i to j. For example, $q_{MCI \rightarrow Dementia}$ can be interpreted as the instantaneous hazard of transition from MCI to dementia. Based on the underlying 3-state model, the corresponding transition intensity matrix Q was expressed as follows:

$$Q = \begin{pmatrix} -q_{<MCI \rightarrow MCI} & q_{<MCI \rightarrow MCI} & 0 \\ q_{MCI \rightarrow <MCI} & -\left(q_{MCI \rightarrow <MCI} + q_{MCI \rightarrow Dementia}\right) & q_{MCI \rightarrow Dementia} \\ 0 & 0 & 0 \end{pmatrix}$$

Here, transition probability describes the likelihood of a certain transition between possible states at a given time. Additional subject-related variables can be incorporated by introducing a regression component into intensity matrix Q, such as demographic characteristics and functional assessments. Mean sojourn time refers to the average dwelling duration of remaining in a transient state before transitioning to the next state. We ran univariate Markov models for each potential factor considered in this study. Multiple multivariate Markov models were constructed, which only incorporated variables that were statistically significant in the univariate analysis ($\alpha = 0.10$). We controlled for potential confounders by setting them up in 3 different ways, and details for each model were described as the −2log likelihood ratio, Akaike information criterion, hazard ratios (HRs), and corresponding 95% CIs. Model 1 was constructed through the first multivariate analysis, which included only demographic characteristics and took no account of genetic information and clinical assessments. The second analysis was limited to demographic characteristics and *APOE* genotype but did not consider clinical assessments and was used to construct model 2. Third, we added clinical assessments to demographic characteristics and *APOE* genotype, which yielded model 3. We also included the same variables that were entered into model 3 in our sensitivity analysis to assess the robustness of the covariate effects. In addition, we simulated changes in prevalence across states and evaluated the model based on comparison of observations and simulated prevalence.

Descriptive statistics were used to describe the demographic characteristics and clinical assessments as medians, interquartile ranges (IQRs), and frequency proportions. The msm package[17] was used to formulate the multistate Markov models, and the mice package[18] was used for multiple imputation procedures for missing data on the basis of existing variables, using a fully conditional specification method to replace each missing observation in R. The R code used for data analysis is available on request from author Y.Q.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

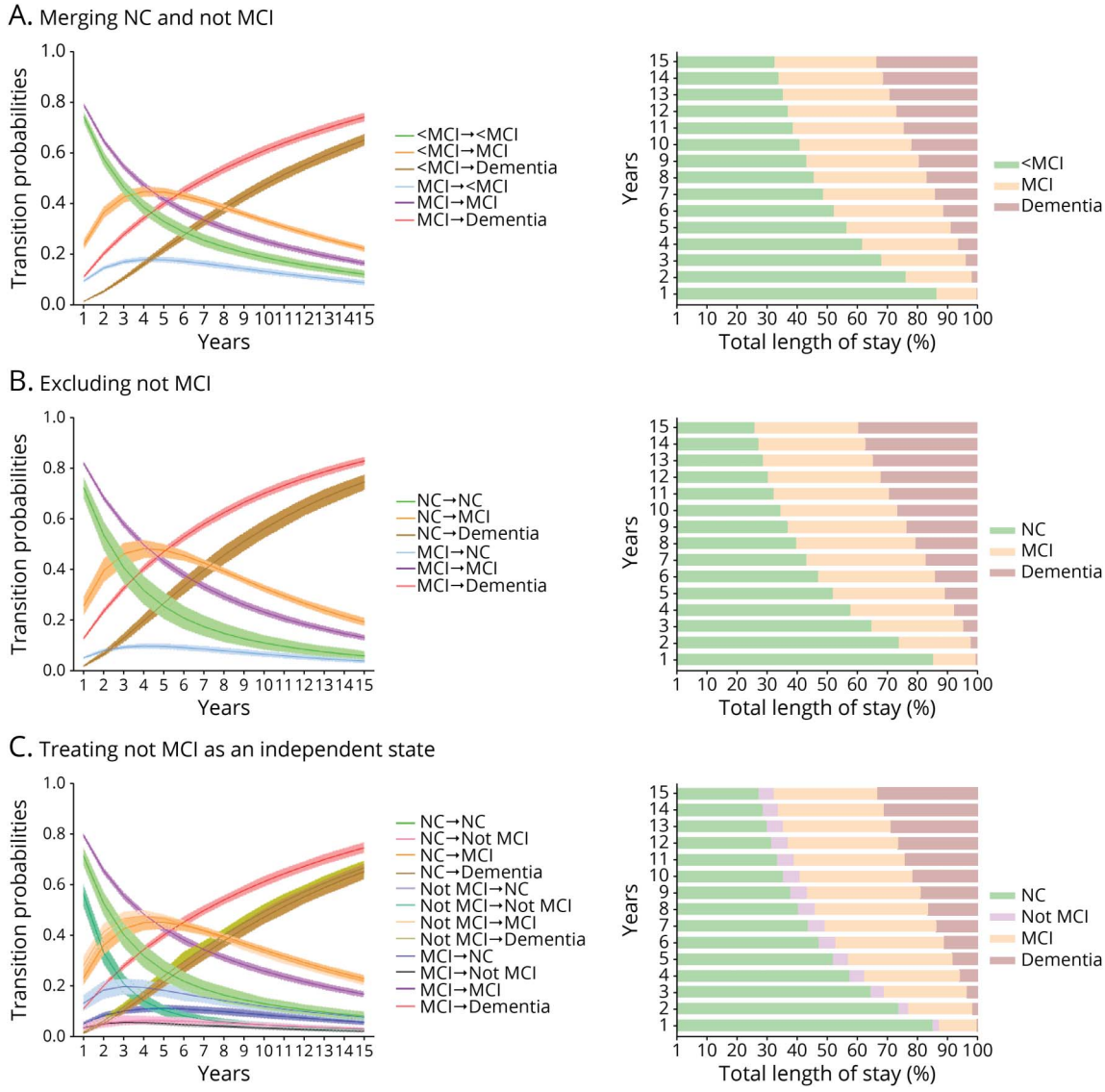
Results

Bidirectional Transitions of MCI

Data in this section included 24,220 observations from 6,651 participants with an MCI diagnosis at study entry. A total of 3,192 observations of NC and 1,190 observations of impaired but not MCI were merged into <MCI. Over a median of 4 years (IQR 2, 6 years) of follow-up, the total follow-up time ranged from 0.364 to 14.784 years, with up to 15 follow-up visits. During the nearly 15 years of follow-up, we identified 2,729 (19.13%) transitions from MCI to dementia, 1,785 (12.51%) transitions from MCI to <MCI, and 9,755 (68.36%) remaining in the MCI state. As for postreversion, we observed 630 (19.09%) transitions from <MCI to MCI, 73 (2.21%) transitions from <MCI to dementia, and 2,597 (78.70%) remaining in the <MCI state. Baseline characteristics of all participants are presented in eTable 1 (supplementary material, http://links.lww.com/WNL/C425).

The transition intensity from MCI to dementia was approximately 0.128, the same as the reversion from MCI to NC. The transition intensity of progression to MCI for postreversion was 2.48-fold higher than that of reversion from MCI to NC and progression from MCI to dementia, which is of concern. The transition probability curves in Figure 2 present multiple possible state transitions and corresponding probabilities over the 15 years. Figure 2, A–C correspond to different scenarios, where impaired but not MCI was excluded, merged with NC into a <MCI state, or treated as an independent transient state. For the estimations merging NC and impaired but not MCI in Figure 2A, the probability of remaining in the same state within 3 years was higher than that of transitioning to a subsequent state for both <MCI and MCI (green and purple lines, respectively). The probability of reversion fluctuated over the 15 years at 10%–20% (blue line). The probability of progression to MCI for postreversion increased with time, peaking at 44.75% in the 5th year and decreasing with time thereafter (orange line). The likelihood of progression to dementia increased yearly, consistent with the slope of the probability from MCI to dementia (brown and red lines, respectively). For the estimations of the exclusion scenario in Figure 2B, the overall trend of transition probability between states was generally similar to the merging scenario. Not surprisingly, the reversion probability from MCI to NC was lower than that from MCI to < MCI, suggesting that the reversion of MCI may be partly attributable to impaired but not MCI participants. In Figure 2C, the high probability transition from impaired but not MCI to NC

Figure 2 Transition Probability Curves and Estimated Percentage of Total Length of Stay for 3 States Over 15 years in 3 Different Scenarios



(A) Corresponds to the scenario in which NC and impaired but not MCI are merged, (B) corresponds to the scenario in which impaired but not MCI is excluded, and (C) corresponds to the scenario in which impaired but not MCI is treated as an independent transient state. MCI = mild cognitive impairment; NC = normal cognition.

reemphasizes the rationality of the merging scenario and the nonignorability of reversion.

Participants remained in the MCI state for approximately 3.912 years (95% CI: 3.762–4.067) before progressing to dementia and remained in the postreversion <MCI state for approximately 3.157 years (95% CI: 2.882–3.457). More than one-third of the time was spent in the <MCI state, as confirmed by the estimated percentage of total length of stay for multiple states over the 15 years in Figure 2. Only about 5% of the time was spent in the impaired but not MCI state, probably related to the high probability of transition to NC. This article mainly focused on results from the merging scenario. Table 1 summarizes the results of setting up confounders in 3 different ways. Advanced age, higher education level, married, poor independence level, lower BMI, *APOE* ε4 carriers status, lower MMSE scores, and higher CDR, FAQ, GDS, and NPI-Q scores were significantly associated with MCI developing to dementia. Younger age, lower education level, higher independence level, *APOE* ε4 noncarriers status, higher MMSE scores, and lower CDR and FAQ scores were protective factors for reversion.

We further stratified participants according to baseline MCI subtypes and constructed multivariate Markov models for aMCI and naMCI, respectively; Figure 3 shows the corresponding transition probability curves over 15 years. Consistent with our expectations, the probability of progression to

Table 1 Effects of Covariates on State Transitions

Variables	Model 1 HR (95% CI)			Model 2 HR (95% CI)			Model 3 HR (95% CI)		
	<MCI→MCI	MCI→<MCI	MCI→Dementia	<MCI→MCI	MCI→<MCI	MCI→Dementia	<MCI→MCI	MCI→<MCI	MCI→Dementia
Bidirectional transitions of MCI[a]									
Sex									
Female	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Male	0.825 (0.696–0.977)	1.079 (0.969–1.201)	1.050 (0.968–1.140)	0.828 (0.698–0.981)	1.102 (1.013–1.032)	1.014 (1.010–1.018)	0.838 (0.702–0.999)	0.995 (0.889–1.113)	1.069 (0.985–1.162)
Age, y	1.021 (1.012–1.031)	0.977 (0.972–0.983)	1.011 (1.007–1.016)	1.022 (1.013–1.032)	0.976 (0.971–0.981)	1.014 (1.010–1.018)	1.023 (1.013–1.033)	0.981 (0.976–0.987)	1.011 (1.006–1.015)
Educational attainment, y	0.987 (0.964–1.011)	0.993 (0.978–1.009)	1.005 (0.993–1.016)	0.987 (0.963–1.011)	0.996 (0.980–1.012)	1.002 (0.991–1.014)	1.004 (0.979–1.029)	0.978 (0.962–0.995)	1.024 (1.012–1.036)
Marital status									
Married	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Single	1.334 (1.039–1.714)	1.154 (0.978–1.361)	0.805 (0.706–0.917)	1.337 (1.034–1.719)	1.109 (0.940–1.308)	0.820 (0.719–0.936)	1.408 (1.083–1.832)	1.072 (0.902–1.273)	0.771 (0.676–0.880)
Living situation									
Alone	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
With others	1.068 (0.829–1.376)	0.990 (0.834–1.176)	1.049 (0.912–1.207)	1.072 (0.831–1.381)	0.974 (0.820–1.156)	1.049 (0.912–1.208)	1.045 (0.804–1.359)	0.982 (0.820–1.176)	0.901 (0.782–1.038)
Independence level, poor	1.580 (1.351–1.847)	0.439 (0.379–0.508)	1.887 (1.781–1.999)	1.575 (1.347–1.842)	0.442 (0.382–0.512)	1.884 (1.778–1.997)	1.223 (1.008–1.484)	0.721 (0.615–0.846)	1.246 (1.162–1.336)
BMI	0.986 (0.970–1.002)	1.010 (1.001–1.019)	0.967 (0.959–0.975)	0.986 (0.970–1.002)	1.008 (0.998–1.017)	0.970 (0.962–0.978)	0.991 (0.975–1.007)	1.005 (0.995–1.014)	0.973 (0.965–0.981)
APOE ε4									
Presence	—	—	—	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Absence	—	—	—	0.892 (0.760–1.047)	1.515 (1.363–1.683)	0.731 (0.678–0.789)	0.894 (0.758–1.054)	1.357 (1.215–1.515)	0.761 (0.705–0.822)
MMSE	—	—	—	—	—	—	0.983 (0.956–1.010)	1.122 (1.098–1.148)	0.935 (0.925–0.946)
CDR	—	—	—	—	—	—	2.244 (1.635–3.080)	0.248 (0.193–0.317)	1.734 (1.409–2.134)
FAQ	—	—	—	—	—	—	1.010 (0.985–1.035)	0.909 (0.891–0.927)	1.065 (1.057–1.073)
GDS	—	—	—	—	—	—	1.039 (1.007–1.072)	1.015 (0.992–1.038)	1.020 (1.006–1.035)
NPI-Q	—	—	—	—	—	—	0.991 (0.960–1.024)	0.992 (0.972–1.013)	1.017 (1.006–1.028)
Postreversion[b]									
Age, y	1.016 (1.005–1.027)	0.957 (0.940–0.973)	1.018 (0.998–1.039)	1.016 (1.005–1.027)	0.956 (0.939–0.973)	1.021 (1.001–1.042)	1.014 (1.001–1.026)	0.959 (0.941–0.978)	1.018 (0.998–1.039)
Educational attainment, y	0.994 (0.967–1.021)	0.999 (0.952–1.047)	0.975 (0.929–1.023)	0.993 (0.967–1.021)	1.001 (0.954–1.050)	0.971 (0.924–1.020)	1.011 (0.981–1.043)	1.005 (0.955–1.058)	0.998 (0.948–1.050)
Marital status									
Married	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Single	1.234 (0.935–1.629)	1.020 (0.639–1.629)	1.406 (0.900–2.197)	1.244 (0.941–1.644)	1.031 (0.642–1.655)	1.327 (0.848–2.078)	1.334 (0.977–1.823)	1.012 (0.613–1.670)	1.452 (0.928–2.271)
Living situation									
Alone	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
With others	1.115 (0.838–1.484)	1.134 (0.700–1.846)	1.449 (0.914–2.298)	1.117 (0.839–1.488)	1.136 (0.698–1.849)	1.380 (0.870–2.191)	1.119 (0.814–1.539)	1.102 (0.658–1.846)	1.366 (0.867–2.153)
Independence level	1.538 (1.298–1.822)	0.460 (0.290–0.729)	1.714 (1.314–2.237)	1.534 (1.295–1.817)	0.455 (0.286–0.724)	1.690 (1.296–2.204)	1.231 (1.002–1.513)	0.655 (0.402–1.068)	1.027 (0.718–1.470)
BMI	0.989 (0.972–1.006)	1.003 (0.976–1.031)	0.968 (0.936–1.002)	0.989 (0.972–1.006)	1.003 (0.975–1.031)	0.971 (0.939–1.005)	0.990 (0.972–1.009)	1.003 (0.974–1.032)	0.983 (0.949–1.019)
***APOE* ε4**									

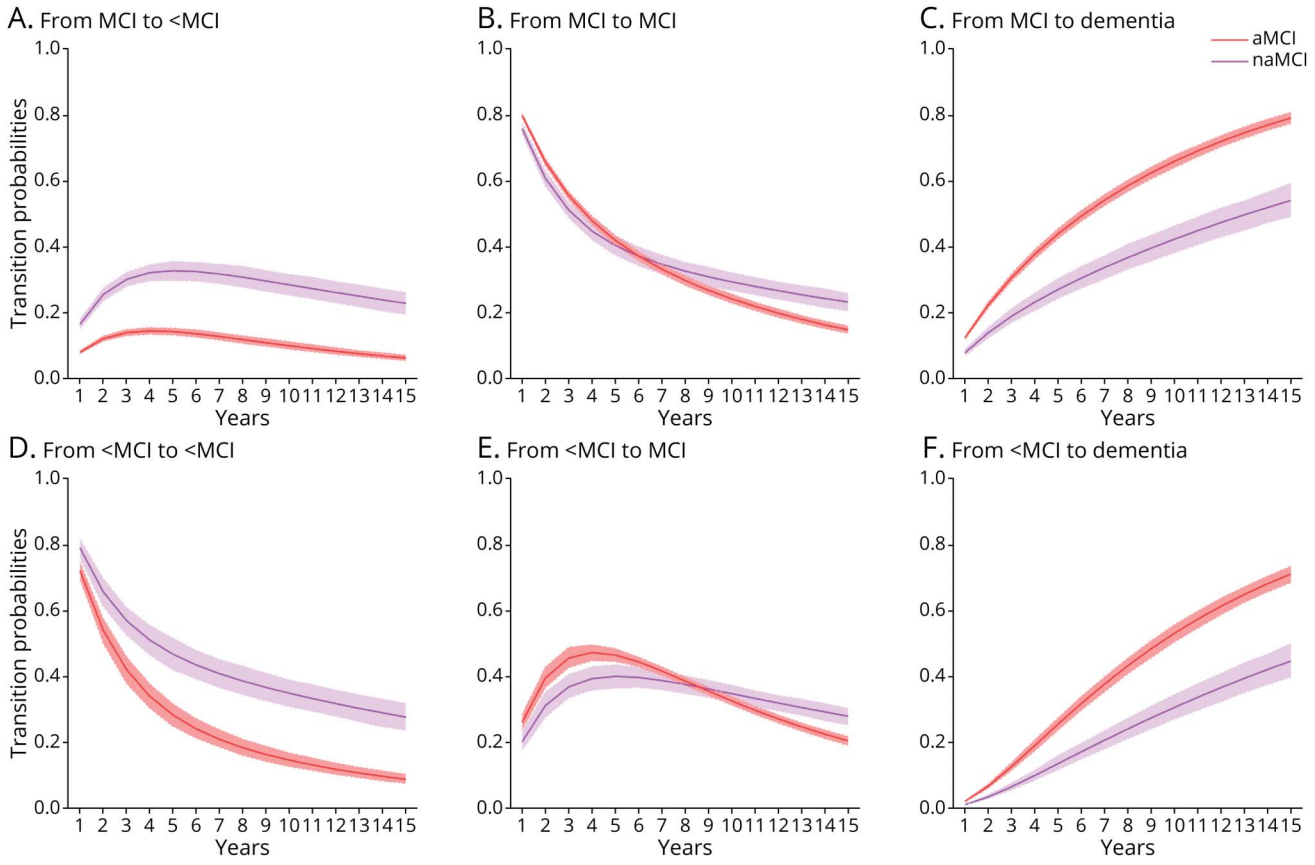
Continued

Table 1 Effects of Covariates on State Transitions *(continued)*

Variables	Model 1 HR (95% CI)			Model 2 HR (95% CI)			Model 3 HR (95% CI)		
	<MCI→MCI	MCI→<MCI	MCI→Dementia	<MCI→MCI	MCI→<MCI	MCI→Dementia	<MCI→MCI	MCI→<MCI	MCI→Dementia
Presence	—	—	—	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Absence	—	—	—	0.885 (0.738–1.061)	1.098 (0.797–1.512)	0.639 (0.459–0.890)	0.915 (0.748–1.120)	1.123 (0.903–1.570)	0.667 (0.473–0.941)
MMSE	—	—	—	—	—	—	0.977 (0.942–1.013)	1.041 (0.976–1.111)	0.927 (0.864–0.994)
CDR	—	—	—	—	—	—	1.644 (1.102–2.452)	0.244 (0.127–0.472)	1.222 (0.506–2.952)
FAQ	—	—	—	—	—	—	1.014 (0.988–1.041)	0.909 (0.854–0.968)	1.074 (1.033–1.118)
GDS	—	—	—	—	—	—	1.027 (0.990–1.066)	0.978 (0.910–1.052)	1.075 (1.014–1.140)
NPI-Q	—	—	—	—	—	—	0.985 (0.951–1.020)	0.968 (0.912–1.029)	1.018 (0.958–1.082)

Abbreviations: AIC = Akaike information criterion; BMI = body mass index; CDR = Clinical Dementia Rating; FAQ = Functional Activities Questionnaire; GDS = Geriatric Depression Scale; HR = hazard ratio; MCI = mild cognitive impairment; <MCI = no impairment or any impairment falling below the MCI criteria threshold; MMSE = Mini-Mental State Examination; NPI-Q = Neuropsychiatric Inventory Questionnaire.
[a] Model 1: adjusted for sex, age, educational attainment, marital status, living situation, independence level, and BMI (−2log likelihood ratio = 28,652.74, AIC = 28,700.74); [a]Model 2: model 1 + *APOE* ε4 (−2log likelihood ratio = 28,507.55, AIC = 28,561.55); [a]Model 3: model 2 + MMSE, CDR, FAQ, GDS, and NPI-Q (−2log likelihood ratio = 27,244.57, AIC = 27,328.57).
[b] Model 1: adjusted for age, educational attainment, marital status, living situation, independence level, and BMI (−2log likelihood ratio = 5,177.08, AIC = 5,219.08); [b]Model 2: model 1 + *APOE* ε4 (−2log likelihood ratio = 5,116.39, AIC = 5,214.39); [b]Model 3: model 2 + MMSE, CDR, FAQ, GDS, and NPI-Q (−2log likelihood ratio = 5,004.32, AIC = 5,082.32).

Figure 3 Transition Probability Curves for Participants With aMCI and naMCI Over 15 Years



(A-C) Diagrams in the first row present the bidirectional transitions of MCI with associated probabilities. (D-F) Diagrams in the second row describe the transition patterns of postreversion. aMCI = amnestic MCI; MCI = mild cognitive impairment; <MCI = no impairment or any impairment falling below the MCI criteria threshold; naMCI = nonamnestic MCI.

dementia was higher for participants with aMCI than for those with naMCI (Figure 3C), with a similar pattern of progression to dementia for postreversion (Figure 3F). Compared with participants with aMCI, those with naMCI were 2–3 times more likely to reversion in any time period (Figure 3A). Details on observed number of state transitions, transition probabilities, total length of stay, and covariate effects are provided as supplementary material (eTables 2–5, http://links.lww.com/WNL/C425).

Postreversion Trajectories

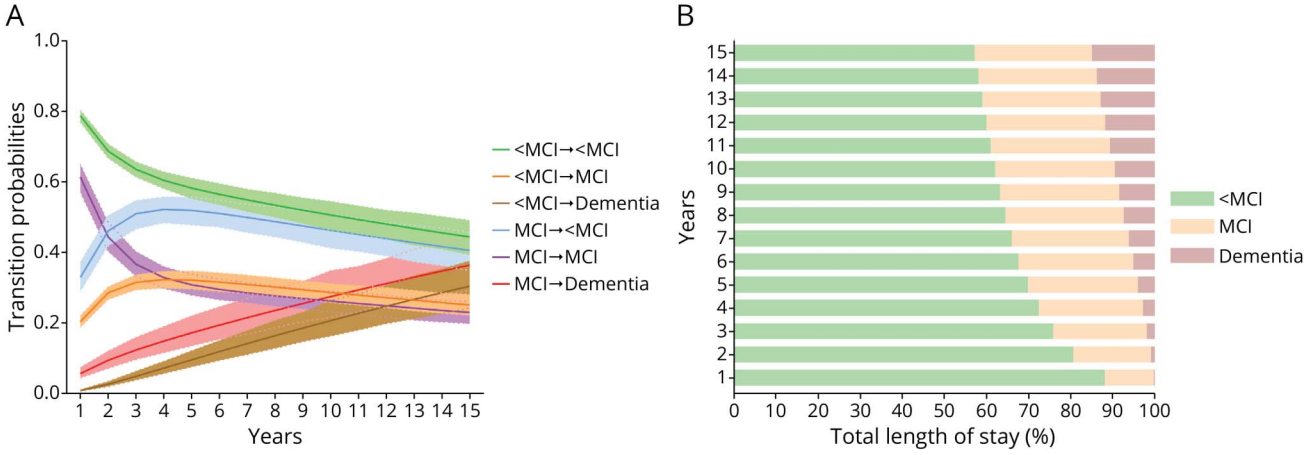
Given the potential for reversion from MCI to NC and near-NC, we explored future cognitive trajectories for post-regression. A new data set was established by considering 5,320 observations of 1,175 participants with at least 2 visits after the initial reversion; dementia was still treated as an absorbing state. Figure 4A presents the estimated transitions probability curves over the 15 years for postreversion. Remaining in the <MCI state occurred more frequently than any transition (green line). The probability of progression to MCI increased from 20.39% to 32.33% within 4 years and then decreased slowly at a rate similar to that of remaining in the <MCI state postreversion (orange line). The probability of postreversion participants progressing to dementia increased by 2% per year (brown line). Participants who progressed to MCI were likely to reverse to < MCI again, with the probability peaking at 52.21% in the 4th year and then decreasing yearly, remaining above 40% for the entire 15 years (blue line). The probability of progression from MCI to dementia increased yearly at a rate consistent with that of progression from <MCI to dementia (red and brown lines, respectively). These findings demonstrated the instability of reversion from MCI to < MCI and the risk of further deterioration. As for postreversion, participants remained in the <MCI state (3.254 years; 95% CI: 2.919–3.629) longer than in the MCI state (1.757 years; 95% CI: 1.510–2.045). Figure 4B shows the estimated percentage of total length of stay for multiple states over the 15 years, suggesting that more than half the time for the postreversion was spent in the <MCI state. Table 1 presents the HRs and their 95% CIs of different transitions for postreversion. Covariates in the multivariate Markov models included age, educational attainment, marital status, living situation, independence level, BMI, APOE ε4 allele status, and MMSE, CDR, FAQ, GDS, and NPI-Q scores. Advanced age, poor independence level, and higher CDR score increased the risk of progression to MCI. Poor independence level, *APOE* ε4 carrier status, and lower MMSE, and higher GDS and FAQ scores were risk factors for the progression to dementia for postreversion. Younger age, higher independence level, and lower CDR and FAQ scores were associated with the reversion from MCI to <MCI. Details on observed number of state transitions, transition probabilities, and total length of stay for postreversion are provided as supplementary material (eTables 6–8, http://links.lww.com/WNL/C425).

The observed and simulated prevalence transitions of each state from the 4 multistate Markov models constructed in this study are shown in eFigure 2 (supplementary material, http://links.lww.com/WNL/C425). Overall, our models captured prevalence trends, although the overestimation or underestimation of prevalence in all 3 states increased over time.

Discussion

The study quantified the bidirectional transitions of MCI and future cognitive trajectories for postreversion using multistate Markov models and a large cohort of 24,220 observations with up to 15 years of follow-up. Our initial analysis revealed that participants with MCI had a 10%–20% probability of reversion,

Figure 4 Transition Probability Curves (A) and Estimated Percentage of Total Length of Stay (B) for Postreversion Over 15 Years



Abbreviations: MCI = mild cognitive impairment; <MCI = no impairment or any impairment falling below the MCI criteria threshold.

and the rate of reversion was similar to that of progression. In other words, nearly 1 in 5 patients with MCI experienced a spontaneous remission of cognitive deficits over time. Participants with aMCI and naMCI were more likely to progress to dementia and reverse to <MCI, respectively. Furthermore, we delineated each transition and sojourn time for participants with aMCI and naMCI, which is yet to be reported. Our exploratory study was of great value, as the trajectory of postreversion has not been extensively investigated in the past. Results of our postreversion analysis strongly suggest that postreversion participants remain at an increased risk of subsequent progression to MCI or dementia over a longer term, with a 40% probability of recurrent reversion. Moreover, participants with a high likelihood of reversion may reap limited benefits from unnecessary antidementia treatments while remaining at risk for potentially harmful consequences, such as overmedication, side effects, discrimination, and stigmatization.[19] Therefore, reversion should be regarded as a factor with equal potential or should at least be acknowledged in the realization of multidimensional MCI research.[20]

In 2019, a meta-analysis reported an overall reversion rate of approximately 27.57%.[5] Reversion rates were much lower in clinic-based studies than in community-based studies. The high heterogeneity of reported reversion rates across studies may be driven by differences in study settings, sample size, duration of follow-up, geographic regions, and other patient-based factors.[10] Our study had a relatively longer follow-up period (up to 15 years) than most previous studies, which allowed for a more thorough assessment of cognitive stability despite the variability of cognitive trajectories. A possible explanation of recurrent reversion is that cognition tends to fluctuate over time. Participants above the MCI threshold, whose next visit happened to be during a period of relatively good cognitive performance, may have subsequently fallen below this threshold.[14] However, the superimposed effect of underlying neurodegenerative mechanisms may cause long-term cognitive deterioration.[9] Cognitive impairment in patients with naMCI has been proposed to be caused by vascular pathology or psychiatric and nutritional deficits or be secondary to concomitant medical disorders that are nondegenerative in nature, and the associated cognitive impairments may disappear at the beginning of the intervention.[21] The lack of data on MCI etiology precluded a more detailed analysis in the current study. Owing to the small sample size, our conclusions cannot be extrapolated to determine the stability or progression of cognitive impairment in all participants with naMCI. Nonetheless, the findings in this study underscore the need to treat distinct subtypes of MCI differently.

In the covariate effects analysis, our observation of married status as a significant predictor of MCI progression is not in line with previous findings.[22] Although spouse-induced social support and intellectual stimulation may prevent cognitive decline or facilitate effective interventions, stress caused by poor marital relationship quality, such as caregiver burden, may contribute to cognitive deterioration.[23] Single individuals do not face such stress. As our study lacked data for assessing marital relationship quality, we cannot speculate on the specific implications of our findings.

The mechanistic relationship between educational attainment and cognitive function has always been controversial. We found that longer education did not uniformly protect against dementia risk, suggesting that the relationship between these factors may be more nuanced than previously thought. It seems that longer education indicates more interest in learning and a greater tendency to seek cognitively stimulating activities throughout life. However, because educational attainment is not a static event, it does not necessarily reflect subsequent cognitive endeavors.[24]

To date, the role of BMI in cognitive impairment is not understood well. Some studies have demonstrated a directional,[25] indirect, inverse,[26] or U-shaped association[27] between low or high BMI and cognitive deterioration. However, changes in body composition with age make BMI a rough measure of nutritional status in older adults. Of interest, in this study, lower BMI was associated with cognitive decline. One possible explanation is that lower BMI may be a sign of poor nutrition and comorbidities, and subtle changes in appetite regulation can enhance neurodegeneration leading to behavior changes, such as depression.[27] Collectively, further studies are required to deepen our understanding of the factors associated with the bidirectional transitions of MCI.

Traditional Cox proportional hazards models are most frequently used to predict the risk of transitions between states, but they only account for the transitions between 2 states. Notably, the natural history of dementia is underscored by complex dynamic transitions between a series of states. Accordingly, models capable of estimating transition risks among multiple states are more suitable for dementia, such as multistate Markov models, which quantify transitions between 3 or more states and provide more information about the dynamic process of dementia.[28] The multistate model describes the underlying, rather than the observed progression of dementia.[29] For example, if a participant reverses to < MCI from MCI at one point but is diagnosed with dementia at the next visit, this does not imply that instantaneous progression from <MCI to dementia is clinically possible. Rather, the participant transits through MCI at some point between these visits. Considering the bidirectional nature of cognitive impairment, the multistate Markov model has the potential to estimate the fate of MCI more accurately, thereby improving our understanding of the natural history of MCI and providing statistical foundations for regular screening and time-targeted interventions.

This study has some limitations. First, the NACC cohort is a large multicenter case series that aggregates data from approximately 30 independent ADC participants and consists primarily of well-educated White people treated at memory clinics or self-referrals, rather than a truly population-based sample.[30] Furthermore, although each ADC collects

standardized data as part of its annual evaluations, different institutions may apply different inclusion/exclusion criteria.[31] Second, a test set distinct from the training set was not used to assess model validity. Instead, we prioritized parameter estimation, using all data to improve accuracy, which is common practice in the literature.[12,29,32,33] Third, the potential effects of confounding covariates or interactions between covariates and modifiable factors, such as lifestyle,[34] were not investigated. Future studies should explore the relationship between frequent reversions and cognitive fluctuations using real-world data and determine the essential cause for this phenomenon. Efforts should also be made to determine cognitive trajectories for bidirectional transitions and postreversion and to realize the personalized dynamic prediction of MCI.

This study makes 3 key contributions to the field. First, we found that the transition intensity of progression from MCI to dementia was equal to the transition intensity of reversion from MCI; that is, the instantaneous risk of cognitive improvement and deterioration in an individual with MCI was similar. Second, we discovered distinct transition dynamics between aMCI and naMCI, whereby aMCI and naMCI were more likely to progress to dementia and to reverse, respectively. Third, postreversion participants remained at an increased risk of progression to MCI or dementia and of recurrent reversion over the longer term. In conclusion, the transition probabilities and sojourn time determined in this study may serve as a valuable reference for future research and enable health care professionals to better understand the natural history of MCI and develop proactive management plans and targeted interventions.

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Disclosure

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Haixia Jia, MD	Department of Neurology, First Hospital of Shanxi Medical University, Taiyuan, China	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data; statistical analysis
Xiaoyan Ge, MD	Department of Health Statistics, School of Public Health, Shanxi Medical University, Taiyuan, China	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; and analysis or interpretation of data

Appendix *(continued)*

Name	Location	Contribution
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Hongmei Yu, PhD	Shanxi Provincial Key Laboratory of Major Diseases Risk Assessment, Taiyuan, China	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data; obtaining funding

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Estimating Bidirectional Transitions and Identifying Predictors of Mild Cognitive Impairment

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