2013

Multistate Markov chains and their application to the Biologically Resilient Adults in Neurological Studies cohort

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MULTISTATE MARKOV CHAINS AND THEIR APPLICATION TO THE BIOLOGICALLY RESILIENT ADULTS IN NUEROLOGICAL STUDIES COHORT

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Public Health
at the University of Kentucky

By
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2013

ABSTRACT OF DISSERTATION

MULTISTATE MARKOV CHAINS AND THEIR APPLICATION TO THE BIOLOGICALLY RESILIENT ADULTS IN NUEROLOGICAL STUDIES COHORT

Dementia is increasingly recognized as a major and growing threat to public health worldwide, and there is a critical need for prevention and treatment strategies. However, it is necessary that appropriate methodologies are used in the identification of risk factors. The purpose of this dissertation research was to develop further the body of literature featuring Markov chains as an analytic tool for data derived from longitudinal studies of aging and dementia.

Data drawn from 649 participants in the University of Kentucky's Alzheimer's Disease Center's (UK ADC) Biologically Resilient Adults in Neurological Studies (BRAiNS) cohort, which was established in 1989 and follows adults age 60 years and older who are cognitively normal at baseline to death, were used to conduct three studies. The first study, "Mild cognitive impairment: Statistical models of transition using longitudinal clinical data," shows that mild cognitive impairment is a stable clinical entity when a rigorous definition is applied. The second study, "Self-reported head injury and risk of cognitive impairment and Alzheimer's-type pathology in a longitudinal study of aging and dementia," shows that when the competing risk of death is properly accounted for, self-reported head injury is a clear risk factor for late-life dementia and is associated with increased beta-amyloid deposition in the brain. The third study, "Incorporating prior-state dependence among random effects and beta coefficients improves multistate Markov chain model fit," shows that the effect of risk factors, like age, may not be constant over time and may be altered based on the subject's cognitive state and that model fit is significantly improved when this is taken into account.

KEYWORDS: Markov chain, longitudinal analysis, dementia, head injury, mild cognitive impairment

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June 28, 2013

Date

MULTISTATE MARKOV CHAINS AND THEIR APPLICATION TO THE BIOLOGICALLY RESILIENT ADULTS IN NUEROLOGICAL STUDIES COHORT

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CHAPTER ONE

Introduction

Although commonly used to refer to a disease state, the term "dementia" does not refer to a disease at all but rather a syndrome characterized by memory loss and impaired activities of daily living (ADLs).[1] Multiple neurological diseases can result in dementia, the most common of which is late onset, or sporadic, Alzheimer's disease (AD), which is estimated to account for 60 to 80 percent of dementia cases.[2] AD is characterized clinically by the appearance of deficits in memory, thinking, and ADLs, which are common to all dementing illnesses. AD is defined pathologically by the presence of beta-amyloid (neuritic plaques) and tau (neurofibrillary tangles) pathology, which can only be determined by autopsy evaluation; current pathological diagnostic criteria describe levels of AD associated changes without regard to clinical phenotype,[3] since AD pathology has been found in non-demented individuals at autopsy.[4,5]

While clinical onset of AD usually occurs after age 65, it is now thought that AD begins as long as decades earlier; it is estimated that latent AD exists in approximately 21% of persons over age 50.[6] Prevalence of AD is currently estimated at 5.4 million cases, and the Alzheimer's Association reports that by 2050 that an estimated 16 million Americans will have AD.[7] Given current costs associated with the care and treatment of AD, in 2050 the cost of AD will reach 1.1 trillion dollars.[7] At this time, there are no effective treatments or prophylactics for AD.

The term "Mild Cognitive Impairment" (MCI) first appeared in the Global Deterioration Scale (GDS),[8] a tool for the clinical staging of dementia, to describe individuals with subjective memory complaints and objective memory impairments, but

without ADL impairment, i.e., without dementia.[9] Individuals diagnosed with MCI may progress to dementia, remain MCI until death, and in some instances have been reported to recover to a normal cognitive state.[9-15] For this reason, whether MCI represents an early stage of dementia or unique clinical syndrome that is an independent risk factor for developing dementia remains controversial despite evidence of AD neuropathology in persons carrying a diagnosis of MCI at the time of death.[16,17] Back transitions—recovery from a worse cognitive state to a better one—are likely heterogeneous in origin and may be explained by misclassification of either the MCI or normal state, inter-study and inter-clinician differences in application of diagnostic criteria, within-patient variability due to medical illness or psychosocial factors, or resistance to cognitive decline due to cognitive reserve.[18-21]

There has been considerable effort to refine diagnostic criteria, separate MCI into amnestic and non-amnestic subtypes, and identify the underlying etiologies of MCI.[10,22-25] Diagnosis of MCI due to AD, for example, may include assessment of biomarkers to determine underlying etiology.[25] Prevalence of MCI is estimated at between 3% and 19% of adults over age 65.[9]

The disease processes that lead to dementia are, in general, continuous, but it is not possible to observe individuals continuously over the many years necessary for dementia to occur. Rather, longitudinal studies of aging and dementia typically assess individuals' cognitive and physical status annually, thus producing discrete rather than continuous units of observation. At each assessment, the clinical status of the individual—normal cognition, MCI, or dementia—may be determined. Additionally, individuals may die or dropout of the study before a dementia occurs.

Familiar modeling tools, such as survival analysis, may be an intuitive choice for the analysis of these longitudinal data, but they have significant limitations. Traditional survival analysis methods, while capable of handling censored data, generally assume that the censoring mechanism is independent of the outcome of interest. However, in prospective cohort studies that enroll cognitively normal older participants and follow them over time with the goal of observing incident dementias, the censoring mechanism is never independent of the outcome of interest. Volunteers for such studies, which often require considerable time and effort from participants and may include invasive study procedures, are often healthier, more affluent, and better educated than their peers who do not enroll in such studies. Many participants will die without ever becoming demented, even when dementing brain diseases are present. Moreover, participants who do begin to show signs of cognitive impairment may be more likely to drop out of the study before a dementia can be observed.

Even when survival analysis techniques that do account for competing risks are employed, however, these methods are still limited in the sense that they do not allow for multiple outcomes of interest. Markov processes, however, have proven to be useful alternatives for modeling data from such longitudinal studies. The Markov chain models the probability of transition between any two temporally adjacent assessments, here called the "prior state" and the "current state," versus remaining in or returning to a "base state." Multistate Markov chains offer two principal advantages over traditional survival analysis: (1) they are capable of handling intervening clinical states between normal cognition and dementia, and (2) they always account for competing risks.

Kryscio *et al*. (2006) carried out the first application of a multistate Markov chain to the study of incident dementia. Results based on data from the Biologically Resilient Adults in Neurological Studies (BRAiNS) cohort, a longitudinal study of aging and cognition at the University of Kentucky Alzheimer's Disease Center (UK ADC), demonstrated that well established risk factors for dementia (i.e., age, education, family history of dementia, apolipoprotein ε-4 status) were also risk factors for transitions from normal cognition to transient MCI states.[26] Kryscio *et al*.'s model was developed further by Salazar *et al*. (2007), who incorporated a shared random effect to account for the correlations among observations arising from the same participant.[27]

Other applications of the Markov model in incident dementia research include Tyas *et al.* (2007), whose examination of data from the Nun Study suggested that factors that increase dementia risk do so by predisposing individuals to MCI rather than dementia directly.[28] The Nun Study, unlike the BRAiNS cohort, includes participants who were already demented at enrollment. Yu *et al*. (2009) evaluated the effect of excluding these baseline dementias from the likelihood and concluded that doing so introduces significant bias into the results.[29] Yu *et al*. (2010) derived absorption statistics for the model, i.e., the overall relative risk of absorption between competing absorbing states and the mean and variance of the number of assessments required before an individual with a particular risk factor profile reaches an absorbing state.[30] Finally, Song *et al.* (2011), in an application to the Einstein Aging Study, studied the effect of including a scaling parameter, dependent on the prior observed state, with the subject-specific random effect.[31]

Each of the aforementioned applications of the Markov chain included MCI states that were defined solely by an individual's performance on one or more cognitive tests; such MCI states are inherently unstable.[32] MCI states defined by clinical criteria, however, are possible and would likely engender fewer back transitions to normal.[10,24] The purpose of this dissertation is to use multistate Markov models to assess the influence of risk factors on transitions from normal cognition to test-based and clinical forms of MCI, dementia, or death without dementia in a group of participants drawn from the BRAiNS longitudinal cohort.

The chapters that follow present studies into the nature of test-based and clinical MCI states, self-reported head injury as a risk factor for MCI and dementia, and the influence of prior states in the chain through the incorporation of a prior state-dependent scaling parameter with the shared random effect and specifying the effect of age as prior-state dependent. In Chapter Two, "Mild cognitive impairment: statistical models of transition using longitudinal clinical data," earlier research that applied Markov models to longitudinal data from the BRAiNS cohort is expanded by including a clinically determined, quasi-absorbing MCI state as a state in the model. The major finding from this study is that in the BRAiNS cohort, once an individual has entered the clinically determined MCI state they do not back transition to less impaired states, i.e., it is a true disease state.

Results presented in Chapter Three, "Self-reported head injury and risk of late-life impairment and AD pathology in an AD Center cohort" support previous findings that individuals who report a history head injury have an increased risks of cognitive impairment, dementia, and death without dementia. This study, the first to assess

neuropathological data from an observational study in relation to head injury status, also reveals an unexpected increase in AD-type pathology among men who reported head injuries, despite those injuries taking place many years before death.

Chapter Four, "Prior-state dependence among random effects and beta coefficients significantly improves multistate Markov chain model fit" begins the process of exploring back transitions among test-based MCI states and normal cognition as a function of modeling strategy and state definitions. Major findings, limitations, and future research problems are discussed in Chapter Five, the conclusion to the dissertation.

CHAPTER TWO

Mild cognitive impairment: statistical models of transition using longitudinal clinical data

Abstract

Mild cognitive impairment (MCI) refers to the clinical state between normal cognition and probable Alzheimer's disease (AD), but persons diagnosed with MCI may progress to non-AD forms of dementia, remain MCI until death, or recover to normal cognition. Risk factors for these various clinical changes, which we term "transitions," may provide targets for therapeutic interventions. Therefore it is useful to develop new approaches to assess risk factors for these transitions. Markov models have been used to investigate the transient nature of MCI represented by amnestic single-domain and mixed MCI states, where mixed MCI comprised all other MCI subtypes based on cognitive assessments. The purpose of this study is to expand this risk model by including a clinically determined MCI state as an outcome. Analyses show that several common risk factors play different roles in effecting transitions to MCI and dementia. Notably, APOE-4 increases the risk of transition to clinical MCI but does not affect the risk for a final transition to dementia, and baseline hypertension decreases the risk of transition to dementia from clinical MCI.

Introduction

Mild cognitive impairment (MCI) often refers to the clinical condition between normal cognition and probable Alzheimer's disease (AD). However, persons diagnosed with MCI may progress to non-AD forms of dementia, remain MCI until death, and in some instances recover to a normal cognitive state.[10,11,32] There has been considerable

effort to refine diagnostic criteria, separate MCI into amnestic and non-amnestic subtypes, and identify the underlying etiologies of MCI.[10,22,23] However, whether MCI is a true precursor to dementia remains controversial[13,33-35] despite evidence of AD neuropathology in amnestic MCI.[16,17] This is due in part to the description of 'back transitions' (i.e., recovery to normal cognition) that have been reported in longitudinal studies.[15,32,35,36] Although the long-term prognosis for such cases is unclear, patients with a Clinical Dementia Rating (CDR) global score of 0.5 often have AD pathology at autopsy regardless of back transitions to CDR global scores of 0.[37] Back transitions are likely heterogeneous in origin and may be explained by misclassification of either the MCI or normal state, inter-clinician differences in application of diagnostic criteria, within-patient variability due to medical illness or psychosocial factors, or resistance to cognitive decline due to cognitive reserve.[18-21]

In a previous study we investigated MCI as defined by cognitive test performance alone. Here, we have added a clinical consensus-based MCI state as defined by the Second International Work Group on MCI[10] and operationalized by the National Alzheimer's Coordinating Center (NACC).[24,38] We now have sufficient data on this MCI state to assess it as risk factor for dementia. The purpose of this study is to describe our statistical model of longitudinal data in the context of studying MCI risks and to update our prior research with additional cognitive assessments and clinical diagnoses from a large longitudinal sample. Over 54% of the sample subjects now have a terminating event (i.e., we have 35 additional dementias and 69 additional deaths) compared to the 36% in the previous study. These additional events provide increased power to detect

potential risks for transition including age, gender, education, APOE-4, family history of dementing illness, and baseline hypertension.

Methods

Subjects

Subjects in the current study are from the Biologically Resilient Adults in Neurological Studies (BRAiNS) at the University of Kentucky's Alzheimer's Disease Center (UK ADC), a longitudinal cohort of 1,030 individuals with ongoing recruitment established in 1989.[39,40] Participants consent to extensive annual cognitive and clinical examinations as well as brain donation upon death. Exclusion criteria include age less than 60 years, active infectious diseases, neurological disorders, psychiatric disorders, disabling medical disorders, and dementing illness. Subjects included in the current study (n=554) comprise those included in the previous report.[26] All subjects were cognitively intact at study entry. All research activities were approved by the University of Kentucky Institutional Review Board. Each participant gave written informed consent.

Cognitive Assessments

Annual cognitive test-based assessments taken on a cohort of initially cognitively normal subjects participating in the BRAiNS project are used to classify subjects into one of three states: normal, test-based amnestic MCI ($aMCI_{TB}$), or test-based mixed MCI ($mMCI_{TB}$) (Table 2.1). Classification of $aMCI_{TB}$ and $mMCI_{TB}$ has been described previously.[26,41] Briefly, a classification of $aMCI_{TB}$ results from a poor score (as defined below) on at least one measure of episodic memory measure (Table 2.1). A classification of $mMCI_{TB}$ requires a poor score on at least one measure of language or executive function (Table 2.1) regardless of the $aMCI_{TB}$ classification status. A poor score is

defined as at least 1.5 standard deviations (SD) below the age-adjusted mean, which is consistent with the Second International Working Group on MCI criteria;[10] normative values were derived from the baseline evaluations of the entire normal cohort.

Classification into clinical consensus-based MCI (MCI_{CC}) results from a diagnosis of MCI, which is determined according to the consensus guidelines on MCI developed by the Second International Working Group on MCI.[10] A diagnosis of MCI requires:

1. a cognitive complaint by the subject or informant, or evidence for longitudinal decline on cognitive test performance (at least 1.5 SD decline);
2. generally intact global cognition;
3. no or minimal functional impairment;
4. not demented by DSM-IV criteria.

Additionally, MCI_{CC} is restricted to those individuals for whom a neurodegenerative etiology is suspected. The NACC diagnostic criteria designate patients with cognitive impairments but without a presumed degenerative etiology as "Cognitive impairment, not MCI".[24] Diagnosis of MCI_{CC} is based on a consensus team review by the examining physicians, neuropsychologists, and the clinical research assistant administering the protocol.[15] This MCI_{CC} designation is equivalent in most respects to the new "MCI-Core Clinical Criteria" as defined by the National Institute on Aging-Alzheimer's Association Workgroup on Diagnostic Guidelines for Alzheimer's Disease.[25] The primary difference is that the new criteria allow the cognitive complaint in number one above to come from a skilled clinician rather than only the patient or informant. A dementia classification also results from a clinical consensus diagnosis of dementia (most often AD), which may be based on the dementia criteria of Diagnostic and Statistical Manual of Mental Disorders

Fourth Edition (DSM-IV),[1] criteria of the Joint Working Group of the National Institute of the Neurologic and Communication Disorders and Stroke-AD and Related Disorders (NINCDS-ADRDA),[42] NINDS-AIREN criteria for vascular dementia,[43] and the 2005 Dementia with Lewy bodies (DLB) Consortium revised criteria.[44] A diagnosis of MCI_{CC} or dementia supersedes a classification of normal cognition, $aMCI_{TB}$ or $mMCI_{TB}$ in our model.

Between their annual assessments subjects may die or become demented, and these states are treated as completely absorbing competing states. MCI_{CC} is treated as a quasi-absorbing state, as subjects do not move backward to a transient state (i.e., normal cognition, $aMCI_{TB}$, or $mMCI_{TB}$), but they may become demented or die.

For 19 subjects, review of the longitudinal record revealed apparent back transitions from MCI_{CC} to normal: nine subjects were diagnosed with MCI_{CC}, reverted to normal, and then reconverted to MCI_{CC}, three of whom eventually became demented; six subjects had a single diagnosis of MCI_{CC} between several diagnoses of normal cognition on either side; and four subjects had a single diagnosis of MCI_{CC} at their initial evaluation following the UK ADC's implementation of the NACC Uniform Data Set (UDS) cognitive and clinical testing protocol[24,45] with all subsequent evaluations classified as normal. Review of each subject's complete study history revealed in all cases that the apparent back transitions were the result of underlying medical conditions, conflicting data from informants, or misclassification. Given that there are differences in the medical comorbidities (e.g., hypothyroidism, B_{12} deficiency) that can mimic MCI_{CC} in both research and general clinic settings (cf., Reference 15), 'treatable' cases of MCI_{CC} were not considered to reflect neurodegenerative conditions. Similarly, a single diagnosis of

'normal' in the midst of many years of MCI_{CC} diagnoses appears to reflect a temporary resolution of a neurodegenerative condition and so strains credulity. Therefore, in light of the available evidence, the six normal to MCI_{CC} to normal cases and the four MCI_{CC} to normal cases were reclassified as never having MCI_{CC}, though they still might be classified $aMCI_{TB}$ or $mMCI_{TB}$, and the nine MCI_{CC} to normal to MCI_{CC} were reclassified as MCI_{CC} at every assessment after the first diagnosis of MCI_{CC}.

Statistical Analysis

The conditional distribution of the cognitive status at any assessment given the status at the prior assessment is assumed to have the Markov property. That is, the status at the current assessment depends only on the status at the prior assessment[46] and possibly other risk factors. A multi-state Markov chain with three transient states (normal cognition, $aMCI_{TB}$, and $mMCI_{TB}$), one quasi-absorbing state (MCI_{CC}), and two absorbing states (death and dementia) was used to model the probability of maintaining the current state or moving to a different state at the next assessment (Figure 1). The Markov chain models the log-odds of transition between any two temporally adjacent assessments, here called the 'prior state' and the 'current state,' versus remaining in or returning to a 'base state' with a series of four random effects polytomous logistic regression models (i.e., one model for each transient state and one model for the quasi-absorbing state, MCI_{cc}).

The base state is normal cognition while a participant's prior state is normal cognition, $aMCI_{TB}$, or $mMCI_{TB}$; once a participant has moved into MCI_{CC} the base state then becomes MCI_{CC}. The model is additive, which means in practice that although we assume the risk factors are independent of the *prior state* (i.e., the effect of sex, for example, is the same whether the prior state is normal cognition, $aMCI_{TB}$, or $mMCI_{TB}$;

there is no interaction between the covariates and the prior state), the estimated risk factor beta coefficients may depend on the *base state*. That is, the effect of sex, for example, may vary with respect to a base state of normal cognition versus a base state of MCI_{CC}. To account for within-subject correlations a normally distributed shared random effect due to Salazar et al. (2007)[27] was included in the model using PROC NLMIXED in SAS 9.2®. The Quasi-Newton method is used to maximize the likelihood function, which due to the presence of the shared random effect is an integral approximated by an adaptive Gaussian quadrature with one quadrature point.[47,48] Transitions to MCI_{CC} and dementia states are assumed to have occurred on the date of assessment as modeling assumptions do not permit the inclusion of interval censoring-type approaches. The model ignores any transitions among the transient states between regularly scheduled assessments. Statistical significance was set at $\alpha = 0.05$.

Covariates

Covariates of interest include age at assessment (centered at 78, the sample median), sex (1 = female, 0 = male), education (two levels: ≤ 12 years, >12 years), presence (1) or absence (0) of any copies of the APOE-4 allele, presence (1) or absence (0) of family history of dementing illness among first degree relatives, and presence (1) or absence (0) of hypertension at study entry. Hypertension status at entry was derived from participant responses to the question, "Have you ever been told by a doctor or nurse that you have high blood pressure?" Use of medications was also recorded; however, reported use of an anti-hypertensive medication did not supersede a participant's response of 'No' since anti-hypertensives are used to treat other illnesses. Also included as covariates (when the base state is normal cognition) are two indicator variables for (1

= yes, 0 = no) $aMCI_{TB}$ and $mMCI_{TB}$; normal cognition is the reference category. Race was not included as a covariate because almost all of the included subjects (99%) are Caucasian.

Results

Study participants contribute an average of 10.8 annual assessments (median = 10 assessments, mode = 10 assessments) with the average time between assessments at approximately 13 months (Table 2.2). Approximately 87% of subjects who reported hypertension at baseline also reported taking at least one anti-hypertensive medication, whereas 15% of those who reported no history of hypertension reported taking at least one anti-hypertensive medication.

One-step transitions

Table 2.3 enumerates the one-step transitions associated with each arrow in Figure 2.1. The majority of transitions from $aMCI_{TB}$, which requires a poor score on a test of episodic memory, are back to normal cognition at the next visit (59.3%), and only 4.4% are transitions to MCI_{CC} or dementia. Mixed MCI ($mMCI_{TB}$), which requires a poor score on a test of executive function or language, appears more predictive of underlying impairment with 43.8% remaining $mMCI_{TB}$ and 7.1% transitioning to MCI_{CC} or dementia at the next visit. Entry into MCI_{CC} is a clear risk factor for transition to dementia since the majority of the transitions into the dementia state come from MCI_{CC} when compared to transitions into dementia from the other states. As previously stated, recovery from MCI_{CC} does not occur. We note that 13 of the 16 subjects who were MCI_{CC} and died without a dementia diagnosis have been autopsied. Of these, five had AD-type pathology insufficient for an AD diagnosis, two had mixed AD and vascular pathology, two had

mixed vascular pathology (one with Lewy bodies and one with hippocampal sclerosis), two had hippocampal sclerosis, one had Parkinson's disease, and one had no histopathologic substrate for dementia (see also Reference 5).

Risk Factors

A number of risk factors alter the probability of transition to an MCI state (Table2.4). Older age increases the risk of movement into $aMCI_{TB}$ ($p = 0.0006$) and $mMCI_{TB}$ ($p < 0.0001$). In addition, 12 years or less of education predicts transition to $mMCI_{TB}$ ($p = 0.0001$) but not $aMCI_{TB}$. Family history of dementia 'protects' against transitions to $mMCI_{TB}$ ($p = 0.011$), and female sex is protective against entry into $aMCI_{TB}$ ($p = 0.013$). Classification as $mMCI_{TB}$ at the prior assessment is predictive of remaining $mMCI_{TB}$ rather than returning to normal at the next assessment ($p < 0.0001$).

Demographic risk factors for transition to the MCI_{CC} state (versus remaining in or returning to a normal state) are older age ($p < 0.0001$), presence of at least one APOE-4 allele ($p = 0.0053$), and high school education (12 years) or less ($p = 0.007$). Classification as either $aMCI_{TB}$ or $mMCI_{TB}$ at the prior assessment also increases the risk of transition to MCI_{CC} ($p = 0.0041$ for $aMCI_{TB}$, $p < 0.0001$ for $mMCI_{TB}$).

In the absence of MCI_{CC}, risk factors for dementia include older age ($p < 0.0001$) and the presence of at least one APOE-4 allele ($p = 0.0057$) (Table 2.4). A classification as $mMCI_{TB}$ ($p <0.0001$) but not $aMCI_{TB}$ at the prior assessment also increases the risk of transition to dementia at the next visit. Risk factors for transition to death without dementia include older age ($p < 0.0001$) and self-reported hypertension at study entry ($p = 0.018$).

Participants in this sample who transitioned from MCI_{CC} to dementia (n = 34) did so in an average of 2.5 ± 1.5 years (median = 2.2 years), and those who transitioned from MCI_{CC} to death without an intervening dementia (n = 16) did so in an average of 2.7 ± 1.7 years (median = 3.4 years). Those cases that remain in the MCI_{CC} state (n = 50) have carried the diagnosis for an average of 4.1 ± 2.4 years (median = 4.2 years). Once a transition to MCI_{CC} has occurred, only history of hypertension at study entry appears to influence further transitions to dementia, or death without dementia, versus remaining in the MCI_{CC} state (Table 2.5). A participant who reported baseline hypertension is more likely to remain MCI_{CC} ($p = 0.037$) than to convert to dementia at the next visit: the yearly transition rate to dementia for those with hypertension at baseline is approximately 4.2% and 12.6% for those without hypertension at baseline.

Discussion

The addition of the MCI_{CC} state to the multi-state Markov chain confirms the utility of cognitive testing in predicting true underlying cognitive impairment. Entry into $aMCI_{TB}$ and particularly $mMCI_{TB}$, both of which are determined solely by poor performance on cognitive assessment, increases the risk of a diagnosis of MCI_{CC} at the next visit versus returning to normal. These results highlight the importance of objective criteria in MCI diagnosis and emphasize the role of cognitive testing, particularly of language and executive function, in early detection. Notably, poor performance limited to tests of episodic memory ($aMCI_{TB}$) in this population can resolve to normal performance at the next annual assessment as much as 60% of the time and progress to MCI_{cc} just 3% of the time (Table 2.3). Poor performance on tests of language and executive function is somewhat more stable, returning to normal performance at the next annual assessment

33% of the time. While there is no question that MCI_{TB} predicts MCI_{cc}, these findings emphasize that clinicians who primarily rely on cognitive testing should obtain longitudinal follow-up before a diagnosis of MCI is given to the patient.[50]

These findings reflect a novel analysis of risk factors for MCI and dementia based on the current NACC UDS criteria that are used across AD Centers in the United States[24] and so represent a standardized diagnostic system in contrast to earlier analyses of MCI risk factors.[50,51] Further, the comparison of two different sets of MCI criteria (MCI_{CC} vs. MCI_{TB}) provides differing risk factors that could be of clinical use in patient care. This is best highlighted in our group's earlier comparison of patients diagnosed with MCI in a clinical research (i.e., the UK ADC BRAiNS cohort) as well as a memory clinic setting where only 9% of patients in the memory clinic had non-neurodegenerative causes for cognitive decline in contrast to 31% of the research clinic cases.[15]

Risk factors for one-step transitions into MCI_{CC} include age, low education, prior classification as either $aMCI_{TB}$ or $mMCI_{TB}$, and the presence of at least one APOE-4 allele. APOE-4 is a known risk factor for AD, and although results for MCI have been mixed, a recent study of a nationally representative sample reported that APOE-4 was a reliable predictor of MCI versus normal cognition,[52] and data from the Religious Orders Study reveal a 1.4 fold increased risk of MCI in persons with an APOE-4 allele.[53]

It is clear that once an individual has transitioned to MCI_{CC} the risk of dementia increases dramatically. In this sample, 38.5% of individuals with MCI_{CC} have transitioned to dementia (at an estimated overall rate of 12.6% per year) compared to 11.8% of individuals with no history of MCI_{CC} (at an estimated overall rate of 0.16% per year). However, common risk factors for dementia (i.e., age, sex, education, family

history, and APOE-4) do not predict whether an individual will remain in MCI_{CC} or transition to dementia, or death without dementia, at the next visit. Similar results have been reported in studies that have examined risk factors for progression of cognitive impairment. Tschanz et al. (2011)[54] noted in the Cache County cohort that while female sex and age at onset were predictive of decline in Mini-Mental State Exam (MMSE) scores, education was not related to rate of MMSE decline, and APOE-4 was related to earlier onset of impairment but not rate of MMSE decline. Fleisher et al. (2007)[55] reported that although APOE-4 did predict conversion from amnestic MCI to AD over a 36-month interval, it did not improve the predictive accuracy of their model (which included only neuropsychological test scores).

Participants who reported hypertension at baseline were significantly less likely to transition from MCI_{CC} to dementia at the next visit, which may indicate a primarily vascular rather than an AD or mixed AD and vascular etiology for MCI_{CC} in these patients. Several studies have shown brain white matter changes are associated with cognitive decline in aging[56,57] and that vascular changes exacerbate the cognitive decline associated with AD.[58,59] Hoffman and colleagues (2009)[60] reported that autopsied subjects who took anti-hypertensive medications had significantly less Alzheimer-type pathology than either those with no history of hypertension or those with hypertension not treated by medication. However, the differences in risks for treated and untreated hypertension could not be assessed here due to the small number of cases of untreated hypertension in the sample.

As with $aMCI_{TB}$, $mMCI_{TB}$, and MCI_{CC}, older age increases the probability of a transition to a dementia state. Baseline hypertension plays no role in transitions to

$aMCI_{TB}$, $mMCI_{TB}$, MCI_{CC}, or dementia (in the absence of MCI_{CC}), predicting only transitions to death (modeled as a competing risk for dementia). This result agrees with our previous research[41] even after four additional years of follow-up, as well as with the results of a recent meta-analysis, which found no increased risk of incidence of AD for either persons with hypertension or those taking anti-hypertensive medications.[61] We note that hypertension is a time-dependent risk factor as the participant's status may change during the course of follow-up. Availability of these time-dependent data is limited for many of the subjects in this sample; the study protocol did not call for annual assessment of health history until the implementation of the UDS in 2005.

All forms of MCI, and dementia as well, reflect a heterogeneous (and not completely understood) group of diseases including AD, hippocampal sclerosis, dementia with Lewy bodies, and vascular dementia.[5,62] This heterogeneity may help explain the lack of significant predictors, other than baseline hypertension, from MCI_{CC} to dementia. We currently lack sufficient sample size to study these dementias as separate entities, but we have recently initiated work that will facilitate future research on which factors influence transitions into dementia subtypes. Similarly, MCI_{CC} is treated as a single entity here despite its well-documented heterogeneity[63] because we lack sufficient sample size to study the individual subtypes, and it is quite possible that risk factors for transitions to each subtype are different.

Limitations of the current study include that the final outcome for the many of the included subjects is unknown as they continue to be followed longitudinally. Additional follow-up may change the results observed here, though they have face validity. The generalizability of the results is also somewhat limited due to the sample's demographic

and geographic homogeneity, which would not be replicated in a population-based sample, and the nature of the longitudinal study, which requires brain donation at death. The volunteers are highly motivated and highly educated, and the frequency of both family history of dementia and APOE-4 is higher than what would be observed in the general population. Biomarker data (i.e., blood, cerebrospinal fluid, and neuroimaging) are for the most part unavailable on these subjects, and studies that have investigated risk factors for transition from clinical MCI to dementia have largely been focused on biomarkers.[64,65] Obtaining biomarkers is extremely expensive, however, and it has been reported that longitudinal neuropsychological testing data provides as good or better accuracy in predicting which clinical MCI cases will convert versus remain stable.[66] Nevertheless, the recently published criteria for the diagnosis of MCI due to AD make extensive use of biomarker data,[25] and this modeling technique will allow us to incorporate these data as they become available in the future.

Finally, a large portion of this University of Kentucky-based longitudinal cohort was not included in this study (n = 476). The decision to exclude all subjects not in the original study (see Reference 26) was due to the fact that the model's power to detect risks is based on the number of events in the sample, not the number of subjects. The excluded subjects, who are relatively recent recruits with about four assessments on average, are unable to contribute events due to this abbreviated follow-up. Potential differences between included and excluded participants were assessed using standard parametric two-group comparisons. Included and excluded subjects compare favorably on distribution of sex, family history, APOE-4, history of hypertension at baseline, and time between assessments (data not shown). Although the excluded subjects were slightly

older at baseline the effect size is small (Cohen's d = -0.05). Excluded subjects also have lower education (χ^2 = 8.8, 2 df, p = 0.01). That the excluded subjects are slightly older and less educated reflects that recruitment goals were changed in 2005 in order to enroll older participants with lower education, and all of the included subjects in the present model were recruited prior to 2005.

Grant Support

This research was partially funded with support from the following grants to the University of Kentucky's Center on Aging: R01 AG038651-01A1 and P30 AG028383 from the National Institute on Aging, as well as a grant to the University of Kentucky's Center for Clinical and Translational Science, UL1RR033173, from the National Center for Research Resources.

Table 2.1. Criteria for state classification

State	Definition
Normal cognition	No cognitive test score more than 1.5 standard deviations (SD) below the age-adjusted mean; absence of MCI_{CC} or Dementia (see below)
Test-based amnestic MCI ($aMCI_{TB}$)	At least one score more than 1.5 SD below the age-adjusted mean on the following measures of episodic memory: Wechsler Logical Memory, Benton Visual Retention Test (number correct or number of errors), a word list (Consortium to Establish a Registry in Alzheimer's Disease word list or California Verbal Learning Test), total learning score, delayed recall score, savings score, the maximum recalled minus delayed recall score
Test-based mixed MCI ($mMCI_{TB}$)	At least one score more than 1.5 SD below the age-adjusted mean on the following measures of language and executive function: phonemic or category verbal fluency, Boston Naming Test (15-item), Trail Making Tests A or B
Clinical consensus-based MCI (MCI_{CC})	A cognitive complaint by the subject or informant, or evidence for longitudinal decline on cognitive test performance (at least 1.5 SD decline); generally intact global cognition; no or minimal functional impairment; not demented by DSM-IV criteria; neurodegenerative etiology suspected
Dementia	Meets DSM-IV criteria for dementia; or NINCDS/ARDRA criteria for possible or probable AD; or NINDS-AIREN criteria for possible or probable vascular dementia; or DLB Consortium criteria for Lewy body disease

Table 2.2. BRAiNS subject characteristics (n = 554)

Characteristic	Summary
Age at entry, y (mean ± SD)	72.7 ± 7.8
Female, %	64.3
Family history of dementia, %	41.3
At least one APOE-4 allele, %	30.0
> 12 years of education, %	88.1
History of hypertension at entry, %	36.6
Hypertension treated with medication, %	86.5
Number of assessments (mean ± SD)	10.8 ± 4.5
Time between assessments, y (mean ± SD)	1.1 ± 0.4

Table 2.3. One-step transition matrix (number of assessments [% of prior visit state])

	Current visit					
Prior visit	Normal	Amnestic MCI_{TB}	Mixed MCI_{TB}	Clinical Consensus MCI	Dementia	Death
Normal	2192	478	385	34	19	100
	(68.3)	(14.9)	(12.0)	(1.1)	(0.6)	(3.1)
Amnestic MCI_{TB}	448	148	108	23	10	18
	(59.3)	(19.6)	(14.3)	(3.1)	(1.3)	(2.4)
Mixed MCI_{TB}	341	88	453	47	27	79
	(33.0)	(8.5)	(43.8)	(4.5)	(2.6)	(7.6)
Clinical Consensus MCI				101	34	16
				(66.9)	(22.5)	(10.6)

Table 2.4. Estimated odds ratios and 95% confidence intervals for one-step transitions to test-based amnestic MCI ($aMCI_{TB}$), test-based mixed MCI ($mMCI_{TB}$), or clinical consensus MCI (MCI_{CC}) versus the base state of normal cognition (bolding denotes statistical significance).

Risk factor*	**$aMCI_{TB}$ vs. Normal**	**$mMCI_{TB}$ vs. Normal**	**MCI_{CC} vs. Normal**
Age	**1.02 (1.01 – 1.04)**	1.07 (1.05 – 1.08)	**1.12 (1.09 – 1.15)**
Female sex (vs. male)	**0.77 (0.62 – 0.95)**	1.01 (0.82 – 1.24)	0.71 (0.46 – 1.09)
Family history of dementia (yes vs. no)	0.81 (0.65 – 1.00)	**0.76 (0.62 – 0.94)**	1.04 (0.66 – 1.64)
≥ one APOE-4 allele (vs. none)	1.04 (0.83 – 1.31)	1.12 (0.89 – 1.40)	**1.89 (1.21 – 2.95)**
≤12 years of education (vs. >12 years)	1.24 (0.89 – 1.74)	1.79 (1.33 – 2.42)	**2.20 (1.24 – 3.91)**
History of hypertension (yes vs. no)	0.95 (0.76 – 1.18)	1.04 (0.84 – 1.28)	0.79 (0.42 – 1.49)
$aMCI_{TB}$ at prior assessment (vs. normal)	1.15 (0.91 – 1.45)	1.00 (0.77 – 1.29)	**2.28 (1.30 – 4.00)**
$mMCI_{TB}$ at prior assessment (vs. normal)	0.76 (0.57 – 1.02)	**4.51 (3.63 – 5.61)**	**4.80 (2.94 – 7.81)**

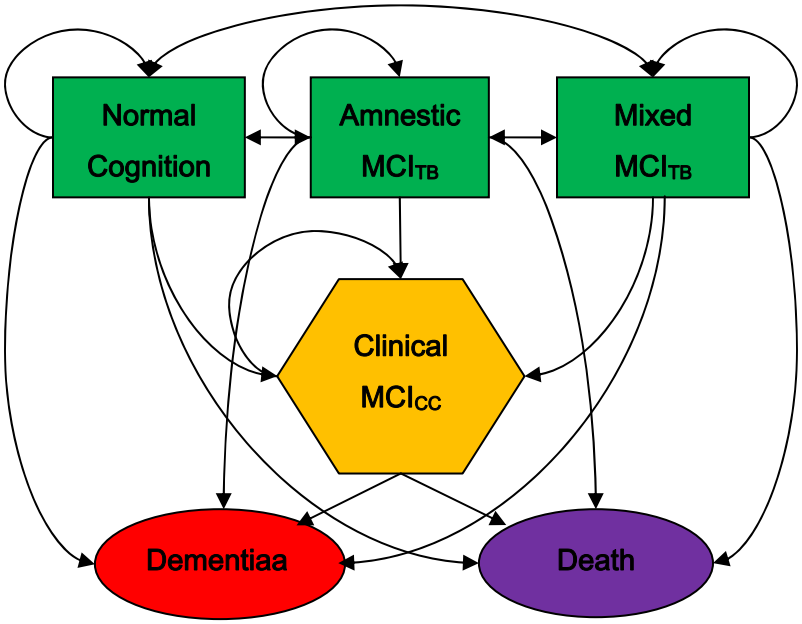
*As risk factors do not depend on the prior state, covariate effects are the same regardless of whether transitions occur from a prior state of normal cognition, $aMCI_{TB}$, or $mMCI_{TB}$.

Table 2.5. Estimated odds ratios and 95% confidence intervals for one-step transitions to dementia or death without dementia versus the base state of normal cognition or clinical consensus MCI (MCI_{CC}) (bolding denotes statistical significance).

Risk factors* (Normal is base state; no history of MCI_{cc})	**Dementia vs. Normal**	**Death vs. Normal**
Age	**1.19 (1.14 – 1.24)**	**1.18 (1.15 – 1.21)**
Female sex (vs. male)	1.87 (0.95 – 3.68)	**0.68 (0.49 – 0.95)**
Family history of dementia (yes vs. no)	1.66 (0.92 – 3.01)	0.82 (0.57 – 1.17)
≥ one APOE-4 allele (vs. none)	**2.33 (1.28 – 4.23)**	0.97 (0.67 – 1.42)
≤12 years of education (vs. >12 years)	0.75 (0.26 – 2.18)	1.33 (0.80 – 2.22)
History of hypertension (yes vs. no)	0.79 (0.42 – 1.49)	**1.49 (1.07 – 2.08)**
$aMCI_{TB}$ at prior assessment (vs. normal)	1.85 (0.82 – 4.21)	0.64 (0.38 – 1.08)
$mMCI_{TB}$ at prior assessment (vs. normal)	**4.90 (2.58 – 9.30)**	**2.67 (1.88 – 3.79)**
Risk factors (MCI_{CC} is base state)	**Dementia vs. MCI_{CC}**	**Death vs. MCI_{CC}**
Age	1.05 (0.98 – 1.13)	1.03 (0.94 – 1.13)
Female sex (vs. male)	1.75 (0.67 – 4.56)	1.15 (0.65 – 3.76)
Family history of dementia (yes vs. no)	2.88 (0.95 – 8.72)	0.68 (0.15 – 3.03)
≥ one APOE-4 allele (vs. none)	0.69 (0.22 – 2.16)	2.33 (0.61 – 8.90)
≤12 years of education (vs. >12 years)	0.97 (0.27 – 3.46)	0.55 (0.10 – 2.99)
History of hypertension (yes vs. no)	**0.30 (0.10 – 0.93)**	0.70 (0.20 – 2.47)

*As risk factors depend only on the base state, covariate effects are in the top half of the table are the same whether transitions occur from a prior state of normal cognition, $aMCI_{TB}$, or $mMCI_{TB}$.

Figure 2.1. Flow diagram of transitions possible between subject visits. Normal cognition is the base state for transitions made from normal cognition, test-based amnestic MCI, and test-based mixed MCI; clinical MCI is the base state otherwise.



CHAPTER THREE

Self-reported head injury and risk of cognitive impairment and Alzheimer's-type pathology in a longitudinal study of aging and dementia

Abstract

Longitudinal studies of premorbid head injury and Alzheimer's-type (AD) clinical dementia to date have been largely limited to antemortem clinical data. In the current study, clinical and neuropathological data from participants in a longitudinal study of aging and cognition (N = 649) were evaluated for the long-term clinical effects of self-reported head injury using a multi-state Markov chain, a statistical model capable of handling intervening cognitive states between normal cognition and dementia, as well as competing risks for dementia (i.e., death without dementia and dropout without dementia). The effect of self-reported head injury on clinical state depends on age at assessment: for a one-year increase in age, the OR for transition to clinically diagnosed Mild Cognitive Impairment (MCI_{CC}) for participants with a history of head injury is 1.21 (95% CI: 1.15 – 3.56). Similarly, for a one-year increase in age, the OR for transition from MCI_{CC} to dementia for participants with head injury history is 1.34 (95% CI: 1.11 – 1.61). We also find that self-reported head injury, without respect to age at assessment, is a significant risk for transition from a clinically unimpaired state to death ($\widehat{OR}$ = 1.54, 95% CI: 1.12 – 2.13). These results support prior work identifying earlier onset and increased risk of cognitive impairment with head injury as well as increased risk of mortality associated with a history of head injury. Since over one-third of the cohort has come to autopsy (n = 238), we examined plaque and tangle counts from the neocortical

and medial temporal areas to determine whether a history of head injury is associated with increased AD-type pathological burden. The odds of having AD pathology sufficient for an AD diagnosis is significantly increased for men with a history of head injury ($\widehat{OR}$= 1.47, 95% CI: 1.03 – 2.09) but not for women ($\widehat{OR}$= 1.18, 95% CI: 0.83 – 1.68), and MANCOVA shows that men with head injury by history have significantly higher mean diffuse and neuritic plaque counts in the neocortex and entorhinal cortex compared to men without.

Introduction

The factors that contribute to late-onset Alzheimer's disease (AD) are at present incompletely understood, but the evidence strongly suggests they include genetics.[67] Apolipoprotein-E (APOE) ε4 alters beta-amyloid deposition in the brain such that even a single copy dramatically increases the risk of AD. AD commonly occurs, however, in individuals without the ε4 allele. A meta-analysis of AD study populations reports an estimated 41% of AD cases (range 23-64%) are APOE-ε4 negative.[68] Further, genetic risks may be modified by environmental factors. Non-genetic risk factors that have been reported include, but are not limited to, head trauma,[69-71] cardiovascular disease and related risk factors,[72] and education.[73,74] These risk factors suggest possible therapeutic or preventive strategies.

Since the first investigation into the association between head injury and dementia,[75] the literature has been limited from the standpoint that none of the epidemiological studies of head injury and AD-type clinical dementia have used autopsy-confirmed diagnosis of AD or examined neuropathological data. This is significant because an estimated 20-30% of cases clinically diagnosed with AD have dementia due

to another cause,[76] and conversely, approximately 80% of individuals neuropathologically diagnosed with AD also have additional pathologies.[77] The purpose of the current study is to re-examine the association between self-reported head injury, risk of clinical dementia, and AD pathology using data from participants with detailed longitudinal cognitive assessments, as well as a subset of participants with textured neuropathologic data, and statistical tools capable of handling competing dementia risks.

Background

Autopsy-based studies of head trauma have reported increases in the number of beta-amyloid precursor protein (βAPP) positive neurons in cases of isolated severe head injury compared to age-matched controls.[78] Long-term increases in tau and beta-amyloid pathology have been noted in patients with a history of a single head injury sustained between 1 and 47 years prior to death.[79] Both acute and chronic axonal injury, including accumulation of proteins associated with neurodegenerative disease, has been observed in individuals with a history of head injury.[80-82] However, the etiological links have not been solidly established in terms of how the brain trauma manifests neuropathologically.

Studies of chronic traumatic encephalopathy (CTE) have involved autopsy series.[83] CTE implies a history of repeated brain injury and is a progressive illness characterized by deficits in motor skills, cognition, and increased psychiatric symptoms such as depression, irritability, and aggression.[84] CTE pathology is marked by increased tau pathology, and in some cases, TAR DNA-binding protein 43[83] with or without diffuse beta-amyloid deposits.[85] Thus, CTE has both clinical and neuropathological overlap with AD, but the two are also distinct diseases in terms of the severity, anatomical distribution, and other manifestations of brain pathology.

Epidemiological studies have yielded conflicting evidence. A meta-analysis of 15 case-control studies found that although there was an overall increased odds of AD for those with a history of head injury with loss of consciousness (LOC) prior to the onset of AD (pooled odds ratio [$\widehat{OR}$] = 1.58 [95% CI: 1.21-2.06]), the odds of AD was increased for men ($\widehat{OR}$ = 2.29 [95% CI: 1.47-3.58]) but not for women ($\widehat{OR}$ = 0.91 [95% CI: 0.56-1.47]).[69] However, the severity of these injuries was not considered in the meta-analysis, and AD diagnosis was not autopsy-confirmed. Again, the imperfect concordance between clinical and pathological diagnoses may play a significant role. For example, in the case of diabetes and AD, studies that rely only on a clinical diagnosis of AD have reported findings largely opposite from those that consider the pathological diagnosis.[67]

Results from cohort studies have also been inconsistent (Table 3.1). Two large, prospective studies—The Rotterdam Study[86] and The Adult Changes in Thought Study[87]—found no increased risk of dementia or AD associated with past head injury. Data from the smaller Betula study, by contrast, did reveal an increased AD risk for those participants with self-reported mild head injury but only for APOE-ε4 carriers.[88]

Retrospective cohort studies have tended to report that head injury is an independent risk factor for AD or decreases time to dementia onset. Plassman *et al.* (2000) reviewed military medical records and compared men with a history of closed head injury to those with an unrelated condition.[70] Dementia, and AD specifically, was associated with both moderate and severe, but not mild, injury. Retrospective review of medical records from Olmsted County, Minnesota residents who were treated for head trauma and were over age 40 years at the time of their last medical assessment showed no increased risk of AD or all-cause dementia.[89] When time to onset was used as the

outcome, however, persons with head trauma developed AD a median eight years earlier than expected when compared to the age-based incidence of AD in the total county population.[90] Similarly, a prospective cohort study of Manhattan residents found that after five years of follow-up, history of head injury with LOC within the preceding 30 years was associated with earlier onset of AD, and the effect was stronger for those reporting a LOC of at least five minutes.[71]

Methods

Subjects

Subjects of this study are volunteers from Biologically Resilient Adults in Neurological Studies (BRAiNS) at the University of Kentucky's Alzheimer's Disease Center, a longitudinal cohort of over 1,100 individuals established in 1989 with ongoing recruitment.[40] The cohort comprises a convenience sample of older adults (age $\geq$ 60 years) from central Kentucky. Exclusion criteria for the BRAiNS cohort include prevalent neurological, psychiatric, and disabling medical disorders, as well as prevalent dementing illness (see Reference 40 for a detailed listing and explanation of recruitment and procedures). Subjects included in the current analysis (n = 649) were enrolled between 1989 and 2004, evaluated at least two times, and had APOE genotyping available. Participants are given annual cognitive and clinical assessments and donate their brains upon death. Participants who died and came to autopsy in the current study were included in a subset analysis. Of these, 17 cases were excluded because quantitative neuropathology data were unavailable. An additional 15 were excluded due to the presence of diffuse Lewy body disease, leaving 238/270 for study. All enrollees were cognitively normal at study entry, and all research activities were approved by the

University of Kentucky Institutional Review Board. Each participant provided written informed consent.

Statistical Analysis

Multistate Markov Chain

To test the hypothesis that self-reported history of head injury promotes transition to impaired cognition, a multistate Markov chain was fit to the data. Multistate Markov chains are attractive for modeling cognitive decline,[26,27,30,31,41,91] and they allow for the inclusion of competing risks for the outcome of interest (all-cause dementia) as participants who die or drop out before dementia onset may bias analyses.[92,93]

Participants were classified into states at each assessment: (1) normal cognition, (2) test-based amnestic mild cognitive impairment ($aMCI_{TB}$), (3) test-based mixed MCI ($mMCI_{TB}$), (4) clinical consensus-based MCI (MCI_{CC}), (5) dementia (all-cause), (6) drop-out without dementia, and (7) death without dementia. The classification method has been described in detail previously.[26,91] Briefly, normal cognition represents the absence of any impairments on testing as well as the absence of any clinical diagnosis of MCI or dementia; test-based MCI indicates at least one observed score of at least 1.5 standard deviations below the expected score for age based on the performance of the entire normal cohort at baseline on tests of episodic memory ($aMCI_{TB}$) or language and executive function ($mMCI_{TB}$); clinical consensus-based MCI (MCI_{CC}) indicates a diagnosis of MCI based on criteria used by the National Alzheimer's Coordinating Center's Uniform Data Set;[24] and dementia indicates a clinical diagnosis of dementia based on DSM-IV criteria.

A multistate Markov chain with four transient states (normal cognition, $aMCI_{TB}$, $mMCI_{TB}$, and MCI_{CC}) and three absorbing states (death, dementia, and drop-out) was used (Figure 1). An individual may move freely among the transient states, but once an absorbing state is reached that individual's follow-up ends for the purposes of the analysis; here records are truncated at the date of diagnosis. The model estimates the log-odds of a one-step transition between any two adjacent assessments, here called the 'prior state' and the 'current state,' versus remaining in or returning to a 'base state' with a series of four polytomous logistic regression models (i.e., one model for each transient state).

To account for within-subject correlation, random intercepts were included in the model as described in Abner *et al.* (2012)[91] via PROC NLMIXED in SAS/STAT 9.3®.[48] Observed transitions are assumed to have occurred on the date of diagnosis, and the model ignores any transitions among the transient states between regularly scheduled assessments. A modified backwards selection procedure was used to fit the model (see Appendix A). Predictor variables stayed in the model only if they significantly affected any one-step transition probability.

Risk Factors

Presence or absence of a history of head injury was derived from participant responses to the intake interview questions, "Have you ever been knocked unconscious? If yes, how long were you unconscious, when did it happen, and how did it happen?" Participants who reported LOC of any duration, as well as participants who reported a diagnosis of concussion without LOC, were coded as positive for history of head injury. Where head injury was reported, approximate age at injury, LOC duration (< 5', ≥ 5'),

and external cause of the injury were recorded. Participants who described their LOC as "a few moments," "a few minutes," "momentarily," or whose LOC duration was not described (n = 6) were coded as < 5'.

Additional injury data were derived from interviews conducted longitudinally by study clinicians. Thus, head injury was treated as a time-varying factor. Two-way interactions between head injury and sex as well as age were tested for inclusion in the model.[95] A two-way interaction between head injury and APOE-ε4 could be not evaluated due to sample size limitations.

Other risk factors of interest include age at assessment (centered at 79 years), sex, education (≤ 12 years, >12 years), APOE-ε4 carrier status (at least one ε4 allele vs. no ε4 alleles), family history of dementia (first-degree relatives only), baseline hypertension (self-report), and baseline smoking history (never, 0 – 10 pack-years, 10 – 20 pack-years, 20+ pack-years).

Generalized Linear Regression

Multivariate analysis of covariance (MANCOVA) was used to test the hypothesis that self-reported history of head injury leads to increased mean AD-type pathology in the neocortex and medial temporal lobe, both of which have been identified as sites with increased βAPP-positive neurons following head injury.[78,95] MANCOVAs estimating the effect of head injury on mean diffuse (DPs) and neuritic plaque counts (NPs) as well as mean neurofibrillary tangle counts (NFTs) in the neocortex (frontal, temporal, parietal, and occipital regions) and medial temporal lobe (entorhinal cortex, amygdala, hippocampus CA1, and subiculum) were fit using PROC GLM in SAS/STAT 9.3®. Logistic regression was used to test the hypothesis that head injury increases the odds of

AD-positive pathology. All models included age at death and indicators for APOE-ε4 status, male sex, presence of at least mild cerebral amyloid angiopathy (CAA) (which is associated with increased numbers of amyloid plaques), and whether clinical dementia was observed before death. Two-way interactions between head injury and age at death, APOE-ε4, and sex were also tested. Statistical significance for all analyses was set at $\alpha = 0.05$.

Pathological Assessments

AD-positive pathology refers to cases with Braak stage V or VI and with moderate or severely dense neuritic amyloid plaques according to CERAD criteria.[96] Neuropathological counting metrics and methods were exactly as described previously.[62,97]

Results

Clinical Data

Study participants contributed an average of 10.4 longitudinal assessments (median = 10 assessments, range = 2-22 assessments), with the average time between assessments at approximately 13 months (Table 3.2). During the study period, 386 (59.5%) participants transitioned to $aMCI_{TB}$ at least one time, 398 (61.3%) transitioned to $mMCI_{TB}$ at least one time, 129 (19.9%) transitioned to MCI_{CC}, 109 (16.8%) transitioned to dementia, 234 (36.1%) died without dementia, and 92 (14.2%) left the study without dementia.

The majority of transitions from $aMCI_{TB}$ are back to normal cognition at the next visit (57.6%), and only 3.7% are transitions to MCI_{CC} or dementia. Mixed MCI ($mMCI_{TB}$) appears more predictive of underlying disease with 45.7% remaining $mMCI_{TB}$

and 7.7% transitioning to MCI_{CC} or dementia at the next visit (Table 3.3). Participants who transitioned to dementia required an average of 10.4 ± 4.4 steps to do so (Table 3.4). The observed number of steps required for death without a dementia (9.8 ± 4.4) or dropout without a dementia (9.3 ± 4.5) underscores the importance of accounting for these competing events in modeling dementia risks.

Self-reported head injury occurred in one-quarter the sample (166/649, 25.6%). Men (83/234, 35.5%) reported a significantly higher proportion of head injury than women (83/415, 20.0%): $\chi^2 = 18.81$, 1 df, $p < 0.0001$). The majority of head injuries reported were listed as having occurred prior to the baseline assessment (156/166, 94.0%). In all but four cases, the head injury preceded the first diagnosis of dementia by at least 10 years. Most participants reported only a single instance of head injury, but some participants reported two (n = 15) or more (n = 3) instances. Men in this cohort tend to have reported injuries that result in LOC of at least five minutes more frequently than women (Table 3.5), though the difference is not statistically significant (31.3% vs. 21.7%: $\chi^2 = 1.98$, 1 df, $p = 0.16$). When the external cause of the injury (Table 3.5) is taken into account, however, men do have significantly increased odds of LOC of at least five minutes compared to women ($\widehat{OR} = 2.55$, 95% CI: 1.1 – 5.9).

The interaction between head injury and sex was not significant and was not retained (see Table 3.6 for final fitted model). Head injury, without respect to age, was a significant risk for the one-step transition from a transient state to death without dementia ($\widehat{OR} = 1.54$, 95% CI: 1.12 – 2.13). The interaction between head injury and age was significant for the one-step transitions from normal cognition, $aMCI_{TB}$, or $mMCI_{TB}$ to MCI_{CC} ($p = 0.017$) and the one-step transition from MCI_{CC} to dementia ($p = 0.0069$). For

a one-year increase in age, the $\widehat{OR}$ for transition from normal cognition, $aMCI_{TB}$, or $mMCI_{TB}$ to MCI_{CC} for participants with a history of head injury is 1.21 (95% CI: 1.15 – 3.56). Similarly, for a one-year increase in age, the $\widehat{OR}$ for transition from MCI_{CC} to dementia for participants with a history of head injury is 1.34 (95% CI: 1.11 – 1.61).

Multistate Markov model results may also be used to estimate the expected number of one-step transitions required to reach the absorbing states.[30] Table 3.7 shows the predicted number of one-step transitions a cognitively intact participant with a particular clinical profile would require before becoming demented or dying. Self-reported head injury, in the absence of other risk factors, decreases the time to an eventual dementia by roughly 6 months. The risk factors presented here decrease the time to dementia in an additive fashion, and it is important to note that in all cases the predicted number of transitions to death without dementia and dropout without dementia (data not shown) are significantly reduced compared to time to dementia, which again underscores the necessity of accounting for these competing risks.

Finally, two sensitivity analyses were conducted to assess the effect of (1) excluding participants whose head injuries occurred after baseline (n = 10) and (2) excluding participants whose head injuries occurred less than 10 years prior to their first diagnosis of clinical dementia (n = 4). All three models produced a similar fit (to two decimal places), and conclusions did not change.

Pathological Data

Of the 238 included participants, 70 (29.4%) reported a history of head injury (36 males [33% of autopsied men] and 34 females [26% of autopsied women]) (Table 3.8). The odds of having AD pathology sufficient for an AD diagnosis is significantly

increased for men with a history of head injury ($\widehat{OR}$= 1.47, 95% CI: 1.03 – 2.09) but not for women ($\widehat{OR}$= 1.18, 95% CI: 0.83 – 1.68).

In the neocortex, men with a history of head injury have higher mean parietal and occipital DPs, and all neocortical areas show more NPs, than men without ($p<0.05$; Figure 3.3). Women with a history of head injury do not have significantly higher neocortical DPs or NPs than women (or men) without head injury (Figure 3.3). Additional analyses were performed to determine if age at injury or source of injury mitigated the observed sex by head injury interaction; the conclusions did not change (data not shown). Mean neocortical NFTs were not associated with head injury history (data not shown).

Pathological burden in the medial temporal structures, except for the entorhinal cortex, was unaffected by history of head injury. Again, men who reported a history of head injury had significantly increased DPs (20.6 ± 2.3 vs. 13.4 ± 1.8, p = 0.0072) and NPs (3.8 ± 0.7 vs. 1.6 ± 0.6, p = 0.013) in the entorhinal cortex compared to men who did not. NFTs in the entorhinal cortex were unaffected (data not shown).

Discussion

Clinical and neuropathological data from participants in a longitudinal study of aging and cognition (N = 649) were analyzed to assess the effects of self-reported head injury. Our results support prior work identifying increased risk of cognitive impairment[97] and earlier onset of clinical dementia with head injury,[71,89] as well as increased risk of mortality associated with a history of head injury.[87] Although the six-month reduction in time to dementia onset we report is much less than the eight years in the Olmstead County study,[89] differences in study design, population, head injury case

definition, and clinical diagnosis could account for the discrepancy. We also found unexpected correlation between head injury, gender, and increased AD neuropathologic changes.

The effect of head injury on dementia risk may be modified not only by age at injury and severity of injury (or injuries) but also by other factors including gender and APOE-ε4 status.[94] We note that while a single injury of sufficient severity can increase the risk of manifesting clinical dementia, it does not necessarily follow that these events lead to the specific features of AD. In experimental studies (i.e., animal studies), however, evidence of long-term neurodegeneration was observed after a single head injury, and accelerated beta-amyloid peptide deposition and cognitive impairment was observed after repeated mild head injury.[98] Thus, animal models have provided hypothesized mechanistic links between head injury and AD, and autopsy-based case series of head injury have also suggested a link between head injury and AD-promoting and AD-type pathology.[79,82,99,100]

Detailed pathological data were available on over one-third of the study participants. History of self-reported head injury was associated with increased levels of amyloid plaque deposition in the neocortex and entorhinal cortex, as well as increased odds of AD pathology for men but not women, which supports prior clinical studies. Fleminger and colleagues (2003)[69] posited that women may be protected from the deleterious effects of head injury by the presence of female sex hormones. Indeed, the women who came to autopsy in the current study were more likely to report two instances of LOC (6/34 vs. 1/36, $p = 0.027$, Fisher's Exact test) and were more likely to have sustained a head injury after age 55 (16/34 vs. 7/36, $p = 0.030$, Fisher's Exact test).

If AD pathology were more affected by more recent or frequent LOC, it should follow that the women and not the men would have elevated plaque counts in association with exposure to head injury.

An alternative explanation is that male gender may be a proxy for severity, repetition, poor reporting, and particular mechanisms (e.g., contact sports) of brain injury. Men in our study tended to report injuries that led to LOC ≥ 5 minutes more often than women, which suggests that their injuries may have been more severe overall. Plassman and colleagues (2000) found increased risk of both all-cause dementia and AD for veterans with moderate and severe injuries but not mild injuries,[70] and Schofield and colleagues (1997) found an increased risk of AD for participants who reported head injuries with LOC ≥ 5 minutes but not for < 5 minutes.[71] Of the 36 autopsied men with a history of head injury, 13 (36%) reported sports and recreation as source of the injury, nine of which were identified as football or boxing. It may be that while the participant reported only one or two instances of head injury where LOC occurred, multiple instances of injury were actually experienced without LOC. Chronic effects of head injury may be due to lifetime cumulative exposure rather than an acute single event.[101] Recent data reveal an increased risk of AD for retired American football players, who are assumed to have been exposed to repeated blows to the head, relative to the general US population ($\widehat{SMR}$ = 3.29, 95% CI: 1.55 – 7.95).[102]

We note that for both genders, reported head trauma is usually quite remote even from study enrollment, in some cases occurring in infancy; however, these injuries could still affect the brain chronically.[79] In addition to the influence of recall bias implicit to the study design, we note that participants in the current study are highly educated compared

to their peers nationally, with 65.7% having at least a Bachelor's degree vs. 24.5% of those over age 60 years nationally.[103] If, as Moretti and colleagues (2012) suggest, cognitive reserve is the best predictor of cognitive outcome and decline following head injury[97], the participants in this study may have been less vulnerable to its effects.

As for the neuropathology, head injury severity occurs along a spectrum, and coding such injuries dichotomously obscures relevant information.[104] Recovery (and wound repair capacity of an individual) may also be graded on a continuum, and all these factors may influence the long-term sequelae of the injury.[104] Future studies of head injury as a risk for dementia and AD should consider collecting detailed data on severity, anatomical location, post-traumatic amnesia, and receipt of treatment if possible.

Despite the limitations inherent in the data, multiple studies have found that even a single reported occurrence of head injury is associated with increased risk of incident dementia years or decades later. Although such knowledge may not be useful to those individuals for whom head injury is not a modifiable risk factor (i.e., having already sustained one), it does underscore the necessity of taking proper precautions for those involved in professions and recreational activities where head injury is common.

Grant Support
This research was partially funded with support from the following grants to the University of Kentucky's Sanders-Brown Center on Aging: R01 AG038651, R01 AG019241, and P30 AG028383 from the National Institute on Aging, as well as a grant to the University of Kentucky's Center for Clinical and Translational Science, UL1TR000117, from the National Center for Advancing Translational Sciences.

Table 3.1. Summary of cohort studies of head injury and dementia

Study	Type*	N	Effect Estimate(s) for Dementia Risk	Exposure Assessment	Head Injury Prevalence	Limitations
Rotterdam Study (Mehta *et al.*, 1999)	P	6,645	$\widehat{RR}$ = 0.8, 95% CI: 0.4-1.9	Self-report to study physician	12.0%	2 years of follow-up, inclusion of younger adults (≤ 60 years), dx not autopsy-confirmed
Adult Changes in Thought (Dams-O'Connor *et al.*, 2012)	P	4,225	Age at injury <25: $\widehat{TR}$ = 1.02, 95% CI: 0.87-1.20 Age at injury 25-54: $\widehat{TR}$ = 1.04, 95% CI: 0.78-1.38 Age at injury 55+: $\widehat{TR}$ = 1.06, 95% CI: 0.81-1.39	Self-report via structured interview by study personnel	15.9%	Dx not autopsy-confirmed
Plassman *et al.* (2000)	R	1,776	Mild injury: $\widehat{HR}$ = 0.76 95% CI: 0.18-3.29 Moderate injury: $\widehat{HR}$ = 2.32, 95% CI: 1.04-5.17 Severe injury: $\widehat{HR}$ = 4.51, 95% CI: 1.77-11.47	Review of military medical records between 1944-1945	n/a	Head trauma sustained outside military service not accounted for, dx not autopsy confirmed
Williams *et al.* (1991) ; Nemetz *et al.* (1999)	R	1,283	$\widehat{SIR}$ = 1.2, 95% CI: 0.8-1.7; median onset shortened by 8 years (p = 0.0015)	Review of Mayo Clinic medical records for cases with traumatic brain injury diagnosed between 1935-1984	n/a	Head trauma not requiring hospital visit not captured, dx based on medical records not clinical interview, dx not autopsy- confirmed
Sundström *et al.* (2007)	P	543	Without APOE-ε4: $\widehat{OR}$ = 0.9 (95% CI: 0.4-1.8) With APOE-ε4: $\widehat{OR}$ = 5.2 (95% CI: 2.0-14.0)	Affirmative response to questionnaire item "have you ever suffered a head injury which required medical care?"	13.1%	Inclusion of younger adults (≤ 60 years), dx not autopsy-confirmed
WHICAP (Schofield *et al.*, 1997)	P	271	LOC <5 min: $\widehat{RR}$ = 1.7, 95% CI: 0.4-7.5 LOC ≥5 min: $\widehat{RR}$ = 11.2, 95% CI: 2.3-59.8	Self-report via structured risk factor interview at baseline and during a one-time physician interview	10.0%	Few participants with head injury in the sample (n = 27), dx not autopsy- confirmed

*P = prospective, R = retrospective

Table 3.2. Characteristics of included participants from the BRAiNS cohort (n = 649); participants were enrolled in the study between 1989 and 2004.

Characteristic	Summary
Age at entry, y (mean ± SD)	72.9 ± 7.4
Female, %	63.9
Family history of dementia, %	38.7
At least one APOE-4 allele, %	30.4
> 12 years of education, %	86.9
History of hypertension at entry, %	38.2
Smoking history at entry, %	
Never smoked	49.2
>0 – 10 pack-years	10.3
10 – 20 pack-years	8.3
More than 20 pack-years	32.2
History of head injury, %	25.6
Number of assessments (mean ± SD)	10.3 ± 4.7
Time between assessments, y (mean ± SD)	1.1 ± 0.3

Table 3.3. One-step transition matrix (number of assessments [% of prior visit state]); total subjects = 649

	Current state						
Prior state	Normal	Amnestic MCI_{TB}	Mixed MCI_{TB}	MCI_{CC}	Dementia	Dropout	Death
Normal	2634 (69.1)	524 (13.8)	464 (12.2)	40 (1.1)	15 (0.4)	33 (0.9)	101 (2.7)
Amnestic MCI_{TB}	497 (57.6)	172 (19.9)	129 (15.0)	23 (2.7)	9 (1.0)	13 (1.5)	20 (2.3)
Mixed MCI_{TB}	404 (30.7)	97 (7.4)	601 (45.7)	66 (5.0)	35 (2.7)	30 (2.3)	80 (6.2)
MCI_{CC}				154 (61.4)	50 (19.9)	16 (6.4)	31 (12.4)

Table 3.4. Mean number of assessments made given last observed state and history of head injury

	All Subjects (N = 649)		Head Injury (N = 166)		No Head Injury (N = 483)	
Last Observed State	**n**	**Assessments (mean ± SD)**	**n**	**Assessments (mean ± SD)**	**n**	**Assessments (mean ± SD)**
Normal	139	12.2 ± 4.0	28	12.8 ± 4.6	111	12.1 ± 3.9
Amnestic MCI_{TB}	7	12.3 ± 3.0	2	11.5 ± 0.7	5	12.6 ± 3.6
Mixed MCI_{TB}	36	12.3 ± 5.2	7	10.4 ± 4.0	29	12.7 ± 5.4
MCI_{CC}	32	12.2 ± 4.0	9	14.3 ± 4.9	23	11.3 ± 3.4
Dementia	109	10.4 ± 4.4	27	10.1 ± 4.8	82	10.5 ± 4.3
Dropout without dementia	92	9.3 ± 4.5	21	9.4 ± 4.7	71	9.3 ± 4.5
Death without dementia	234	9.8 ± 4.4	72	9.7 ± 4.1	162	9.8 ± 4.5

Table 3.5. Reported sources of head injury by gender and loss of consciousness (LOC)*

Source	Men		Women		Total	
	LOC < 5’	LOC ≥ 5’	LOC < 5’	LOC ≥ 5’	LOC < 5’	LOC ≥ 5’
Sports and recreation	22	7	9	2	31	9
Automobile accident	9	10	22	8	31	18
Fall	7	5	15	7	22	12
Interpersonal violence	5	2	2	0	7	2
Other blow to the head**	8	2	7	0	15	2
Not described	8	1	12	2	20	3

*Cell entries reflect number of unique participants reporting the source; **e.g., being struck by falling objects, striking head on ceilings or walls

Table 3.6. Multistate Markov chain results for risk factors affecting transitions from transient states (T: normal cognition, $aMCI_{TB}$, or $mMCI_{TB}$)

Parameter	Risk Comparison	Odds Ratio	95% Confidence Interval	p
T → $aMCI_{TB}$				
Age	1-year difference	1.03	1.02-1.04	<0.0001
Sex	Female vs. Male	0.79	0.66-0.93	0.0056
Prior = $aMCI_{TB}$	$aMCI_{TB}$ vs. Normal	1.27	1.03-1.58	0.0277
Prior = $mMCI_{TB}$	$mMCI_{TB}$ vs. Normal	0.77	0.59-1.01	0.0561
T → $mMCI_{TB}$				
Age	1-year difference	1.07	1.06-1.09	<0.0001
Education	≤ 12 years vs. > 12 years	1.70	1.38-2.10	<0.0001
Prior = $aMCI_{TB}$	$aMCI_{TB}$ vs. Normal	1.06	0.84-1.34	0.6473
Prior = $mMCI_{TB}$	$mMCI_{TB}$ vs. Normal	4.78	3.93-5.81	<0.0001
T → MCI_{CC}				
Family History	Present vs. Absent	1.42	1.11-1.83	0.0063
APOE-ε4	Present vs. Absent	1.85	1.27-2.69	0.0014
Age*Head Injury	1-year difference in age when head injury is present	1.21	1.15-3.56	0.0173
Prior = $aMCI_{TB}$	$aMCI_{TB}$ vs. Normal	2.20	1.29-3.75	0.0038
Prior = $mMCI_{TB}$	$mMCI_{TB}$ vs. Normal	5.86	3.81-9.00	<0.0001
T → Dementia				
Age	1-year difference	1.18	1.13-1.23	<0.0001
APOE-ε4	Present vs. Absent	2.58	1.52-4.38	0.0005
Prior = $aMCI_{TB}$	$aMCI_{TB}$ vs. Normal	2.24	0.97-5.17	0.0596
Prior = $mMCI_{TB}$	$mMCI_{TB}$ vs. Normal	7.65	4.08-14.34	<0.0001
T → Death				
Age	1-year difference	1.19	1.16-1.22	<0.0001
<1 – 10 pack-years	<1 – 10 pack-years vs. Never smoked	1.16	0.68-1.96	0.5914
10 – 20 pack-years	10 – 20 pack-years vs. Never smoked	1.20	0.65-2.22	0.5566
≥20 pack-years	≥20 pack-years vs. Never smoked	2.05	1.49-2.83	<0.001
Hypertension	Present vs. Absent	1.46	1.08-1.96	0.0133
Head Injury	Present vs. Absent	1.54	1.12-2.13	0.0089
Prior = $aMCI_{TB}$	$aMCI_{TB}$ vs. Normal	0.72	0.43-1.19	0.1980
Prior = $mMCI_{TB}$	$mMCI_{TB}$ vs. Normal	2.60	1.85-3.64	<0.0001
T → Dropout				
Age	1-year difference	1.06	1.02-1.09	0.0008
Hypertension	Present vs. Absent	1.90	1.20-3.00	0.0060
Prior = $aMCI_{TB}$	$aMCI_{TB}$ vs. Normal	1.49	0.77-2.89	0.2324
Prior = $mMCI_{TB}$	$mMCI_{TB}$ vs. Normal	1.98	1.77-2.22	<0.0001

Table 3.6 Continued

Parameter	Risk Comparison	Odds Ratio	95% Confidence Interval	p
MCI_{CC} → Dementia				
<1 – 10 pack-years	<1 – 10 pack-years vs. Never smoked	0.28	0.08-0.94	0.0388
10 – 20 pack-years	10 – 20 pack-years vs. Never smoked	0.27	0.07-1.09	0.0654
≥20 pack-years	≥20 pack-years vs. Never smoked	0.31	0.13-0.71	0.0054
Age*Head Injury	1-year difference in age when head injury is present	1.34	1.11-1.61	0.0069
MCI_{CC} → Death				
Age	1-year difference	1.12	1.04-1.20	0.0023

Table 3.7. Head injury appears to lead at-risk individuals to transition into a dementia state faster than individuals without history of head injury. Shown are the average numbers of visits required for eventual transitions from cognitively normal to the absorbing states of dementia or death.

Age	Risk Factor Profile	Dementia	Death
65	None	13.8	3.3
	APOE-ε4 only	12.6	2.9
	Head injury only	13.3	3.1
	APOE-ε4 + Head injury	12.4	2.8
	APOE- ε4 + Head injury + Hx HTN + Hx ≥ 20 pack-years smoking	10.4	2.3
85	None	4.0	1.1
	APOE-ε4 only	3.5	0.9
	Head injury only	3.4	0.9
	APOE-ε4 + Head injury	3.0	0.7
	APOE- ε4 + Head injury + Hx HTN + Hx ≥ 20 pack-years smoking	2.4	0.5

Table 3.8. Characteristics of autopsied participants from the BRAiNS cohort by gender and history of lifetime head injury (n = 238)

Sex	Head Injury	N	Final MMSE*	Age at death*	APOE-ε4+	CAA+
Men	Yes	36	26.4 ± 4.5	84.4 ± 6.9	22.2%	63.9%
	No	61	25.8 ± 4.3	86.9 ± 7.0	39.3%	54.1%
Women	Yes	34	27.5 ± 3.5	86.0 ± 8.0	20.6%	48.4%
	No	107	24.4 ± 7.7	87.1 ± 7.5	28.0%	52.3%

*Results presented are mean ± SD

Figure 3.1. Participant flow diagram

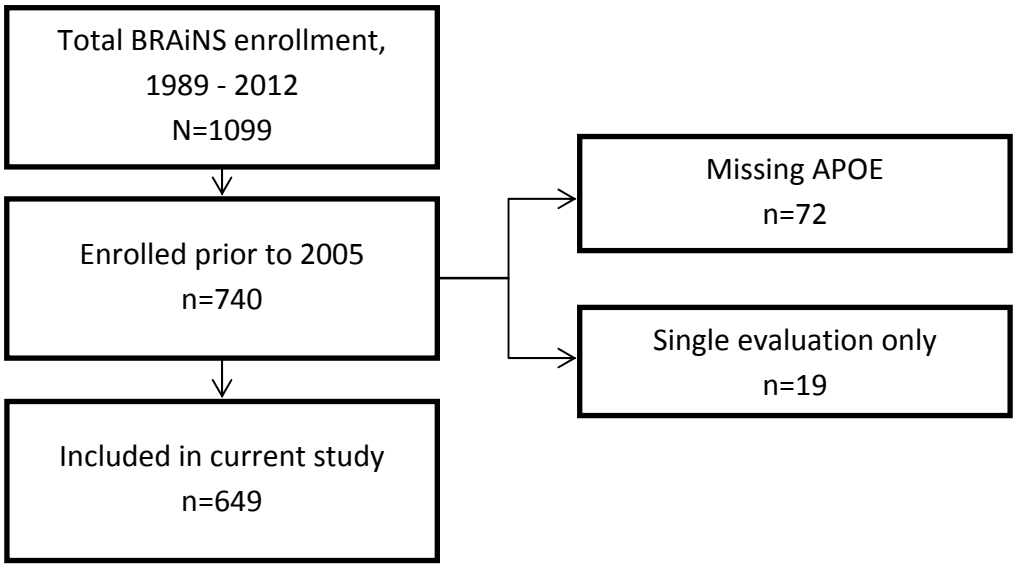


Figure 3.2. Flow diagram of transitions possible between subject visits. Normal cognition is the base state for transitions made from normal cognition, test-based amnestic MCI, and test-based mixed MCI; clinical MCI is the base state otherwise.

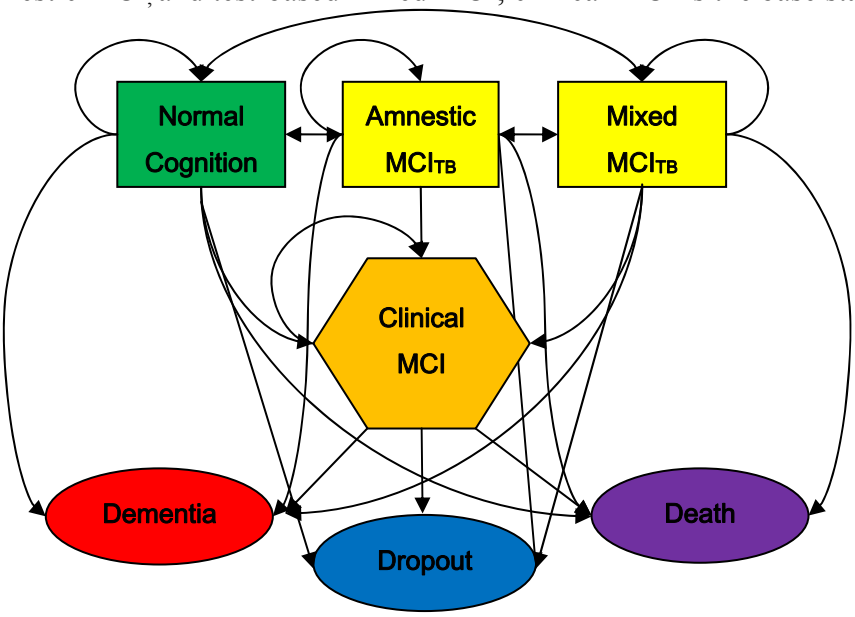
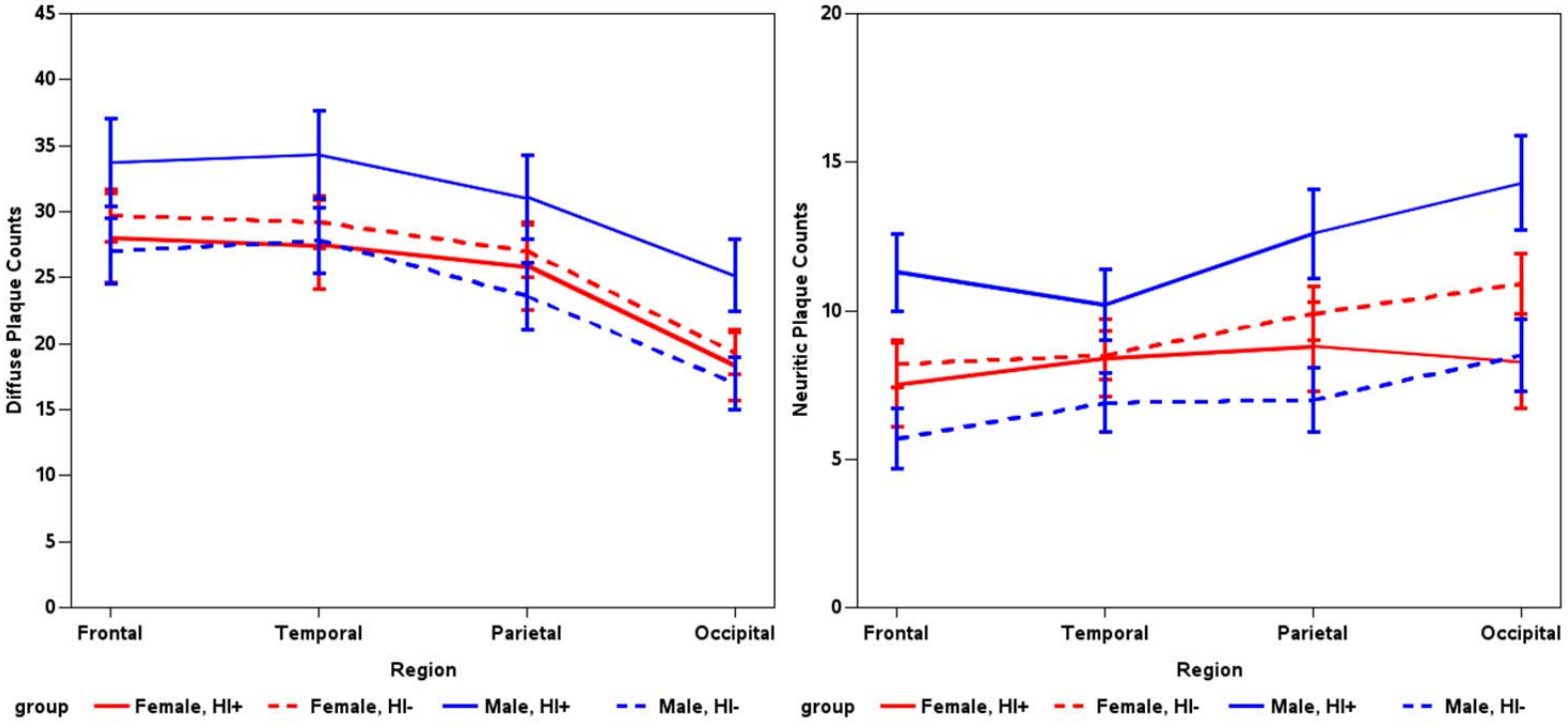


Figure 3.3. Estimated mean number of diffuse and neuritic neocortical plaque counts by region; whiskers are SEM (n = 238). The final MANCOVA models included main effects for age at death, clinical dementia status, APOE-ε4, CAA, and an interaction term and main effects for head injury (HI) and male gender.



CHAPTER FOUR

Incorporating prior-state dependence among random effects and beta coefficients improves multistate Markov chain model fit: Application to the Biologically Resilient Adults in Neurological Studies cohort

Abstract

Identifying risk factors that promote specific transitions, perhaps especially back transitions, is desirable because they might suggest avenues for intervention. However, it is important to establish that such risk factors are not an artifact of methodology or misclassification. The current study represents the first portion of a larger project investigating the nature of back transitions, which occur when an individual moves from a more cognitively impaired state to a less cognitively impaired state. Longitudinal clinical data from 649 participants in the BRAiNS cohort were used to investigate the scaling of subject-specific random effects based on the prior observed state as described in Song *et al.* (2011), who used data from the Einstein Aging Study (EAS), which has more subjects than the BRAiNS dataset but less follow-up per subject. Where the 833 EAS subjects contributed 2,152 transitions, the 649 BRAiNS subjects contributed 6,240 transitions. We evaluated four multistate Markov chain models –two models specified the effect of age as dependent on the prior state and two models included prior-state dependent scaling parameters—in order to investigate the influence of model architecture on model fit and parameter estimation. Both strategies improved fit as determined by likelihood ratio tests, although at a cost of extra parameters, which is a concern for models that already tend to have a high number of parameters that must be estimated as

more parameters require more data. Finally, this study provides evidence that the magnitude of the effect of age on study outcomes, like dropout, changes as clinical status changes. While increasing age does not appear to lead cognitively normal individuals to discontinue their study participation, increasing age does promote dropout among participants with non-amnestic memory impairments. For these participants, a one-year increase in age produces an odds ratio for dropping out of 1.08 (95% CI: 1.03-1.14).

Introduction

Alzheimer's disease (AD) is thought to follow a chronic disease course with a lengthy preclinical phase that begins years before the onset of observable clinical symptoms.[105] This preclinical phase is followed by a period of clinically detectable but relatively subtle cognitive impairment that is unaccompanied by functional impairment termed mild cognitive impairment (MCI) that typically lasts for several years.[31] Evaluation of risk factors for incident AD then, as well as estimation of disease progression rates through and/or including MCI, require a period of observation also lasting many years. Prospective cohort designs with multiple annual or biennial evaluations are a natural choice for such studies.

While the course of AD is a continuous process, it is observed discretely over the study period. At each study visit a participant may be classified by where he or she falls along the continuum—for example, as cognitively normal, MCI, or demented. Multistate Markov chains (see Table 1 for definition of terms) are useful for modeling the movement of participants through transient states (normal cognition and forms of MCI) to absorbing states (dementia or death)[26,27,30,31,91] and can identify risk factors for each

specific one-step transition defined in the data (see Figure 4.1). A first-order Markov chain estimates the probability of transition between clinical states at any two temporally adjacent assessments, here called the "prior state" and the "current state," versus remaining in or returning to a "base state." States may be either transient, where movement out of the state is permitted, or absorbing, where no further movement is permitted once a subject has entered the state.

In addition to allowing for non-linear trajectories, analysis of longitudinal clinical data generally requires some method of addressing within-subject correlation among observations arising from the same subject. A normally distributed shared random effect (i.e., all observations from the same participant share a common random effect) due to Salazar *et al.* (2007)[27] was used in prior applications of the multistate Markov chain to data from the Biologically Resilient Adults in Neurological Studies (BRAiNS) cohort.[91]

It has been observed, however, that the inclusion of this shared random effect does not appreciably improve the fit of the model over a fixed effects only model.[31] Song and colleagues (2011) proposed including prior state-dependent scaling parameters with the shared random effect to adjust for the variance of the random effects given the last observed state.[31] Their model comprised four states: transient states normal cognition and memory impairment and absorbing states dementia and death. The purpose of this investigation is to evaluate the effect prior state-dependence—implemented through the scaling parameter and through specification of the effect of age as prior-state dependent—on model fit and parameter estimation when applied to the BRAiNS data.

Methods

Subjects

Subjects in this study are drawn from research volunteers in the BRAiNS cohort at the University of Kentucky's Alzheimer's Disease Center, a longitudinal cohort of approximately 1,100 individuals at least 60 years of age at study entry, established in 1989 with ongoing recruitment.[40] Exclusion criteria for the BRAiNS cohort include prevalent neurological disorders, psychiatric disorders, disabling medical disorders, and prevalent dementing illness (see Reference 40 for a detailed listing). Subjects included in the current analysis (n = 649) were all enrolled between 1989 and 2004, were evaluated at least two times, and had APOE genotyping available. Participants are given detailed annual cognitive and clinical assessments and donate their brains upon death. Annual assessments have been described in detail previously.[40] All enrollees were clinically cognitively normal at study entry, and all research activities were approved by the University of Kentucky Institutional Review Board. Each participant provided written informed consent.

States

Participants were classified into states at each assessment: (1) normal cognition, (2) test-based amnestic mild cognitive impairment ($aMCI_{TB}$), (3) test-based mixed MCI ($mMCI_{TB}$), (4) clinical consensus-based MCI (MCI_{CC}), (5) dementia (all-cause), (6) drop-out without dementia, and (7) death without dementia. The classification method has been described in detail previously.[26,91] Briefly, normal cognition represents the absence of any impairments on testing as well as the absence of any clinical diagnosis of MCI or dementia; amnestic and mixed MCI are neuropsychological test-based and indicate at least one observed component score of at least 1.5 standard deviations below the expected score for age based on the performance of those members of the cohort assessed

as cognitively normal at baseline on tests of episodic memory (amnestic MCI) or language and executive function (mixed MCI)—mixed MCI supersedes amnestic MCI; clinical consensus-based MCI indicates a medical diagnosis of MCI based on criteria used by the National Alzheimer's Coordinating Center's Uniform Data Set;[24] and dementia indicates a clinical diagnosis of dementia based on Diagnostic and Statistical Manual-IV (DSM-IV) criteria.[1] In this cohort, back transitions from clinical MCI to normal cognition or test-based MCI were small in number (n = 19) and were judged to be the result of medical conditions (which preclude the diagnosis of clinical MCI based on our operational definition) or diagnostic misclassification. Such events were coded as described in Abner *et al.* (2012).[91]

Model

Let $\mathbf{Y_i} = (y_{it_1}, \ldots, y_{it_{n_i}})$ be the vector representing the observed states (see Figure 4.1) for the i^{th} subject at the t_{n_i} ordered assessments. Assuming the Markov property holds, we find the joint distribution of this vector by conditioning on y_{i1}: $f(\mathbf{y}_i|y_{i1}) = f(y_{i2}|y_{i1}) f(y_{i3}|y_{i1}, y_{i2}) \cdots f(y_{it_{ni}}|y_{i1}, y_{i2}, \ldots, y_{it_{ni-1}})$, which can be simplified as $f(\mathbf{y}_i|y_{i1}) = f(y_{i2}|y_{i1}) f(y_{i3}|y_{i2}) \cdots f(y_{it_{ni}}|y_{it_{ni-1}})$. Each term in the product is a one-step transition probability of moving from state *s*, the prior state, to state *v*, the current state. To simplify notation we define this probability, p_{sv}, as $f(y_{iv}|y_{is}) = p_{y_{is},y_{iv}} = p_{sv}$.

The goal is to construct a model for these one-step transition probabilities, which may depend on covariates, some of which may be time-dependent, as well as random effects. To this end, let the prior state *s* be a transient state (i.e., normal [1], amnestic MCI [2], mixed MCI [3], or clinical MCI [4]) observed for subject i at the prior assessment and *v* be the state observed for subject i at the current assessment ($v = 1, .., 7$).

We assume the log-odds of transition may be modeled as

$$\log[p_{sv}(\boldsymbol{\theta}|\mathbf{x}_{iv}, \mathbf{u_i})/p_{s1}(\boldsymbol{\theta}|\mathbf{x}_{iv},\mathbf{u_i})] = \alpha_{sv} + \boldsymbol{\beta}_v^{\mathrm{T}}\mathbf{x}_{iv} + u_{i1}, \text{ if } s \in \{1, 2, 3\}, \text{ and}$$

$$\log[p_{4v}(\tilde{\boldsymbol{\theta}}|\mathbf{x}_{iv}, \mathbf{u_i})/p_{44}(\tilde{\boldsymbol{\theta}}|\mathbf{x}_{iv},\mathbf{u_i})] = \tilde{\alpha}_{4v} + \tilde{\boldsymbol{\beta}}_v^{\mathrm{T}}\mathbf{x}_{iv} + u_{i2}, \text{ if } s = 4 \text{ and } v \geq 4. \quad (1)$$

Here $\boldsymbol{\theta}$ is the vector of alpha intercepts and beta coefficients when normal (state 1) is the base state, $\tilde{\boldsymbol{\theta}}$ is the vector of alpha intercepts and beta coefficients when clinical MCI (state 4) is the base state, $\mathbf{x}_{iv}$ is the vector of covariates for the i^{th} subject observed at the current visit, and $\mathbf{u}_i = (u_{i1}, u_{i2})$ is the vector of random effects for the i^{th} subject. We assume $\mathbf{u}_i$ is independently and identically distributed as bivariate normal: $N_2(\mathbf{0}, \boldsymbol{\Sigma})$, where $\mathbf{0} = (0, 0)^{\mathrm{T}}$ and $\boldsymbol{\Sigma} = \begin{pmatrix} \mathrm{var}(u_{i1}) & \mathrm{cov}(u_{i1,}u_{i2}) \\ \mathrm{cov}(u_{i1,}u_{i2}) & \mathrm{var}(u_{i2}) \end{pmatrix}$. Given seven defined states (see Figure 4.1), and $\sum_{v=1}^{7} p_{sv}\left(\boldsymbol{\theta} \mid \mathbf{x}_{iv}, \mathbf{u}_i\right) = 1$ for any $s \in \{1, 2, 3\}$, we have

$$p_{sv}(\boldsymbol{\theta}|\mathbf{x}_{iv},\mathbf{u_i}) = \exp\{\alpha_{sv} + \boldsymbol{\beta}_v^{\mathrm{T}}\mathbf{x}_{iv} + u_{i1}\}/[1 + \Sigma\exp\{\alpha_{sh} + \boldsymbol{\beta}_h^{\mathrm{T}}\mathbf{x}_{ih} + u_{i1}\}] \quad (2)$$

where h = [2,…, 7] and "exp" indicates the term in braces is an exponent with Euler's number as its base, and

$$p_{s1}(\boldsymbol{\theta}|\mathbf{x}_{i1},\mathbf{u_i}) = 1/[1 + \Sigma\exp\{\alpha_{sh} + \boldsymbol{\beta}_h^{\mathrm{T}}\mathbf{x}_{ih} + u_{i1}\}] \quad (3)$$

Equations similar to (2) and (3) hold for $p_{4v}(\tilde{\boldsymbol{\theta}}|\mathbf{x}_{iv},\mathbf{u_i})$ and $p_{44}(\tilde{\boldsymbol{\theta}}|\mathbf{x}_{i4},\mathbf{u_i})$ respectively, where the sum is over h = 5,..,7. Given $\Theta = (\boldsymbol{\theta}, \tilde{\boldsymbol{\theta}})$, the complete vector of alpha intercepts and beta coefficients, $p_{sv}(\Theta \mid \mathbf{x}_{iv,}\mathbf{u}_i) =$

$$\begin{cases} 1/[1 + \Sigma\exp\{\alpha_{sh} + \boldsymbol{\beta}_h^{\mathrm{T}}\mathbf{x}_{ih} + u_{i1}\}, \text{ if } s \in \{1, 2, 3\}] \text{ and } v = 1 \\ \exp\{\alpha_{sv} + \boldsymbol{\beta}_v^{\mathrm{T}}\mathbf{x}_{iv} + u_{i1}\}/[1 + \Sigma\exp\{\alpha_{sh} + \boldsymbol{\beta}_h^{\mathrm{T}}\mathbf{x}_{ih} + u_{i1}\}], \text{ if } s \in \{1, 2, 3\} \text{ and } v > 1 \\ 1/[1 + \Sigma\exp\{\alpha_{4h} + \boldsymbol{\beta}_h^{\mathrm{T}}\mathbf{x}_{ih} + u_{i2}\}], \text{ if } s = 4 \text{ and } v = 4 \\ \exp\{\alpha_{4v} + \boldsymbol{\beta}_v^{\mathrm{T}}\mathbf{x}_{iv} + u_{i2}\}/[1 + \Sigma\exp\{\alpha_{4h} + \boldsymbol{\beta}_h^{\mathrm{T}}\mathbf{x}_{ih} + u_{i2}\}], \text{ if } s = 4 \text{ and } v > 4 \end{cases}$$

When the base state is normal (i.e., state 1), it is clear that larger values of u_{i1} lead to larger values for p_{sv} and smaller values for p_{s1} (see Equations 2 and 3) . Thus, larger values of u_{i1} are associated with subjects who are more likely to make transitions away from the base state (here normal cognition). Because transitions from clinical MCI to normal do not occur here, a subject-specific random effect u_{i2} is needed when considering transitions from clinical MCI to dementia, death, or dropout. As with u_{i1}, larger values of u_{i2} are associated with subjects who are more likely to make transitions away from the base state, clinical MCI. The random effects may be—but are not necessarily—correlated because they represent the same individual's tendency to make transitions.

Given y_{it_i}, the contribution of subject i to the likelihood can be expressed as follows:

$$\prod_{t=1}^{n_i} p_{y_{i(t-1)},y_{it_i}}(\Theta \mid \mathbf{x}_{it_i}, \mathbf{u}_i) \qquad (4)$$

where n_i is the number of ordered observations for subject i. The marginal likelihood for the i^{th} subject can be written as:

$$\iint_{\mathbb{R}_2} \prod_{t=1}^{n_i} p_{y_{i(t_i-1)},y_{it_i}}(\Theta \mid \mathbf{x}_{it_i}, \mathbf{u}_l) \mathrm{d}F(\mathbf{u}_i) \qquad (5)$$

where $\mathbb{R}_2$ represents the support for the bivariate normal distribution of $\mathbf{u}_i$, and F is its cumulative distribution function. When this integral is evaluated for all N subjects under study, the likelihood function is expressed as

$$L(\Theta \mid \mathbf{x}, \mathbf{u}) = \prod_{i=1}^{N} \iint_{\mathbb{R}_2} \prod_{t=1}^{n_i} p_{y_{i(t_i-1)},y_{it_i}}(\Theta \mid \mathbf{x}_{it_i}, \mathbf{u}_l) \mathrm{d}F(\mathbf{u}_l) \qquad (6)$$

This model can be implemented with PROC NLMIXED in SAS®, which uses an adaptive Gaussian quadrature to approximate the bivariate integral.

Song *et al.* (2011) propose that the model be revised such that the subject specific random effect is scaled based on the prior observed state:[31] for example, $\log[p_{sv}(\boldsymbol{\theta}^*|\mathbf{x}_{iv},\mathbf{u}_i)|p_{s1}(\boldsymbol{\theta}^*|\mathbf{x}_{iv},\mathbf{u}_i)] = \alpha^*_{sv} + \boldsymbol{\beta}^*_v{}^T\mathbf{x}_{iv} + \lambda_s u_{i1}$, where $\boldsymbol{\theta}^*$ represents the vector of alpha intercepts and beta coefficients when normal (state 1) is the base state and the random effects are scaled based on the prior state. The scaling parameters, $\boldsymbol{\lambda}$, improve the fit of the model by adjusting for the magnitude of the variance of the shared random effects as a function of the prior state. In other words, without the scaling parameter a subject's tendency to make transitions to and away from the normal state is assumed to be constant regardless of the prior observed state, which may not be the case. A unique λ_s is associated with transitions from each non-absorbing state s_i, in this case normal ($s = 1$), amnestic MCI ($s = 2$), mixed MCI ($s = 3$), and clinical MCI ($s = 4$). To avoid identifiability problems, λ_1 is set equal to 1, and λ_2, λ_3, and λ_4 must be estimated.

To assess the impact of the scaling parameter on model fit and beta parameter estimation, four proposed models were fit to the data:

(1) Model 1: beta coefficients depend only on base state and current state; no scaling parameter:

$\log[p_{sv}(\boldsymbol{\theta}|\mathbf{x}_{iv},\mathbf{u_i})/p_{s1}(\boldsymbol{\theta}|\mathbf{x}_{iv},\mathbf{u_i})] = \alpha_{sv} + \boldsymbol{\beta}_v{}^T\mathbf{x}_{iv} + u_{i1}$, where $s \in \{1, 2, 3\}$, and

$\log[p_{4v}(\widetilde{\boldsymbol{\theta}}|\mathbf{x}_{iv},\mathbf{u_i})/p_{44}(\widetilde{\boldsymbol{\theta}}|\mathbf{x}_{iv},\mathbf{u_i})] = \tilde{\alpha}_{4v} + \widetilde{\boldsymbol{\beta}}_v{}^T\mathbf{x}_{iv} + u_{i2}$, where $s = 4$ and $v \geq 4$;

(2) Model 2: beta coefficients depend only on base state and current state; scaling parameter:

$\log[p_{sv}(\boldsymbol{\theta}^*|\mathbf{x}_{iv},\mathbf{u}_i)|p_{s1}(\boldsymbol{\theta}^*|\mathbf{x}_i,\mathbf{u_i})] = \alpha^*_{sv} + \boldsymbol{\beta}^*_v{}^T\mathbf{x}_{iv} + \lambda_s u_{i1}$, where $s \in \{1, 2, 3\}$, and

$\log[p_{4v}(\widetilde{\boldsymbol{\theta}}^*|\mathbf{x}_{iv},\mathbf{u}_i)|p_{44}(\widetilde{\boldsymbol{\theta}}^*|\mathbf{x}_i,\mathbf{u_i})] = \tilde{\alpha}^*_{4v} + \widetilde{\boldsymbol{\beta}}^*_v{}^T\mathbf{x}_{iv} + \lambda_4 u_{i2}$, where $s = 4$ and $v \geq 4$;

(3) Model 3: Beta coefficients for age depends on prior state while all other beta coefficients depend only on current state; no scaling parameter:

$\log[p_{sv}(\boldsymbol{\theta}|\mathbf{x}_{iv},\mathbf{u_i})|p_{s1}(\boldsymbol{\theta}|\mathbf{x}_i,\mathbf{u_i})] = \alpha_{sv} + \beta_{sv}^{age} * age_{iv} + \boldsymbol{\beta}_v^T \mathbf{x}_{iv} + u_{i1}$, where $s \in \{1, 2, 3\}$, and

$\log[p_{4v}(\widetilde{\boldsymbol{\theta}}|\mathbf{x}_{iv},\mathbf{u_i})/p_{44}(\widetilde{\boldsymbol{\theta}}|\mathbf{x}_{iv},\mathbf{u_i})] = \tilde{\alpha}_{4v} + \tilde{\beta}_{4v}^{age} * age_{iv} + \widetilde{\boldsymbol{\beta}}_v^T \mathbf{x}_{iv} + u_{i2}$, where $s = 4$ and $v \geq 4$;

(4) Model 4: Beta coefficients for age depends on prior state while all other beta coefficients depend only on base and current states; scaling parameter:

$\log[p_{sv}(\boldsymbol{\theta}^*|\mathbf{x}_{iv},\mathbf{u_i})|p_{s1}(\boldsymbol{\theta}^*|\mathbf{x}_i,\mathbf{u_i})] = \alpha^*_{sv} + \beta_{sv}^{*age} * age_{iv} + \boldsymbol{\beta}^*_v{}^T \mathbf{x}_{iv} + \lambda_s u_{i1}$, where $s \in \{1, 2, 3\}$, and

$\log[p_{4v}(\widetilde{\boldsymbol{\theta}}^*|\mathbf{x}_{iv},\mathbf{u_i})|p_{44}(\widetilde{\boldsymbol{\theta}}^*|\mathbf{x}_i,\mathbf{u_i})] = \tilde{\alpha}^*_{4v} + \tilde{\beta}_{4v}^{*age} * age_{iv} + \widetilde{\boldsymbol{\beta}}^*_v{}^T \mathbf{x}_{iv} + \lambda_4 u_{i2}$, where $s = 4$ and $v \geq 4$.

Models 3 and 4, where the effect of age depends on the prior state, are motivated by the idea that if model fit can be improved by scaling the random effects based on the prior state, it might also be improved by making at least one of the beta coefficients depend on the prior state. Since the four models are nested, differences in fit between models can be assessed with likelihood ratio (LR) tests.

Participant characteristics included in the model as independent variables are age at assessment, sex, years of education, APOE-ε4 status (present vs. absent), which are associated with risk of dementia,[67,74,106,107] and self-reported baseline hypertension (present vs. absent), which is associated with risk of mortality.[41] Statistical significance was set at α=0.05.

Results

The 649 BRAiNS participants in the current study (Table 4.2) made a total of 6,240 one-step transitions (Table 4.2), including 433 terminating events (i.e., a transition

to an absorbing state), and were followed for 6,719 person-years. Among the transient states, the majority of transitions from amnestic MCI are back to normal cognition at the next visit (57.6%), and only 3.7% are transitions to clinical MCI or dementia. Mixed MCI appears more predictive of underlying disease with 45.7% remaining mixed MCI and 7.7% transitioning to clinical MCI or dementia at the next visit (Table 4.3). Subjects who make transitions out of clinical MCI to an absorbing state do so in relatively few assessments, with 38.1% (44/118) reaching an absorbing state in one transition, and 60.1% (71/118) reaching an absorbing state in two transitions.

Model Convergence

The simplest of the proposed models, Model 1, did not reach achieve convergence as specified. Efforts to achieve convergence included specifying initial parameter estimates based on results from a fixed effects only model, removing predictors to decrease the number of parameters being estimated, increasing the maximum number of iterations PROC NLMIXED attempts before terminating the likelihood optimization algorithm to 2000, and increasing the sample size with 246 additional subjects from the BRAiNS cohort. Given that an earlier version of the model that used only a single random effect to account for within-subject correlations without regard to the base state successfully converged,[91] it would appear that convergence was most likely not achieved due to the inclusion of the base state-dependent random effects. Results from models that almost achieved convergence suggested that $\mathbf{u_{i1}}$ and $\mathbf{u_{i2}}$ were only weakly correlated ($\text{cov}[\mathbf{u}_1,\mathbf{u}_2] \approx -0.111$) and that the estimated variance of $\mathbf{u_{i2}}$ was close to zero ($S^2_{\mathbf{u}_2} \approx 0.0197$).

To investigate further the behavior of u_{i1} and u_{i2},the proposed likelihood function was split into two independent components where the first component modeled $\log[p_{sv}(\boldsymbol{\theta}|\mathbf{x}_{iv},u_{i1})/p_{s1}(\boldsymbol{\theta}|\mathbf{x}_{iv},u_{i1})] = \alpha_{sv} + \boldsymbol{\beta}_v^T\mathbf{x}_{iv} + u_{i1}$, where $s \in \{1, 2, 3\}$, and the second component modeled $\log[p_{4v}(\widetilde{\boldsymbol{\theta}}|\mathbf{x}_{iv},u_{i2})/p_{44}(\widetilde{\boldsymbol{\theta}}|\mathbf{x}_{iv},u_{i2})] = \tilde{\alpha}_{4v} + \widetilde{\boldsymbol{\beta}}_v^T\mathbf{x}_{iv} + u_{i2}$, where s = 4 and $v \geq 4$. Note that this assumes u_{i1} and u_{i2} are independent (i.e., $\text{cov}[u_{i1},u_{i2}] = 0$), and $u_{i1} \sim N(0, \sigma_1^2)$ and $u_{i2} \sim N(0, \sigma_2^2)$. Random effect estimates produced by the latter model suggest that u_{i2} is unnecessary, with estimates for all subjects being zero or near zero depending on the number of specified quadrature points. Thus, u_{i2} and λ_4 were taken to be zero for all subjects in all models. Since the lack of model convergence was due to the inclusion of u_{i2}, its elimination allowed the full likelihood to be used rather than the split likelihood. The results below were derived from the following models:

(1) Model 1*: beta coefficients depend only on base state and current state; no scaling parameter:

$\log[p_{sv}(\boldsymbol{\theta}|\mathbf{x}_{iv},u_{i1})/p_{s1}(\boldsymbol{\theta}|\mathbf{x}_{iv},u_{i1})] = \alpha_{sv} + \boldsymbol{\beta}_v^T\mathbf{x}_{iv} + u_{i1}$, where $s \in \{1, 2, 3\}$, and

$\log[p_{4v}(\widetilde{\boldsymbol{\theta}}|\mathbf{x}_{iv},u_{i1})/p_{44}(\widetilde{\boldsymbol{\theta}}|\mathbf{x}_{iv},u_{i1})] = \tilde{\alpha}_{4v} + \widetilde{\boldsymbol{\beta}}_v^T\mathbf{x}_{iv}$, where s = 4 and $v \geq 4$;

(2) Model 2*: beta coefficients depend only on base state and current state; scaling parameter:

$\log[p_{sv}(\boldsymbol{\theta}^*|\mathbf{x}_{iv},u_{i1})|p_{s1}(\boldsymbol{\theta}^*|\mathbf{x}_i,u_{i1})] = \alpha^*_{sv} + \boldsymbol{\beta}_v^T\mathbf{x}_{iv} + \lambda_s u_{i1}$, where $s \in \{1, 2, 3\}$, and

$\log[p_{4v}(\widetilde{\boldsymbol{\theta}}^*|\mathbf{x}_{iv},u_{i1})|p_{44}(\widetilde{\boldsymbol{\theta}}^*|\mathbf{x}_i,u_{i1})] = \tilde{\alpha}^*_{4v} + \widetilde{\boldsymbol{\beta}}^*_v{}^T\mathbf{x}_{iv}$, where s = 4 and $v \geq 4$;

(3) Model 3*: beta coefficients for age depends on prior state while all other beta coefficients depend only on current state; no scaling parameter:

$\log[p_{sv}(\boldsymbol{\theta}|\mathbf{x}_{iv},u_{i1})|p_{s1}(\boldsymbol{\theta}|\mathbf{x}_i,u_{i1})] = \alpha_{sv} + \beta_{sv}^{age} * age_{iv} + \boldsymbol{\beta}_v^T\mathbf{x}_{iv} + u_{i1}$, where $s \in \{1, 2, 3\}$, and,

$\log[p_{4v}(\widetilde{\boldsymbol{\theta}}|\mathbf{x}_{iv},u_{i1})/p_{44}(\widetilde{\boldsymbol{\theta}}|\mathbf{x}_{iv},u_{i1})] = \tilde{\alpha}_{4v} + \tilde{\beta}_{4v}^{age} * age_{iv} + \widetilde{\boldsymbol{\beta}}_v^T \mathbf{x}_{iv}$, where s = 4 and v ≥ 4;

(4) Model 4*: beta coefficients for age depends on prior state while all other beta coefficients depend only on base and current states; scaling parameter:

$\log[p_{sv}(\boldsymbol{\theta}^*|\mathbf{x}_{iv},u_{i1})|p_{s1}(\boldsymbol{\theta}^*|\mathbf{x}_i,u_{i1})] = \alpha^*_{sv} + \beta_{sv}^{*age} * age_{iv} + \boldsymbol{\beta}^*_v{}^T \mathbf{x}_{iv} + \lambda_s u_{i1}$, where s ∈ {1, 2, 3}, and

$\log[p_{4v}(\widetilde{\boldsymbol{\theta}}^*|\mathbf{x}_{iv},u_{i1})|p_{44}(\widetilde{\boldsymbol{\theta}}^*|\mathbf{x}_i,u_{i1})] = \tilde{\alpha}^*_{4v} + \tilde{\beta}_{4v}^{*age} * age_{iv} + \widetilde{\boldsymbol{\beta}}^*_v{}^T \mathbf{x}_{iv}$, where s = 4 and v ≥ 4.

Model Comparisons

Full Models

There was perfect concordance between the nested full models regarding which parameters were significant predictors of transition, but while the beta coefficient and standard error estimates are stable in general, a small number of beta parameters vary dramatically (i.e., greater than 20% in magnitude) between the models with and without scaling parameters (Tables 4.4 and 4.5). For Models 1* and 2*, percent change in beta parameter estimates ranges from -237.17 to 102.96 (median = 0.26), while percent change in standard errors ranges from -1.85 to 94.62 (median = 0). For Models 3* and 4*, percent change in beta parameter estimates ranges from -96.18 to 135.19 (median = 0.34), while percent change in standard errors ranges from -10.67 to 8.91 (median = 0).

The addition of the scaling parameters to the subject-specific random effects does significantly improve fit (Table 4.6). Model 2* fits the data significantly better than Model 1* (LR test = 6, df = 2, p = 0.0497), and Model 4* fits the data significantly better than Model 3* (LR test = 6, df = 2, p = 0.0497). Model 4* has the best fit overall, as it is also significantly better than Model 2* (LR test = 22, df = 12, p = 0.038).

Reduced Models

The full models were reduced using a modified backward selection procedure: all beta parameters with p-values higher than prespecified cut-points (0.25 at stage 1, 0.15 at stage 2, 0.10 at stage 3) were removed from the models and a LR test was conducted. If the reduced model fit as well as the full model, the reduced model was accepted. The next cut-point was used to further reduce the model, and the process was repeated until all beta parameters left in the model were significant at the 0.10 level. At this point the traditional backward selection procedure was used on the remaining beta parameters.

As with the full models, fit in the reduced models is significantly improved with the addition of scaling parameters to the subject-specific random effects (Table 4.7). Here, Model 2* does not fit the data significantly better than Model 1* (LR test = 3, df = 3, p = 0.40), but Model 4* still fits the data significantly better than Model 3* (LR test = 6, df = 2, p = 0.0497). Model 4* again has the best fit overall, as it is also significantly better than Model 2* (LR test = 23, df = 10, p = 0.011).

Reduced Models 1*and 2* agree on the significance of almost all beta parameters with the exception of education for transitions made from a transient state (normal, amnestic MCI, or mixed MCI) to dropout (Table 4.8). Percent change in parameters between Models 1* and 2* ranges from -46.14 to 26.71 (median = 0.00), and percent change in standard errors ranges from -3.57 to 274.77 (median = 0.19). Likewise, reduced Models 3* and 4* agree on the significance of all beta parameters with the exception of age for transitions made from mixed MCI to amnestic MCI (Table 4.9). Percent change in parameters ranges from -21.64 to 14.73 (median = -0.11), and percent change in standard errors ranges from -3.57 to 5.54 (median = 0.12).

Prior state dependence

Scaling Parameters

In Model 2*, where the beta coefficients do not depend on the prior state, the effect of the amnestic state-dependent scaling parameter, λ_2, is to reduce the magnitude of the subject-specific random effect, u_{i1}, by about 38%. This speaks to the tendency of subjects in this dataset to return to the normal state following transitions to amnestic MCI, as 57.6% of all transitions from amnestic MCI (prior state) are to normal at the next assessment (current state). The effect of λ_3, which scales u_{i1} for transitions made from mixed MCI, is to increase the magnitude of u_i by about 9%. This speaks to the tendency of these subjects to continue to make transitions away from normal after entry into mixed MCI, as only 30.7% of such transitions are back to the normal state at the next assessment. In Model 4*, where the beta coefficients for age depend on the prior state, λ_2 and λ_3 have similar but reduced estimates compared to Model 2*. Unlike in Model 2*, where λ_3 increases the magnitude of u_{i1}, here λ_3 decreases the magnitude of u_{i1} by about 8%. This suggests that treating the effect of age as prior-state dependent explains an additional portion of the variance accounted for by the random effects in Model 2*.

Beta Parameters

Results from Model 4* (Table 4.9) show that a one-year increase in age leads to a 10.8% (95% CI: 5.9% –15.9%) increase in odds of transition to clinical MCI when the prior state is normal and to a 16.3% (95% CI: 11.5%-21.2%) increase in odds when the prior state is mixed MCI. More saliently, a one-year increase in age has no effect on the odds of dropping out when the prior state is normal but increases the odds of dropping out by 8.4% (95% CI: 2.8%-14.3%) when the prior state is mixed MCI. Other

explanatory variables may also be better specified as prior-state dependent, and more research is needed to determine which methods work best and in what circumstances since specifying prior-state dependence necessarily increases the number of parameters being estimated.

Discussion

Longitudinal clinical data from 649 participants in the UK ADC BRAiNS cohort were used to investigate the scaling of subject-specific random effects and the incorporation of beta parameters dependent on the prior observed state in a multistate Markov chain. We evaluated four models describing the timing and sequence of elderly participants' transitions in relation to seven states: normal cognition, amnestic MCI (test-based), mixed MCI (test-based), clinical MCI (diagnosis-based), dementia, death without dementia, and dropout without dementia. Two models specified the effect of age as independent of the prior state and two models included prior-state dependent scaling parameters. Previous applications of the multistate Markov chain to studies of aging and dementia have treated the effect of risk factors as both independent of[26,27,30,91] and dependent on[31] the prior state, although in the latter case this dependence was implemented through using the age at the prior visit to predict the current state. Results from the current study support treating the effect of age as prior-state dependent, which makes intuitive sense as well as producing a better fitting model.

Achieving model convergence was a substantial difficulty in this study. There are several issues that could account for the lack of convergence, but two are most likely: 1) inadequate sample size, and 2) a misspecified model. Although the simplest model still failed to converge as initially specified with an increased sample size, the number of

subjects making transitions from a prior state of clinical MCI only increased from 118 to 142. It might be the case that far more subjects are needed in order to estimate the random effects covariance matrix. However, model misspecification is also plausible. PROC NLMIXED currently requires any random effect to be distributed normally and multiple random effects to be distributed as multivariate normal. While a normal distribution appears a reasonable choice for u_{i1}, this is perhaps not the case for u_{i2}. Further, while subject-specific effects may be meaningful in explaining an individual's movement within the transition matrix prior to entering the clinical MCI state, they may be much less important thereafter. That is, once an individual has entered into a symptomatic clinical state, the effect of the disease is relatively uniform across individuals given their risk factors, and the random effect u_{i2} is truly unnecessary. More data are needed to answer these questions.

When interpreting the prior-state dependent scaling parameter estimates, we should ask: (1) is the scaling parameter different from zero, and (2) is the scaling parameter different from one? The first question is addressed by examining the associated p-value. Scaling parameters that are not different from zero should be removed, along with their random effects, from the model. Second, is the estimated scaling parameter different from one? This question is answered by examining the confidence interval around the estimate. If the scaling parameter is not different from one, as is the case here with λ_3 in both Models 2* and 4*, then whether the extra parameter is necessary must be examined.

While Song *et al.* found that the prior-state dependent scaling parameters improve model fit as determined by Akaike's Information Criteria (AIC),[108] only very modest

improvements in AIC were observed here. The discrepancy may be partially explained by important differences in the models and datasets: Song *et al.* used data from the Einstein Aging Study (EAS), which has more subjects than the BRAiNS dataset but less follow-up per subject. Where the 833 EAS subjects contributed 2,152 transitions, the 649 BRAiNS subjects contributed 6,240 transitions. Further, the EAS subjects experienced 148 terminating events (i.e., dementia or death without dementia) while the BRAiNS subjects experienced 433 terminating events. The most important difference, however, is likely the complexity of the models. The EAS model has two transient and two absorbing states, while our model has four transient and three absorbing states. Where adding scaling parameters to the EAS model resulted in only one additional parameter, here it adds two. Finally, the improvement in fit reported by Song *et al.* was a 1.8% reduction in AIC. Thus, even in the simpler model, the relative improvement in AIC was small.

We note, however, that expecting the AIC to decrease by adding parameters to the model is somewhat counterintuitive. Since AIC estimates model fit by adding a penalty of $2k$ to -2log-likelihood, where k is the number of model parameters, improving fit by adding parameters to the model will necessarily require that such improvements outweigh the penalty. Here, the addition of the two scaling parameters did significantly improve model fit as measured by LR tests, and the AIC did decrease in absolute terms despite the four-point penalty from the additional parameters.

Overall, specifying the effect of age as prior-state dependent had the most impact on model fit. Where adding the two random effects scaling parameters led to a six-point reduction in -2log-likelihood in Model 2* vs. Model 1* (Table 4.6), adding 12 parameters to make age prior-state dependent leads to a 22-point reduction in the -2log-likelihood in

Model 3* vs. Model 1*. When both the prior-state dependent scaling parameters and prior-state dependent beta coefficients for age are implemented (i.e., Model 4*), both -2LogL and AIC are improved despite the addition of 14 parameters compared to Model 1*.

In the final reduced models, parameter estimates and standard errors were relatively stable between the models with and without random effect scaling parameters. The majority of parameter estimates were within 10%: 86.5% for Models 1* and 2*, 91.7% for Models 3* and 4*. Likewise, the majority of standard error estimates were within 5%: 89.2% for Models 1* and 2*, 95.8% for Models 3* and 4. Of the four models investigated, Model 4*, where the effect of age depends on the prior state and there are scaling parameters for the random effects, is preferred.

In addition to the criteria used to define clinical states, neuropsychological test data engender specific considerations. Neuropsychological tests are typically administered to participants in longitudinal cohort studies to track cognitive performance over time. Measurements taken on the same participant over time may induce a learning effect, some study visits may be missed, and participants may drop out of the study or die before the clinical onset of dementia would be observed. Selection bias is an additional concern since participants in longitudinal studies, particularly those requiring brain donation upon death and/or invasive clinical procedures such as lumbar puncture, are inherently different from the general population. However, these issues are beyond the scope of this paper.

It is also important to note that individual performance over time need not be linear. Although increasing age is generally associated with some degree of decline in

cognitive performance,[109] observed performance need not decline monotonically. Increased familiarity and practice due to repeated exposure to the instruments may lead to improving scores for many years before declines are observed.[110] In addition to practice effects, cognitive performance may be influenced by transient comorbid medical conditions as well as psychosocial issues such as stress, anxiety, grief, and depression.[15] Thus, it is not unusual for a participant to back transition, i.e., appear cognitively impaired, even seriously so, at a given assessment and then unimpaired at the next assessment.

Identifying risk factors that promote specific transitions, perhaps especially back transitions, is desirable because they might suggest avenues for intervention. However, it is important to establish that such risk factors are not an artifact of methodology or misclassification. In the current study, for example, classification into the test-based MCI states, amnestic and mixed, requires only a single poor score from among multiple tests. If the number of poor scores required for impairment was increased from one to two, or the definition of poor score changed from 1.5 SDs below the expected score to 2.0 SDs below the expected score, this would presumably affect the pattern of transitions observed and perhaps the associated risk factors.

The current study will serve as the basis for a larger project examining the influence of four factors on modeling back transitions from more impaired to less impaired states: (1) the effect subject-specific random effect scaling parameters, (2) the effect of prior-state dependent beta coefficients, (3) the effect of altering the definition of the test-based states to include at least two poor scores, and (4) the effect of altering the cut-point for impairment on the neuropsychological tests such that repeated

administrations are accounted for not only by the subject specific random effects but also by adjusting for practice effects. While sample size within the BRAiNS cohort is limited, data from five similar longitudinal cohorts will be soon be available for analysis via the NIA-funded study “Role of Impaired Cognitive States & Risk Factors in Conversion to Mixed Dementias” (R01AG038651-01A1).

Table 4.1. Summary of terms used to describe a multistate Markov chain

Term	Definition
One-step transition	Movement between or within states over two temporally adjacent assessments
Current state	The latter of two temporally adjacent states, e.g., state observed at time *j*
Prior state	The earlier of two temporally adjacent states, e.g., state observed at time *j -1*
First-order	A Markov chain that meets the assumption that the probability of observing the current state (*j*) depends on the prior state (*j-1*) and not, for example, the (*j-2*) or (*j-3*) state
Transient state	Any state from which a transition is possible
Absorbing state	Any state from which a transition is not possible
Base state	A transient state that has been designated as the reference category in a model

Table 4.2. Characteristics of included participants from the BRAiNS cohort (N=649); participants were enrolled in the study between 1989 and 2004.

Characteristic	**Summary**
Age at entry, y (mean ± SD)	72.9 ± 7.4
Age group, n (%)	
60 – 69	214 (33.0)
70 – 79	307 (47.3)
80 – 89	118 (18.2)
≥ 90	10 (1.5)
Female, %	63.9
At least one APOE-4 allele, %	30.4
Years of education, y (mean ± SD)	15.9 ± 2.5
Education level, n (%)	
≤ 12 (High school or less)	85 (13.1)
13 – 16 (College)	340 (52.4)
≥ 17 (More than college)	224 (34.5)
History of hypertension at entry, %	38.2
Number of assessments (mean ± SD)	10.3 ± 4.7
Time between assessments, y (mean ± SD)	1.1 ± 0.3

Table 4.3. Observed one-step transition matrix (number of assessments [% of prior visit state]); total subjects = 649.

	Current state						
Prior state	Normal	Amnestic MCI	Mixed MCI	Clinical MCI	Dementia	Dropout	Death
Normal	2634 (69.1)	524 (13.8)	464 (12.2)	40 (1.1)	15 (0.4)	33 (0.9)	101 (2.7)
Amnestic MCI	497 (57.6)	172 (19.9)	129 (15.0)	23 (2.7)	9 (1.0)	13 (1.5)	20 (2.3)
Mixed MCI	404 (30.7)	97 (7.4)	601 (45.7)	66 (5.0)	35 (2.7)	30 (2.3)	80 (6.2)
Clinical MCI				154 (61.4)	50 (19.9)	16 (6.4)	31 (12.4)

Table 4.4. Full model fit comparison: all beta coefficients are independent of the prior state (T: normal cognition, amnestic MCI, or mixed MCI).

	No scaling parameters (Model 1*)			Scaling parameters (Model 2*)			Estimate %	SE %
Parameter	**Estimate**	**SE**	**p**	**Estimate**	**SE**	**p**	**Change**	**Change**
T → Amnestic MCI								
Intercept (prior=normal)	-0.213	0.398	0.59	-0.211	0.394	0.59	-0.94	-1.01
Intercept (prior=amnestic)	0.00728	0.399	0.99	0.0691	0.395	0.86	849.18	-1.00
Intercept (prior=mixed)	-0.513	0.397	0.20	-0.553	0.395	0.16	7.80	-0.50
Age (1-yr increment)	0.0285	0.00666	<0.0001	0.0285	0.00663	<0.0001	0.00	-0.45
Sex (F vs. M)	-0.268	0.108	0.013	-0.275	0.106	0.010	2.61	-1.85
Baseline hypertension (Y vs. N)	-0.0756	0.107	0.48	-0.0615	0.106	0.56	-18.65	-0.93
APOE-ε4 (Y vs. N)	-0.0756	0.114	0.51	-0.0839	0.113	0.46	10.98	-0.88
Education (1-yr increment)	-0.0608	0.0226	0.0073	-0.0608	0.0224	0.0067	0.00	-0.88
T → Mixed MCI								
Intercept (prior=normal)	0.954	0.369	0.01	0.986	0.371	0.0081	3.35	0.54
Intercept (prior=amnestic)	0.983	0.373	0.0087	1.0623	0.374	0.0047	8.07	0.27
Intercept (prior=mixed)	2.441	0.359	<0.0001	2.434	0.362	<0.0001	-0.29	0.84
Age (1-yr increment)	0.0748	0.00637	<0.0001	0.0756	0.00647	<0.0001	1.07	1.57
Sex (F vs. M)	-0.0135	0.104	0.90	-0.0274	0.105	0.79	102.96	0.96
Baseline hypertension (Y vs. N)	0.0875	0.101	0.39	0.106	0.102	0.30	21.14	0.99
APOE-ε4 (Y vs. N)	0.0724	0.108	0.50	0.0614	0.110	0.58	-15.19	1.85
Education (1-yr increment)	-0.157	0.0212	<0.0001	-0.159	0.0213	<0.0001	1.27	0.47
T → Clinical MCI								
Intercept (prior=normal)	-2.533	0.721	0.0005	-2.502	0.722	0.0006	-1.22	0.14
Intercept (prior=amnestic)	-1.786	0.725	0.014	-1.743	0.726	0.017	-2.41	0.14
Intercept (prior=mixed)	-0.840	0.695	0.23	-0.864	0.697	0.22	2.86	0.29
Age (1-yr increment)	0.133	0.0140	<0.0001	0.134	0.0141	<0.0001	0.75	0.71
Sex (F vs. M)	-0.274	0.203	0.18	-0.276	0.203	0.17	0.73	0.00

Table 4.4. Continued

	No scaling parameters (Model 1*)			Scaling parameters (Model 2*)			Estimate % Change	SE % Change
Parameter	**Estimate**	**SE**	**p**	**Estimate**	**SE**	**p**		
Baseline hypertension (Y vs. N)	0.0210	0.203	0.92	0.0229	0.204	0.91	9.05	0.49
APOE-ε4 (Y vs. N)	0.604	0.205	0.0033	0.584	0.206	0.0047	-3.31	0.49
Education (1-yr increment)	-0.0991	0.0411	0.016	-0.0995	0.0412	0.016	0.40	0.24
T → Dementia								
Intercept (prior=normal)	-3.520	1.0113	0.0005	-3.524	1.0124	0.0005	0.11	0.11
Intercept (prior=amnestic)	-2.782	1.0246	0.0068	-2.752	1.0234	0.0073	-1.08	-0.12
Intercept (prior=mixed)	-1.546	0.973	0.11	-1.603	0.975	0.10	3.69	0.21
Age (1-yr increment)	0.164	0.0201	<0.0001	0.164	0.0202	<0.0001	0.00	0.50
Sex (F vs. M)	0.385	0.316	0.22	0.371	0.615	0.24	-3.64	94.62
Baseline hypertension (Y vs. N)	-0.423	0.309	0.17	-0.389	0.308	0.208	-8.04	-0.32
APOE-ε4 (Y vs. N)	0.985	0.283	0.0005	0.981	0.283	0.0006	-0.41	0.00
Education (1-yr increment)	-0.135	0.0577	0.019	-0.134	0.0578	0.021	-0.74	0.17
T → Death								
Intercept (prior=normal)	-2.551	0.623	<0.0001	-2.502	0.6230	<0.0001	-1.92	0.00
Intercept (prior=amnestic)	-2.890	0.647	<0.0001	-2.840	0.647	<0.0001	-1.73	0.00
Intercept (prior=mixed)	-1.608	0.609	0.0084	-1.607	0.610	0.0086	-0.06	0.16
Age (1-yr increment)	0.173	0.0120	<0.0001	0.174	0.0121	<0.0001	0.58	0.83
Sex (F vs. M)	-0.408	0.171	0.017	-0.440	0.171	0.010	7.84	0.00
Baseline hypertension (Y vs. N)	0.380	0.166	0.023	0.406	0.167	0.015	6.84	0.60
APOE-ε4 (Y vs. N)	-0.107	0.193	0.58	-0.103	0.194	0.60	-3.74	0.52
Education (1-yr increment)	-0.0427	0.0351	0.23	-0.0443	0.0352	0.209	3.75	0.28
T → Dropout								
Intercept (prior=normal)	-1.938	0.883	0.029	-1.967	0.884	0.026	1.50	0.11
Intercept (prior=amnestic)	-1.562	0.901	0.084	-1.503	0.900	0.095	-3.78	-0.11
Intercept (prior=mixed)	-0.805	0.853	0.346	-0.829	0.854	0.33	2.98	0.12

Table 4.4. Continued

Parameter	No scaling parameters (Model 1*)			Scaling parameters (Model 2*)			Estimate % Change	SE % Change
	Estimate	SE	p	Estimate	SE	p		
Age (1-yr increment)	0.0598	0.0166	0.0003	0.0599	0.0166	0.0003	0.17	0.00
Sex (F vs. M)	-0.0485	0.261	0.85	-0.0529	0.261	0.84	9.07	0.00
Baseline hypertension (Y vs. N)	0.648	0.243	0.0078	0.656	0.242	0.007	1.23	-0.41
APOE-ε4 (Y vs. N)	0.144	0.265	0.59	0.115	0.266	0.67	-20.14	0.38
Education (1-yr increment)	-0.155	0.0510	0.0025	-0.154	0.0510	0.0027	-0.65	0.00
Clinical MCI → Dementia								
Intercept (prior=clinical MCI)	-2.893	1.174	0.014	-2.909	1.173	0.013	0.55	-0.09
Age (1-yr increment)	0.0296	0.0264	0.26	0.0299	0.0264	0.26	1.01	0.00
Sex (F vs. M)	0.832	0.362	0.022	0.820	0.361	0.84	-1.44	-0.28
Baseline hypertension (Y vs. N)	-0.347	0.361	0.34	-0.311	0.360	0.387	-10.37	-0.28
APOE-ε4 (Y vs. N)	0.751	0.360	0.038	0.741	0.360	0.040	-1.33	0.00
Education (1-yr increment)	0.0593	0.0670	0.38	0.0604	0.0670	0.37	1.85	0.00
Clinical MCI → Death								
Intercept (prior= clinical MCI)	-4.503	1.502	0.0028	-4.542	1.503	0.0026	0.87	0.07
Age (1-yr increment)	0.0777	0.0351	0.027	0.0779	0.0351	0.027	0.26	0.00
Sex (F vs. M)	0.595	0.444	0.18	0.593	0.443	0.182	-0.34	-0.23
Baseline hypertension (Y vs. N)	0.404	0.410	0.33	0.380	0.410	0.35	-5.94	0.00
APOE-ε4 (Y vs. N)	0.280	0.451	0.54	0.269	0.451	0.551	-3.93	0.00
Education (1-yr increment)	0.110	0.0835	0.19	0.114	0.0835	0.17	3.64	0.00
Clinical MCI → Dropout								
Intercept (prior=clinical MCI)	-2.124	1.584	0.18	-2.160	1.589	0.17	1.69	0.32
Age (1-yr increment)	0.0287	0.0458	0.53	0.0289	0.0459	0.53	0.70	0.22
Sex (F vs. M)	-0.196	0.543	0.72	-0.210	0.545	0.70	7.14	0.37
Baseline hypertension (Y vs. N)	-0.920	0.662	0.16	-0.924	0.664	0.17	0.43	0.30
APOE-ε4 (Y vs. N)	0.204	0.580	0.73	0.194	0.582	0.74	-4.90	0.34
Education (1-yr increment)	-0.00113	0.0932	0.99	0.00155	0.0934	0.99	-237.17	0.21

Table 4.4. Continued

Parameter	No scaling parameters (Model 1*)			Scaling parameters (Model 2*)			Estimate % Change	SE % Change
	Estimate	SE	p	Estimate	SE	p		
Scaling Parameters								
Prior=amnestic MCI	1.00	0.00	--	0.619	0.172	0.0004	--	--
Prior=mixed MCI	1.00	0.00	--	1.142	0.213	<0.0001	--	--

Table 4.5. Full model fit comparison: age depends on prior state, all other beta coefficients are independent of the prior state.

Parameter	No scaling parameters (Model 3*)			Scaling parameters (Model 4*)			Estimate % Change	SE % Change
	Estimate	SE	p	Estimate	SE	p		
T → Amnestic MCI								
Intercept (prior=normal)	-0.259	0.398	0.52	-0.241	0.395	0.54	-6.95	-0.75
Intercept (prior=amnestic)	-0.0368	0.399	0.93	0.0309	0.396	0.94	-183.97	-0.75
Intercept (prior=mixed)	-0.564	0.397	0.16	-0.572	0.394	0.15	1.42	-0.76
Age (1-yr increment, prior=normal)	0.0330	0.00781	<0.0001	0.0346	0.00802	<0.0001	4.85	2.69
Age (1-yr increment, prior=amnestic MCI)	0.0345	0.0136	0.011	0.0272	0.0132	0.040	-21.16	-2.94
Age (1-yr increment, prior=mixed MCI)	-0.00131	0.0160	0.94	-0.00005	0.0165	1.00	-96.18	3.13
Sex (F vs. M)	-0.268	0.108	0.013	-0.270	0.106	0.011	0.75	-1.85
Baseline hypertension (Y vs. N)	-0.0736	0.107	0.49	-0.0690	0.106	0.52	-6.25	-0.93
APOE-ε4 (Y vs. N)	-0.0772	0.114	0.50	-0.0722	0.114	0.53	-6.48	0.00
Education (1-yr increment)	-0.0577	0.0226	0.01	-0.0585	0.0224	0.0093	1.39	-0.88
T → Mixed MCI								
Intercept (prior=normal)	0.920	0.368	0.013	0.938	0.370	0.012	1.96	0.54
Intercept (prior=amnestic)	0.958	0.373	0.010	1.0246	0.374	0.0063	6.95	0.27
Intercept (prior=mixed)	2.433	0.359	<0.0001	2.426	0.359	<0.0001	-0.29	0.00
Age (1-yr increment, prior=normal)	0.0855	0.00822	<0.001	0.0872	0.00844	<0.0001	1.99	2.68
Age (1-yr increment, prior=amnestic MCI)	0.0756	0.0151	<0.0001	0.0675	0.0149	<0.0001	-10.71	-1.32
Age (1-yr increment, prior=mixed MCI)	0.0580	0.0101	<0.0001	0.0595	0.0110	<0.0001	2.59	8.91
Sex (F vs. M)	-0.0158	0.105	0.88	-0.0207	0.104	0.84	31.01	-0.95
Baseline hypertension (Y vs. N)	0.0901	0.101	0.37	0.096	0.102	0.34	6.55	0.99
APOE-ε4 (Y vs. N)	0.0691	0.108	0.52	0.0739	0.109	0.50	6.95	0.93
Education (1-yr increment)	-0.155	0.0211	<0.0001	-0.156	0.0213	<0.0001	0.65	0.95

Table 4.5. Continued

Parameter	No scaling parameters (Model 3*)			Scaling parameters (Model 4*)			Estimate % Change	SE % Change
	Estimate	SE	p	Estimate	SE	p		
T → Clinical MCI								
Intercept (prior=normal)	-2.436	0.721	0.0008	-2.429	0.722	0.0008	-0.29	0.14
Intercept (prior=amnestic)	-1.725	0.732	0.0019	-1.675	0.732	0.022	-2.90	0.00
Intercept (prior=mixed)	-1.0188	0.702	0.15	-1.0324	0.702	0.14	1.33	0.00
Age (1-yr increment, prior=normal)	0.102	0.0228	<0.001	0.104	0.0230	<0.0001	1.96	0.88
Age (1-yr increment, prior=amnestic MCI)	0.116	0.0320	0.0003	0.108	0.0318	0.0007	-6.90	-0.62
Age (1-yr increment, prior=mixed MCI)	0.154	0.0212	<0.0001	0.155	0.0218	<0.0001	0.65	2.83
Sex (F vs. M)	-0.255	0.204	0.21	-0.264	0.203	0.19	3.53	-0.49
Baseline hypertension (Y vs. N)	-0.00540	0.204	0.98	-0.0127	0.204	0.95	135.19	0.00
APOE-ε4 (Y vs. N)	0.608	0.205	0.0032	0.617	0.206	0.0028	1.48	0.49
Education (1-yr increment)	-0.0992	0.0412	0.016	-0.0990	0.0412	0.017	-0.20	0.00
T → Dementia								
Intercept (prior=normal)	-3.796	1.0445	0.0003	-3.789	1.0464	0.0003	-0.18	0.18
Intercept (prior=amnestic)	-3.0532	1.0918	0.0053	-2.982	1.0900	0.0064	-2.33	-0.16
Intercept (prior=mixed)	-1.612	0.976	0.10	-1.630	0.977	0.096	1.12	0.10
Age (1-yr increment, prior=normal)	0.186	0.0374	<0.0001	0.189	0.0375	<0.0001	1.61	0.27
Age (1-yr increment, prior=amnestic MCI)	0.194	0.0535	0.0003	0.184	0.0530	0.0006	-5.15	-0.93
Age (1-yr increment, prior=mixed MCI)	0.138	0.0268	<0.0001	0.140	0.0273	<0.0001	1.45	1.87
Sex (F vs. M)	0.367	0.315	0.24	0.357	0.315	0.26	-2.72	0.00
Baseline hypertension (Y vs. N)	-0.375	0.307	0.22	-0.388	0.309	0.21	3.47	0.65
APOE-ε4 (Y vs. N)	1.010	0.282	0.0004	1.0253	0.283	0.0003	1.51	0.35
Education (1-yr increment)	-0.126	0.0580	0.030	-0.126	0.0581	0.030	0.00	0.17

Table 4.5. Continued

Parameter	No scaling parameters (Model 3*)			Scaling parameters (Model 4*)			Estimate % Change	SE % Change
	Estimate	SE	p	Estimate	SE	p		
T → Death								
Intercept (prior=normal)	-2.611	0.626	<0.0001	-2.579	0.628	<0.0001	-1.23	0.32
Intercept (prior=amnestic)	-2.638	0.655	<0.0001	-2.576	0.656	<0.0001	-2.35	0.15
Intercept (prior=mixed)	-1.595	0.613	0.0095	-1.612	0.614	0.0089	1.07	0.16
Age (1-yr increment, prior=normal)	0.187	0.0160	<0.0001	0.188	0.0162	<0.0001	0.53	1.25
Age (1-yr increment, prior = amnestic MCI)	0.123	0.0345	0.0004	0.116	0.0343	0.0008	-5.69	-0.58
Age (1-yr increment, prior=mixed MCI)	0.162	0.0200	<0.0001	0.165	0.0207	<0.0001	1.85	3.50
Sex (F vs. M)	-0.422	0.171	0.014	-0.426	0.171	0.013	0.95	0.00
Baseline hypertension (Y vs. N)	0.386	0.166	0.020	0.406	0.167	0.015	5.18	0.60
APOE-ε4 (Y vs. N)	-0.110	0.193	0.57	-0.104	0.194	0.59	-5.45	0.52
Education (1-yr increment)	-0.0424	0.0351	0.23	-0.0440	0.0353	0.21	3.77	0.57
T → Dropout								
Intercept (prior=normal)	-2.0515	0.885	0.021	-2.0521	0.886	0.021	0.03	0.11
Intercept (prior=amnestic)	-1.625	0.905	0.073	-1.561	0.904	0.085	-3.94	-0.11
Intercept (prior=mixed)	-0.911	0.856	0.29	-0.927	0.857	0.28	1.76	0.12
Age (1-yr increment, prior=normal)	0.0180	0.0251	0.47	0.0193	0.0253	0.46	7.22	0.79
Age (1-yr increment, prior=amnestic MCI)	0.0925	0.0403	0.022	0.0838	0.0398	0.036	-9.41	-10.67
Age (1-yr increment, prior=mixed MCI)	0.0821	0.0271	0.0025	0.0836	0.0274	0.0024	1.83	1.11
Sex (F vs. M)	-0.0483	0.261	0.85	-0.0459	0.261	0.86	-4.97	0.00
Baseline hypertension (Y vs. N)	0.614	0.243	0.012	0.605	0.243	0.013	-1.47	0.00
APOE-ε4 (Y vs. N)	0.121	0.267	0.65	0.130	0.267	0.63	7.44	0.00
Education (1-yr increment)	-0.151	0.0510	0.0032	-0.151	0.0510	0.0032	0.00	0.00

Table 4.5. Continued

Parameter	No scaling parameters (Model 3*)			Scaling parameters (Model 4*)			Estimate % Change	SE % Change
	Estimate	SE	p	Estimate	SE	p		
Clinical MCI → Dementia								
Intercept (prior=clinical MCI)	-2.941	1.176	0.013	-2.935	1.175	0.013	-0.20	-0.09
Age (1-yr increment)	0.0300	0.0264	0.26	0.0300	0.0264	0.26	0.00	0.00
Sex (F vs. M)	0.829	0.361	0.022	0.829	0.361	0.022	0.00	0.00
Baseline hypertension (Y vs. N)	-0.295	0.359	0.41	-0.295	0.359	0.41	0.00	0.00
APOE-ε4 (Y vs. N)	0.750	0.360	0.037	0.749	0.360	0.038	-0.13	0.00
Education (1-yr increment)	0.0612	0.0671	0.36	0.0609	0.0671	0.36	-0.49	0.00
Clinical MCI → Death								
Intercept (prior=clinical MCI)	-4.611	1.511	0.0024	-4.601	1.510	0.0024	-0.22	-0.07
Age (1-yr increment)	0.0781	0.0352	0.027	0.0781	0.0352	0.027	0.00	0.00
Sex (F vs. M)	0.594	0.444	0.18	0.594	0.444	0.18	0.00	0.00
Baseline hypertension (Y vs. N)	0.371	0.412	0.37	0.371	0.412	0.37	0.00	0.00
APOE-ε4 (Y vs. N)	0.270	0.453	0.55	0.268	0.453	0.55	-0.74	0.00
Education (1-yr increment)	0.118	0.0834	0.16	0.117	0.0839	0.16	-0.85	0.60
Clinical MCI → Dropout								
Intercept (prior=clinical MCI)	-2.204	1.593	0.17	-2.199	1.592	0.17	-0.23	-0.06
Age (1-yr increment)	0.0293	0.0459	0.52	0.0294	0.0459	0.52	0.34	0.00
Sex (F vs. M)	-0.207	0.545	0.71	-0.212	0.545	0.70	2.42	0.00
Baseline hypertension (Y vs. N)	-0.919	0.663	0.17	-0.924	0.664	0.16	0.54	0.15
APOE-ε4 (Y vs. N)	0.196	0.582	0.74	0.193	0.582	0.74	-1.53	0.00
Education (1-yr increment)	0.00389	0.0936	0.97	0.00379	0.0936	0.97	-2.57	0.00
Scaling Parameters								
Prior = amnestic MCI	1.00	0.00	--	0.568	0.173	0.0011	--	--
Prior = mixed MCI	1.00	0.00	--	1.00520	0.218	<0.0001	--	--

Table 4.6. Full model characteristics.

	Betas independent of prior state		Beta for age depends on prior state	
Fit statistics	**No scaling parameters (Model 1*)**	**Scaling parameters (Model 2*)**	**No scaling parameters (Model 3*)**	**Scaling parameters (Model 4*)**
-2LogL	13303	13297	13281	13275
AIC	13437	13435	13439	13437
AICC	13439	13437	13441	13439
BIC	13737	13744	13792	13800
Parameters	67	69	79	81

Table 4.7. Reduced model characteristics.

	Betas independent of prior state		Beta for age depends on prior state	
Fit statistics	**No scaling parameters (Model 1*)**	**Scaling parameters (Model 2*)**	**No scaling parameters (Model 3*)**	**Scaling parameters (Model 4*)**
-2LogL	13333	13330	13313	13307
AIC	13407	13410	13409	13407
AICC	13407	13410	13409	13408
BIC	13573	13589	13624	13631
Parameters	37	40	48	50

Table 4.8. Reduced model fit comparison: all beta coefficients are independent of the prior state (T: normal cognition, amnestic MCI, or mixed MCI).

	No scaling parameters (Model 1*)			Scaling parameters (Model 2*)			Estimate % Change	SE % Change
Parameter	**Estimate**	**SE**	**p**	**Estimate**	**SE**	**p**		
T → Amnestic MCI								
Intercept (prior = normal)	-1.266	0.0826	<0.0001	-1.283	0.0824	<0.0001	1.34	-0.24
Intercept (prior = amnestic)	-1.0484	0.112	<0.0001	-0.992	0.108	<0.0001	-5.38	-3.57
Intercept (prior = mixed)	-1.562	0.136	<0.0001	-1.584	0.141	<0.0001	1.41	3.68
Age (1-yr increment)	0.0294	0.00666	<0.0001	0.0286	0.00659	<0.0001	-2.72	-1.05
Sex (F vs. M)	-0.211	0.0885	0.018	-0.203	0.0876	0.021	-3.79	-1.02
T → Mixed MCI								
Intercept (prior = normal)	0.308	0.264	0.25	0.329	0.267	0.22	6.82	1.14
Intercept (prior = amnestic)	0.322	0.278	0.25	0.408	0.280	0.15	26.71	0.72
Intercept (prior = mixed)	1.788	0.263	<0.0001	1.803	0.267	<0.0001	0.84	1.52
Age (1-yr increment)	0.0744	0.00636	<0.0001	0.0740	0.00643	<0.0001	-0.54	1.10
Education (1-yr increment)	-0.114	0.0164	<0.0001	-0.116	0.0165	<0.0001	1.75	0.61
T → Clinical MCI								
Intercept (prior = normal)	-4.272	0.187	<0.0001	-4.287	0.187	<0.0001	0.35	0.00
Intercept (prior = amnestic)	-3.538	0.237	<0.0001	-3.496	0.236	<0.0001	-1.19	-0.42
Intercept (prior = mixed)	-2.574	0.176	<0.0001	-2.600	0.179	<0.0001	1.01	1.70
Age (1-yr increment)	0.133	0.0140	<0.0001	0.133	0.0141	<0.0001	0.00	0.71
APOE-ε4 (Y vs. N)	0.607	0.190	0.0015	0.617	0.190	0.0012	1.65	0.00
T → Dementia								
Intercept (prior = normal)	-5.520	0.309	<0.0001	-5.538	0.311	<0.0001	0.33	0.65
Intercept (prior = amnestic)	-4.751	0.378	<0.0001	-4.713	0.378	<0.0001	-0.80	0.00
Intercept (prior = mixed)	-3.529	0.260	<0.0001	-3.523	0.261	<0.0001	-0.17	0.38
Age (1-yr increment)	0.165	0.0206	<0.0001	0.165	0.0207	<0.0001	0.00	0.49
APOE-ε4 (Y vs. N)	0.939	0.270	0.0005	0.919	0.271	0.0007	-2.13	0.37

Table 4.8. Continued

Parameter	No scaling parameters (Model 1*)			Scaling parameters (Model 2*)			Estimate % Change	SE % Change
	Estimate	SE	p	Estimate	SE	p		
T → Death								
Intercept (prior = normal)	-3.257	0.165	<0.0001	-3.280	0.165	<0.0001	0.71	0.00
Intercept (prior = amnestic)	-3.599	0.262	<0.0001	-3.573	0.260	<0.0001	-0.72	-0.76
Intercept (prior = mixed)	-2.320	0.189	<0.0001	-2.354	0.192	<0.0001	1.47	1.59
Age (1-yr increment)	0.174	0.0120	<0.0001	0.174	0.0120	<0.0001	0.00	0.00
Sex (F vs. M)	-0.399	0.153	0.0092	-0.382	0.153	0.013	-4.26	0.00
Baseline hypertension (Y vs. N)	0.369	0.151	0.015	0.375	0.151	0.013	1.63	0.00
T → Dropout								
Intercept (prior = normal)	-4.412	0.214	<0.0001	-2.865	0.802	0.0004	-35.06	274.77
Intercept (prior = amnestic)	-4.0203	0.308	<0.0001	-2.369	0.825	0.0042	-41.07	167.86
Intercept (prior = mixed)	-3.190	0.232	<0.0001	-1.718	0.770	0.026	-46.14	231.90
Age (1-yr increment)	0.0566	0.0166	0.0007	0.0580	0.0165	0.0005	2.47	-0.60
Baseline hypertension (Y vs. N)	0.637	0.234	0.0067	0.630	0.233	0.0070	-1.10	-0.43
Education (1-yr increment)	--	--	--	-0.0972	0.0489	0.047	--	--
Clinical MCI → Dementia								
Intercept (prior = clinical MCI)	-1.566	0.273	<0.0001	-1.559	0.272	<0.0001	-0.45	-0.37
Sex (F vs. M)	0.741	0.335	0.028	0.728	0.335	0.030	-1.75	0.00
Clinical MCI → Death								
Intercept (prior = clinical MCI)	-2.148	0.341	<0.0001	-2.210	0.349	<0.0001	2.89	2.35
Age (1-yr increment)	0.0772	0.0338	0.023	0.0823	0.0343	0.017	6.61	1.48
Clinical MCI → Dropout								
Intercept (prior = clinical MCI)	-2.263	0.263	<0.0001	-2.263	0.262	<0.0001	0.00	-0.38
Scaling Parameters								
Prior = amnestic MCI	1.00	0.00	--	0.619	0.175	0.0004	--	--
Prior = mixed MCI	1.00	0.00	--	1.0860	0.212	<0.0001	--	--

Table 4.9. Reduced model fit comparison: age depends on prior state, all other beta coefficients are independent of the prior state (T: normal cognition, amnestic MCI, or mixed MCI).

	No scaling parameters (Model 3*)			Scaling parameters (Model 4*)			Estimate %	SE
Parameter	**Estimate**	**SE**	**p**	**Estimate**	**SE**	**p**	**Change**	**% Change**
T → Amnestic MCI								
Intercept (prior=normal)	-1.276	0.0819	<0.0001	-1.271	0.0833	<0.0001	-0.39	1.71
Intercept (prior=amnestic)	-1.0479	0.112	<0.0001	-0.990	0.108	<0.0001	-5.53	-3.57
Intercept (prior=mixed)	-1.546	0.136	<0.0001	-1.553	0.141	<0.0001	0.45	3.68
Age (1-yr increment, prior=normal)	0.0329	0.00767	<0.0001	0.0346	0.00789	<0.0001	5.17	2.87
Age (1-yr increment, prior=amnestic MCI)	0.0342	0.0135	0.011	0.0268	0.0132	0.043	-21.64	-2.22
Age (1-yr increment, prior=mixed MCI)	0.0913	0.0406	0.025	--	--	--	--	--
Sex (F vs. M)	-0.204	0.0882	0.021	-0.202	0.0879	0.022	-0.98	-0.34
T → Mixed MCI								
Intercept (prior=normal)	0.355	0.266	0.18	0.356	0.267	0.18	0.28	0.38
Intercept (prior=amnestic)	0.387	0.280	0.17	0.444	0.279	0.11	14.73	-0.36
Intercept (prior=mixed)	1.888	0.264	<0.0001	1.878	0.264	<0.0001	-0.53	0.00
Age (1-yr increment, prior=normal)	0.0839	0.00810	<0.0001	0.0859	0.00833	<0.0001	2.38	2.84
Age (1-yr increment, prior=amnestic MCI)	0.0739	0.0151	<0.0001	0.0655	0.0148	<0.0001	-11.37	-1.99
Age (1-yr increment, prior=mixed MCI)	0.0566	0.00921	<0.0001	0.0565	0.00972	<0.0001	-0.18	5.54
Education (1-yr increment)	-0.118	0.0165	<0.0001	-0.117	0.0165	<0.0001	-0.85	0.00

Table 4.9. continued

Parameter	No scaling parameters (Model 3*)			Scaling parameters (Model 4*)			Estimate % Change	SE % Change
	Estimate	SE	p	Estimate	SE	p		
T → Clinical MCI								
Intercept (prior=normal)	-4.178	0.184	<0.0001	-4.193	0.186	<0.0001	0.36	1.09
Intercept (prior=amnestic)	-3.504	0.254	<0.0001	-3.419	0.249	<0.0001	-2.43	-1.97
Intercept (prior=mixed)	-2.726	0.205	<0.0001	-2.726	0.208	<0.0001	0.00	1.46
Age (1-yr increment, prior=normal)	0.100	0.0225	<0.0001	0.103	0.0229	<0.0001	3.00	1.78
Age (1-yr increment, prior=amnestic MCI)	0.117	0.0327	0.0004	0.107	0.0320	0.0009	-8.55	-2.14
Age (1-yr increment, prior=mixed MCI)	0.152	0.0209	<0.0001	0.151	0.0212	<0.0001	-0.66	1.44
APOE-ε4 (Y vs. N)	0.604	0.191	0.0016	0.608	0.191	0.0015	0.66	0.00
T → Dementia								
Intercept (prior=normal)	-5.620	0.365	<0.0001	-5.629	0.369	<0.0001	0.16	1.10
Intercept (prior=amnestic)	-5.107	0.550	<0.0001	-5.0157	0.541	<0.0001	-1.79	-1.64
Intercept (prior=mixed)	-3.380	0.268	<0.0001	-3.386	0.271	<0.0001	0.18	1.12
Age (1-yr increment, prior=normal)	0.186	0.0376	<0.0001	0.190	0.0379	<0.0001	2.15	0.80
Age (1-yr increment, prior=amnestic MCI)	0.215	0.0578	0.0002	0.203	0.0569	0.0004	-5.58	-1.56
Age (1-yr increment, prior=mixed MCI)	0.134	0.0269	<0.0001	0.134	0.0272	<0.0001	0.00	1.12
APOE-ε4 (Y vs. N)	0.926	0.271	0.007	0.925	0.271	0.0007	-0.11	0.00

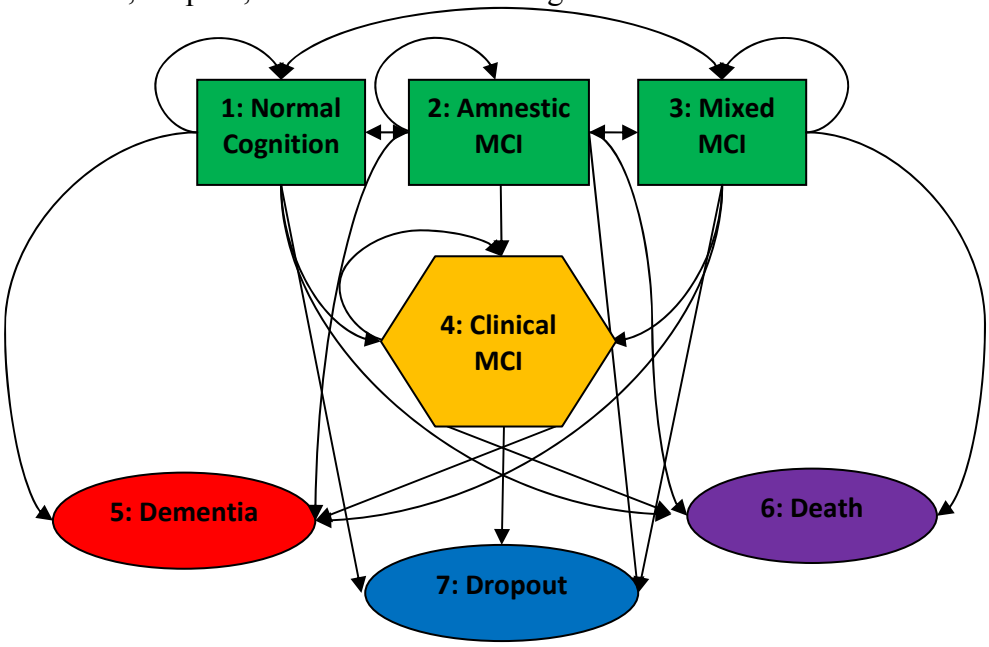
Table 4.9. continued

Parameter	No scaling parameters (Model 3*)			Scaling parameters (Model 4*)			Estimate % Change	SE % Change
	Estimate	SE	p	Estimate	SE	p		
T → Death								
Intercept (prior = normal)	-3.322	0.176	<0.0001	-3.324	0.178	<0.0001	0.06	1.14
Intercept (prior = amnestic)	-3.393	0.284	<0.0001	-3.310	0.279	<0.0001	-2.45	-1.76
Intercept (prior = mixed)	-2.296	0.212	<0.0001	-2.323	0.217	<0.0001	1.18	2.36
Age (1-yr increment, prior = normal)	0.186	0.0159	<0.0001	0.188	0.0161	<0.0001	1.08	1.26
Age (1-yr increment, prior = amnestic MCI)	0.125	0.0350	0.0004	0.115	0.0343	0.0008	-8.00	-2.00
Age (1-yr increment, prior = mixed MCI)	0.162	0.0196	<0.0001	0.163	0.0200	<0.0001	0.62	2.04
Sex (F vs. M)	-0.390	0.153	0.011	-0.380	0.153	0.013	-2.56	0.00
Baseline hypertension (Y vs. N)	0.362	0.151	0.017	0.358	0.151	0.018	-1.10	0.00
T → Dropout								
Intercept (prior = normal)	-2.930	0.803	0.0003	-2.946	0.804	0.0003	0.55	0.12
Intercept (prior = amnestic)	-2.475	0.833	0.0031	-2.428	0.834	0.0037	-1.90	0.12
Intercept (prior = mixed)	-1.710	0.776	0.028	-1.754	0.778	0.024	2.57	0.26
Age (1-yr increment, prior = amnestic MCI)	0.0913	0.0406	0.025	0.0829	0.0402	0.040	-9.20	-0.99
Age (1-yr increment, prior = mixed MCI)	0.0795	0.0265	0.0028	0.0805	0.0270	0.0029	1.26	1.89
Baseline hypertension (Y vs. N)	0.618	0.234	0.0083	0.606	0.234	0.010	-1.94	0.00
Education (1-yr increment)	-0.0990	0.0489	0.043	-0.0973	0.0490	0.047	-1.72	0.20
Clinical MCI → Dementia								
Intercept (prior = clinical MCI)	-1.556	0.271	<0.0001	-1.555	0.272	<0.0001	-0.06	0.37
Sex (F vs. M)	0.728	0.334	0.030	0.729	0.335	0.030	0.14	0.30

Table 4.9. continued

Parameter	No scaling parameters (Model 3*)			Scaling parameters (Model 4*)			Estimate % Change	SE % Change
	Estimate	SE	p	Estimate	SE	p		
Clinical MCI → Death								
Intercept (prior = clinical MCI)	-2.177	0.345	<0.0001	-2.175	0.344	<0.0001	-0.09	-0.29
Age (1-yr increment)	0.0795	0.0340	0.020	0.0794	0.0340	0.020	-0.13	0.00
Clinical MCI → Dropout								
Intercept (prior = clinical MCI)	-2.277	0.264	<0.0001	-2.261	0.262	<0.0001	-0.70	-0.76
Scaling Parameters								
Prior = amnestic MCI	1.00	0.00	--	0.552	0.173	<0.0001	--	--
Prior = mixed MCI	1.00	0.00	--	0.917	0.212	<0.0001	--	--

Figure 4.1. Diagram of one-step transitions possible between adjacent subject visits in the Biologically Resilient Adults in Neurological Studies (BRAiNS) cohort study. Double-headed arrows indicate back transitions are possible from more impaired to less impaired states. Dementia, dropout, and death are absorbing states.



CHAPTER FIVE

Conclusion

Summary

Dementia is increasingly recognized as a major and growing threat to public health worldwide,[111] and there is a critical need for prevention and treatment strategies. However, it is necessary that appropriate methodologies are used in the identification of risk factors. The purpose of this dissertation research was to develop further the body of literature featuring Markov chains as an analytic tool for data derived from longitudinal studies of aging and dementia. Data drawn from the University of Kentucky's Alzheimer's Disease Center's (UK ADC) Biologically Resilient Adults in Neurological Studies (BRAiNS) cohort, which was established in 1989 and follows adults age 60 years and older who are cognitively normal at baseline to death, were used to conduct three studies: (1) "Mild cognitive impairment: Statistical models of transition using longitudinal clinical data," (2) "Self-reported head injury and risk of cognitive impairment and Alzheimer's-type pathology in a longitudinal study of aging and dementia, " and (3) "Incorporating prior-state dependence among random effects and beta coefficients improves multistate Markov chain model fit." The major findings from these studies are summarized below.

Chapter Two examined risk factors associated with both cognitive test-based and clinically determined forms of mild cognitive impairment (MCI). MCI has existed as a clinical diagnosis only since 2004.[10] These initial criteria were independent of suspected etiology, which meant that forms of cognitive impairment due treatable (e.g., depression) and untreatable (e.g., Alzheimer's disease) causes of MCI were considered the same

diagnostic entity. This conflation of etiologies, along with the tendency of large observational studies to determine MCI based on only a single measure of cognition, such as the Mini-Mental State Examination, led to the perception that MCI is unstable and that recovery to normal cognition frequently occurs. It was demonstrated in Chapter Two, however, when a suspected neurodegenerative etiology is included in the MCI criteria, and adequate follow-up is available to characterize the trajectory of participants, MCI is in fact quite stable. Apparent recoveries to normal cognition are due to misclassification or underlying medical conditions.

Other important findings from this chapter concern the role of test-based cognitive impairments in predicting future clinical states. Although test-based amnestic impairments (i.e., episodic memory) in this study were highly transient in nature, with almost 60% returning to normal cognition at the next assessment, they were still predictive of clinically determined impairment ($\widehat{OR}$ for clinical MCI = 2.3 [95% CI: 1.3-4.0]). More striking, however, was the association between non-amnestic impairments (i.e., language, attention, or executive function) and clinical impairment ($\widehat{OR}$ for clinical MCI = 4.8 [95% CI: 2.9-7.8] and $\widehat{OR}$ for dementia = 4.9 [95% CI: 2.6-9.3]. The bottom line is that there are clinically significant cognitive impairments that can be detected at least one year before the criteria for a clinical diagnosis are met. While those impairments will often not be followed by a clinical impairment within one year, and thus should not—especially in the absence of longitudinal evidence of impairment—be used as the basis for a diagnosis by clinicians, they do place individuals at an increased risk of eventual MCI and dementia.

Chapter Three represents the first application of a Markov chain to analysis of self-reported head injury as a risk factor for cognitive impairment, dementia, and death, as well as the first study to incorporate both longitudinal observational and neuropathological data. This study confirmed that head injury is a risk factor for both dementia and death, and this was the first study to show that head injury is also a risk factor for MCI. Additionally, the inclusion of neuropathological data in the analysis shed some light on earlier findings from case-control studies that suggested that only men are at increased risk of dementia following a head injury. Among the subset of participants who came to autopsy, men with a history of head injury had significantly increased numbers of mean diffuse and neuritic plaques in both the neocortical and medial temporal areas. There was no observable difference between women with a history of head injury and women without.

While Fleminger and colleages (2003) suggested that women may be offered protection against head injury by the presence of female sex hormones,[69] the BRAiNS data suggest that men and women of this generation may have qualitatively different head injury exposures. Men in this study tended to have injuries that resulted in longer periods of unconsciousness. Moreover, men in this study also tended to participate in activities—like boxing, football, and military service—that could lead to repeated blows to the head that do not result in loss of consciousness. Despite growing evidence that it is cumulative lifetime exposure that determines chronic effects,[101] studies of head injury are typically focused on only the most severe injuries, i.e., those resulting a loss of consciousness or, in many cases, the subset of those injuries requiring medical attention. Thus, perhaps it is not sex hormones that protected the women included in earlier studies but rather the

tendency of men to sustain more severe and/or frequent injuries. Severity of injury was not considered in Fleminger *et al*.'s analysis.

Chapter Four shifted focus from risk factors for MCI and dementia to Markov model mechanics. Markov chains are rather complex, and there are many possibilities as to how they may be constructed. Song *et al*. (2011) proposed scaling the subject-specific random effects based on the observed prior state and demonstrated that the addition of these scaling parameters improved model fit as measured by Akaike's information criterion.[31] These prior-state dependent scaling parameters, along with prior-state dependent beta coefficients, were evaluated in an application to the data from the BRAiNS cohort. Major findings from this study include the confirmation that scaling the random effects based on the prior state does improve model fit, as measured by likelihood ratio tests, along with the finding that treating the effect of age as prior-state dependent not only improves model fit but also reveals previously hidden associations. When the effect of age is independent of the prior state, it has no significant effect on a participant's probability of dropping out of the study. However, when the effect of age depends on the prior state, participants with a non-amnestic impairment at the previous assessment are more likely to drop out with older age: a one-year increase in age raises the odds of dropping out by 8% (95% CI: 3%-14%).

Strengths and Limitations

Markov chains are an underutilized tool in the analysis of data from longitudinal studies of aged volunteers since death is always a competing risk[93] for any outcome of interest. Although they have the advantages of flexibility (i.e., the number of transient

and absorbing states can vary), handling correlated observations, as well as handling multiple outcomes and competing risks, they can be quite complicated to implement as no “off-the-shelf” software is available. A fair amount of technical knowledge is necessary to program the analysis within procedures like PROC NLMIXED, and there is little guidance available in the literature on how best to fit these models, which can have easily over 100 parameters in a full model evaluating multiple risk factors. Other limitations of the Markov model include sensitivity to sparse cells, which can limit the evaluation of interaction terms, and the need for mature datasets where most participants have reached an absorbing state.

A major strength of this dissertation is that the data were drawn from a large, clinically well characterized cohort with lengthy (mean 10.3±4.7 assessments) follow-up. Adequate follow-up helps reduce misclassification errors, as demonstrated in Chapter Two, as well as mitigates the sparse cell problems that can limit the utility of Markov chain analyses. At the same time, however, it is crucial to note that the participants in the BRAiNS cohort are not representative of the general population of individuals age 60 years and older. Study volunteers are highly educated compared to their peers nationally, and thus the generalizability of the results may be limited. However, the concept of cognitive reserve would imply that these participants are less susceptible to risk factors that would affect their peers. Thus, risk factors identified in the studies of this dissertation should also affect the general population of aged individuals, whose brains may be less able to compensate for neuropathological insults.

Furthermore, despite the large sample there still were not enough participants with dementia to separate the dementia state into etiologically determined categories.

Although most cases of dementia in any older population will involve Alzheimer's disease, up to 40% may be due to some other cause entirely.[7] In addition, multiple pathologies may be present, especially as participants reach their mid-80s. Thus, information about risk factors for specific dementing diseases is inevitably lost when all dementias are treated as being the same.

Other limitations include the possibility of uncontrolled confounding and effect modification. Again, because of the sparse cell problem, the ability to test interactions terms was somewhat limited. Furthermore, despite the prospective cohort design, data on time-varying comorbidities and measurements—such as blood pressure—are limited, and key social and lifestyle factors, such as characterization of time devoted to hobbies (e.g., reading, travelling, music) as well as diet and exercise routines are not available.

Finally, the addition of the dropout state to the Markov chain is a strength of this dissertation. Prior applications of the Markov chain to the BRAiNS cohort excluded participants who dropped out of the study, as was done in Chapter Two. The inclusion of the dropout state in Chapters Three and Four makes more efficient use of the cohort data and provides a method of identifying risk factors that may aid in refining participant retention efforts.

Future Research

There are several avenues for future research suggested by the studies in this dissertation. First, additional research into Markov chain model fitting is needed. As mentioned above, there is nothing in the literature to provide guidance about how best to fit these models. Since fitting the models is expensive in terms of time and computational

resources, particularly when random effects are included, methods are needed that clearly demonstrate the advantages and disadvantages of various selection algorithms.

In Chapter Two, it is posited that a clinical diagnosis of MCI is a semi-absorbing state from which participants do not recover. While that may be the case at the UK ADC, it is not necessarily true for all patients in all study populations. Additional data are needed to evaluate the true stability of the clinical MCI diagnosis, and more importantly, to evaluate its utility as a clinical entity distinct from dementia.

The study of head injury as a risk factor for AD remains underdeveloped, and neuropathological data obtained from participants in other longitudinal observational studies need to be evaluated. In addition, prospective studies, such as those being conducted at all 29 federally funded Alzheimer's Disease Centers, should be collecting more detailed data about such injuries. Currently, ADCs are only required to determine whether a head injury with a loss of consciousness (LOC) has occurred, and if so whether it lasted more or less than five minutes, and whether there are chronic effects.[24] These data should be expanded to capture, at minimum, the age at injury, the estimated length of LOC, and whether medical treatment was obtained immediately following the injury.

As mentioned in Chapter Four, additional research into the transient states in the Markov chain is necessary. There is a strong association between the test-based impairments that determine the transient states in the Markov chain and risk of future clinical impairment, despite the heavy back flow of participants from these states to normal cognition. The criteria that determine these states are somewhat arbitrary, however, and additional research is needed to determine the influence of cutpoints for

impairment (currently set at 1.5. standard deviations below the expected mean score for age) and the number of poor scores necessary to be classified as impaired (currently only one is needed) on the back transition rate.

Finally, as noted above, there is a critical need for studies with enough participants and follow-up to examine risk factors and cognitive profiles for mixed dementias, i.e., dementias resulting from multiple brain diseases. For example, of the autopsied participants in the current study, 20/81 (24.7%) of individuals with a pathological diagnosis of AD also had either Lewy body disease, hippocampal sclerosis, or cerebrovascular disease sufficient to cause dementia. There are clear implications here for clinical trials, which are likely to enroll participants with mixed pathologies while working under the assumption that only AD is present.

Appendix A. Model selection strategy

To fit the model to the data, a modified backward selection algorithm was used due to the large number of parameters in the full models (e.g., p = 129 in Chapter 3). First, the full model was fit. Next all parameters with a p-value greater than or equal to 0.25 were removed and the model was refit; baseline smoking, which was specified in the model as three indicator variables, was only removed when all three levels of smoking had p-values at or above the cutoff.

The reduced model was compared to the full model with a likelihood ratio (LR) test. If the LR test had a p-value > 0.05, the reduced model was accepted. This process was repeated until all parameters remaining in the model were significant at the $\alpha = 0.10$ level. At this point, predictor variables were removed one at a time based on the highest p-value until all remaining predictors were significant at the $\alpha = 0.05$ level.

Table A.1. Chapter 3 model fitting iteration history.

Model	Parameters	-2 Log-L	α to stay in next model	LR (current vs. previous model)	p
Full	129	13326	0.25	--	--
Reduced 1	92	13341	0.20	15	0.99
Reduced 2	78	13350	0.15	9	0.83
Reduced 3	74	13357	0.10	7	0.14
Reduced 4	67	13368	--	11	0.14
Final	47	13409	--	41	0.037

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PROFESSIONAL EXPERIENCE

2012-present	Statistician, Principal, Sanders-Brown Center on Aging, University of Kentucky
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2002-2004	Data Coordinator, Institute for HIV, other STDs, and Pregnancy Prevention's Rural Health Project, Department of Communications, University of Kentucky

TEACHING EXPERIENCE

2007	Part-time Instructor, Department of Statistics (STA 200), Spring Semester, University of Kentucky (full responsibility)
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AWARDS & HONORS

2006	Delta Omega, UK College of Public Health

2006	Academic Excellence Award, UK College of Public Health
2006	Promising Investigator Award, UK College of Public Health
2006	Department of Biostatistics Award, UK College of Public Health
2005	Best Oral Presentation, UK College of Public Health 2nd Annual Research Symposium
2000	William Sowder Award for Best Critical Paper by a Graduate Student in English
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PUBLICATIONS

Mathews M, **Abner E**, Caban-Holt A, Kryscio R, Schmitt F. CERAD practice effects and attrition bias in a dementia prevention trial. *Int Psychogeriatr* 2013;Apr 10: 1-9. [Epub ahead of print].

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