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Adjusting for mortality when identifying risk factors for transitions to MCI and dementia

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Abstract

Risk factors for mild cognitive impairment (MCI) and dementia are often investigated without accounting for the competing risk of mortality, which can bias results and lead to spurious conclusions, particularly regarding protective factors. Here, we apply a semi-Markov modeling approach to 531 participants in the University of Kentucky Biologically Resilient Adults in Neurological Studies (BRAiNS) longitudinal cohort, over one-third of whom died without transitioning to a cognitively impaired clinical state. A semi-Markov approach enables a statistical study of clinical state transitions while accounting for the competing risk of death and facilitates insights into both the odds that a risk factor will affect clinical transitions as well as the age at which the transition to MCI or dementia will occur. Risk factors assessed in the current study were identified by matching those reported in the literature with the data elements collected on participants. The presence of Type II diabetes at baseline shortens the time it takes cognitively intact individuals to transition to MCI by seven years on average while use of estrogen replacement therapy at enrollment (baseline) decreases the time required to convert from MCI to dementia by 1.5 years. Finally, smoking and being overweight do not promote transitions to impaired states but instead hasten death without a dementia. In contrast, conventional statistical analyses based on Cox proportional hazards models fail to recognize diabetes as a risk and show that being overweight increases the risk of clinical MCI while high blood pressure at baseline increases the risk of a dementia.

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Keywords

MCI; dementia; multi-state models; semi-Markov; risk factors; competing events

Introduction

There is considerable interest in identifying risk factors for dementia. Multiple reports have identified genetic, lifestyle, and metabolic factors that may promote late life dementia. However, these reports may be limited by selective dropout due to medical factors and, most importantly, mortality within the cohort being studied. One study design to address dementia risk factors is to follow a cohort of non-demented individuals longitudinally using periodic cognitive assessments and evaluate changes in cognition in terms of annotated risk factors. However, there are several issues that arise in the analysis of these data.

Handling of competing events (for example, death and leaving the study) is a primary concern. One approach is to use a survival model to estimate the hazard rate associated with a risk factor for conversion to dementia [1–3]. This approach involves the key assumption that all non-events are independent of conversions and, hence, are right censored, including participants who die without cognitive impairment and/or dementia. It is now increasingly more recognized that statistical tools such as the Kaplan-Meier estimator of the survival function or the Cox regression model could lead to biased estimates of the time to an event if death without dementia is treated as non-informative right censored event rather than a competing risk for dementia [4–7].

A second issue is that although dementia is the outcome of interest, study participants could have clinically relevant outcomes other than a dementia at a given assessment. For example, a person often first converts to a state such as clinical mild cognitive impairment (MCI) for several years before finally entering a demented state.

Third, participants in longitudinal studies are assessed only periodically (e.g., annually). The natural history of cognitive decline, however, reflects a continuous rather than a discrete process. Thus, it follows that the date of a clinical diagnosis of MCI or a dementia (i.e., the date the event was first observed) is unlikely to coincide with the true date of the event (i.e., the date the event first occurred, should such a date exist) implying that the events of interest are necessarily interval censored events.

Here we report a model related to clinical status in a longitudinally-followed cohort that treats deaths without dementia as competing events, allows for intervening diagnoses such as a clinical MCI, and accommodates interval censored diagnoses. The approach relies on semi-Markov models to appropriately handle the interval censoring. This statistical method has the flexibility to model both the effect that a risk factor for a transition into clinical MCI or dementia has on both (1) the time it takes for the transition to occur and (2) the probability that such a transition occurs. While multi-state semi-Markov models have been used successfully in other contexts including cancer, HIV, and transplant studies, they have not been implemented in studies of dementia [8–10].

The modeling is applied to the Biologically Resilient Adults in Neurological Studies (BRAiNS) cohort, in which 198 of the 531 baseline clinically unimpaired subjects died prior to transition to clinical MCI or dementia. This offers a novel way to interpret the effect of a risk factor for an event of interest. For example, the model is able to facilitate insights into the impact on cognitive state from risk factors such as diabetes, smoking, and estrogen replacement therapy.

Materials and Methods

Subjects

BRAiNS is a longitudinal cohort of 1,030 older individuals at the University of Kentucky's Alzheimer's Disease Center (UK ADC) [11]. Participants consent to extensive annual cognitive and clinical examinations as well as brain donation upon death. Exclusion criteria at enrollment include age less than 60 years, active infectious diseases, neurological disorders, psychiatric disorders, disabling medical disorders, and dementing illness [11]. Subjects included in the current study (n=531) were assessed at least two times and comprise those included in a previous report [12]. All subjects were cognitively intact at study entry, and all research activities were approved by the University of Kentucky Institutional Review Board. Each participant gave written informed consent.

Cognitive Assessments

Annual cognitive assessments are administered to each participant and used to classify them into one of three cognitive states: normal or no serious impairment (NSI), clinical MCI, or dementia. The cognitive battery varied somewhat across time and has been discussed in detail in [11]. A diagnosis of clinical MCI requires each of the following:

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;
5. neurodegenerative etiology suspected [13].

The diagnosis of clinical MCI is based on a consensus team review by the examining physician, neuropsychologist, and the clinical research assistant who administered the cognitive assessment. A dementia classification results from a clinical consensus diagnosis of dementia (most often AD). An AD diagnosis is based on the criteria of the Joint Working Group of the National Institute of the Neurologic and Communication Disorders and Stroke-AD and Related Disorders (NINCDS-ARDA) [14]. Given the need for evidence of cognitive and functional decline, MCI and dementia diagnoses made by the clinical team are therefore difficult to complete in a fashion that is 'blinded' to prior assessments. However, given that participants have had 'back transitions' to the 'normal' state [12], bias based on the prior clinical state is somewhat mitigated as several clinicians who provide input for the consensus diagnosis are less informed concerning the participant's prior diagnosis.[14].

Cognitive States

Between assessments, participants may die or transition to clinical MCI or dementia. The flow of participants among the four states is depicted in Figure 1. Notice that the not seriously impaired (NSI) state is reserved for all participants who did not die or transition into clinical MCI and/or dementia between assessments. Hence, subjects in the NSI state could have memory complaints or perform worse than expected for age on some cognitive assessments but fail to qualify for a more severe diagnosis. Also, all transitions flow unidirectionally since it is assumed that once a participant meets the criteria for a diagnosis of clinical MCI (or dementia) they do not return to the NSI state. In the application to these participants from the BRAiNS cohort, 19 subjects made an apparent reverse transition from clinical MCI to NSI, but as discussed in Abner et al. 2012 these were determined to be the result of either underlying medical comorbidities that influenced cognition or diagnostic misclassification; the errant diagnoses were recoded.

Risk Factors

The list of factors to be examined as potential risks for transitions among the states in Figure 1 were selected by matching factors reported in the literature with the data elements collected on participants in the BRAiNS cohort. The factors examined and entered as indicator variables in the statistical models below are: APOE-ε4 carrier status (with and without an ε4 allele), female gender, low education (defined as high school or less), family history of dementia among 1st degree relatives, smoking (never smoker, former smoker, or current smoker), high blood pressure, use of estrogen hormone replacement therapy, and presence of Type II diabetes. The latter four variables were based on self-report data recorded at study entry.

Statistical Analysis

Semi-Markov Model—A semi-Markov model is used to model the flow of participants through the four states shown in Figure 1. The model is defined by attaching to each arrow in the diagram the probability of the transition and, independently, the holding time it takes for that transition to occur (e.g., age of the transition from initial state NSI or the time spent in MCI). The probabilities are assumed to follow one of two standard logistic models depending on the current state (NSI or MCI), while each holding time is assumed to follow a Weibull distribution that depends on both the current state as well as the state being entered. The purpose of the data analysis is to determine how the risk factors impact these models; effects are expressed as odds ratios (logistic models) or mean holding times (Weibull models). Readers can proceed to the Results section unless they wish to read a more formal definition of these models and the assumptions involved:

- A. $T_{i,j}$ = the transition holding time from state $i = 1$ or 2 into state $j > i$.
- B. $p_{i,j}$ = the probability of a transition from state $i = 1$ or 2 into state $j > i$.

Notice that the $T_{1,j}$ refers to the age at which a subject transitions from NSI ($j = 1$) into clinical MCI ($j = 2$) or dementia ($j = 3$) or death without dementia ($j = 4$), whichever comes first. We assume in the model that each participant entered the cohort at age 60 in the NSI state, and even though in fact almost all participants entered at a later age, the first assessment was always NSI since anyone assessed as clinical MCI or dementia was not enrolled in the BRAiNS cohort. Thus, we assume that a participant who was NSI at baseline was also NSI at age 60. The $T_{2,j}$ refers to the time it takes a participant to transition from clinical MCI into one of the competing absorbing states dementia ($j = 3$) or death without dementia ($j = 4$). These quantities are left censored since the exact time it takes to transition from NSI into clinical MCI is interval censored due to annual assessments. We assume that each $T_{i,j}$ is distributed as a Weibull random variable with survival distribution function:

$$S_{i,j}(t) = P(T_{i,j} > t) = \exp \{ - [t - a_{i,j}] / b_{i,j}]^{C_{i,j}} \exp(-\theta_{i,j}' \mathbf{X}_{i,j}) \} \text{ for } t \geq a_{i,j}$$

Here $a_{i,j}$ is a known age/time centering parameter, $\mathbf{X}_{i,j}$ is a vector of risk factors affecting the holding time for a transition from state i to state j , $b_{i,j}$ is an unknown age/time scaling parameter, $C_{i,j}$ is the Weibull scale parameter, and the vectors $\theta_{i,j}$ are unknown quantities to be estimated by the data. We assume $a_{1,j} = 60$ for $j = 2, 3$, or 4 and that $a_{2,j} = 0$ for $j = 3$ and 4 .

The sets $(p_{1,2}, p_{1,3}, p_{1,4})$ and $(p_{2,3}, p_{2,4})$ are probability vectors determined by polytomous logistic models as follows:

$$\text{Logit}(p_{i,j}/p_{i,4}) = \alpha_{i,j} + \beta_{i,j}' \mathbf{X}_{i,j}^* \text{ for } i = 1 \text{ or } 2 \text{ and } i < j < 4.$$

Here the $\alpha_{i,j}$ and the vectors $\beta_{i,j}$ represent unknown parameters while the $\mathbf{X}_{i,j}^*$ represent vectors of risk factors, many of which are observed at baseline. Notice that $p_{1,4} = 1 - p_{1,2} -$

$p_{1,3}$ and $p_{2,4} = 1 - p_{2,3}$. We assume that all participants in states 1 or 2 at the last observation are right censored since they will eventually enter states 3 or 4 if followed long enough; thus, $p_{1,1}$ and $p_{2,2}$ are considered survival rather than transition probabilities.

Likelihood and Estimation

Except for death, all transitions are interval censored. Each participant in this longitudinal study contributes either a single or double transition to the data analysis. Single transitions are denoted $NSI \rightarrow j$ for state $j = 2, 3$, or 4 in Figure 1, with the possibility that the study ends while the participant is still in NSI ($j = 1$). Double transitions are denoted $NSI \rightarrow MCI \rightarrow k$, where clinical MCI is observed between two successive assessments, and then a transition into dementia or death without a dementia ($k = 3, 4$) occurs at a later assessment. Again, the study may end, due to death or study dropout, while the participant is still in clinical MCI ($k = 2$).

Equations defining the contribution of each of these different types of transitions to the likelihood function for the model are expressed in terms of the survival distribution function (or probability density function) of the holding time variables and the logit functions for the transition probabilities. Each term in the likelihood function involves numerical integration, which implies a nonlinear algorithm is needed to determine the maximum likelihood estimates of the model parameters and their standard errors. To this end we programmed Equations 1–4 of [15] in PROC NLIN in PC-SAS/STAT 9.3® to fit the model to the data; this program is available upon request.

The strategy for model fitting was based on a modified backwards regression analysis. A basic model was fit to the data using known risk factors for conversion to clinical MCI and/or dementia (low education, $APOE-\epsilon 4$ carrier status, family history of dementia, and female sex). Note that age, a common risk factor, is entered into the model as the age at which a transition from NSI occurs after centering at age 60. The remaining factors were then entered one at a time into the model. In all cases a risk could affect the model in any one or more of eight areas (four affecting the time to a transition and four affecting the risk of a transition). A backwards algorithm was used to eliminate non-significant predictors as variables were entered into the model. A sensitivity analysis was conducted in which a stepwise procedure was used instead to identify significant predictors, but since this solution produced a poorer fit to the data as determined by Akaike's Information Criteria, only the solution produced by the backward algorithm is reported here. Statistical significance for a predictor to stay in the model was set at the 0.05 level.

Results

The baseline characteristics of the first 531 participants in the BRAiNS cohort are provided in Table 1. Note that the mean age at the first cognitive assessment was 72.6 ± 7.5 years. Further, the cohort is dominated by highly educated females, 30.4% are $APOE-\epsilon 4$ carriers, and 40.3% have a positive family history of dementia. A majority (52.7%) reported a history of smoking, with 9.2% smoking at baseline, and 42.8% had body mass indices (BMI) over 25 (overweight). Few participants were underweight (3.6% with BMI < 19) or obese (11.3% with BMI > 30 and 1.5% with BMI > 35).

The mean number of cognitive assessments for the cohort was 10.3 ± 4.1 . During this follow-up period participants made transitions into clinical MCI and/or dementia while many others died before such transitions. The frequency of each type of transition is provided in Table 2. Note that over one-third of the subjects (35.6%) are still at risk for a serious cognitive impairment while another third (35.8%) died before converting to a clinical MCI and/or dementia state. Also, another 19 MCI subjects (3.6%) died before

converting to dementia. Hence, the proportion of subjects who experienced the competing risk of death before dementia is substantial, representing 39.4% of the cohort. Also, note that 105 (19.8%) of the participants transitioned to clinical MCI during follow-up and 31 of these remain at risk for a dementia or death. Finally, 88 participants (16.6%) developed dementia during follow-up, with 52 of these transitioning directly from NSI to dementia between successive cognitive assessments.

Regression Model

Factors affecting transitions among the states in Figure 1 are listed in Table 3. As expected, having at least one APOE-ε4 allele increases the odds of a transition from NSI into either clinical MCI (OR = 2.11, P = 0.0045) or dementia (OR = 2.16, P = 0.021). Female gender only affects the odds of a transition from NSI directly into dementia (OR = 2.20, P = 0.020), and a positive family history of dementia increases the odds of a transition from clinical MCI into dementia (OR = 3.20, P = 0.036). On the other hand, current smoking at baseline appears to protect against a transition from NSI into clinical MCI, while presence of high blood pressure at baseline appears to protect against a transition from clinical MCI into dementia. Both are due to the competing risk of death. In the case of high blood pressure, a person in clinical MCI must either die or develop dementia. Therefore, if a risk protects against dementia, it promotes mortality. The role of smoking in these transitions is slightly more complicated and is clarified below. Factors affecting the time it takes to make a transition are listed in Table 4. Note that diabetes decreases the expected age of a transition from NSI into clinical dementia by 7 years (P = 0.0096). Both baseline current smoker and the baseline use of estrogen replacement therapy abbreviate the expected time it takes to transition from clinical MCI into dementia by 2.1 (P = 0.0029) and 1.5 (P = 0.043) years. Finally, being overweight at study entry promotes the competing risk of death and decreases the expected lifetime by 2.4 years (P = 0.027). A history of smoking (i.e., former smoker) decreases life expectancy by 2.8 years (P = 0.0092), and smoking at study entry (i.e., current smoker) decreases lifetime by 6.6 years (P < 0.0001).

Discussion

The identification of risk factors for the onset of MCI and dementia has been a topic of intense study for the past three decades in order to identify etiology and brain mechanisms as well as to inform prevention and symptomatic treatment efforts. These studies, despite the strengths and weaknesses of study methodologies (cf. [16],[17] for reviews) have identified risks, for example, including hypertension, obesity, and metabolic syndrome, as well as potential protective factors such as diet, exercise, and intellectual activity. However, as reviewed by Reitz and colleagues [16], there are disadvantages to different types of epidemiological studies (and their analytical approaches) that could influence our identification of dementia/MCI risk. In this manuscript we examined longitudinal data from a cohort of elderly subjects while taking into account the effect of an intervening death (one potential bias in epidemiological study outcomes) without a serious cognitive impairment. A given risk factor could affect a participant's clinical course in one of two ways: either it could affect the time it takes for a transition to occur, or it could affect the risk of a transition. The risk factors evaluated are frequently cited as risks for dementia and included family history, low education, APOE-ε4 carrier status, gender, body mass index (BMI), smoking, high blood pressure, Type II diabetes, and use of hormone replacement therapy.

An important caveat to our study is that clinical transitions between cognitive states are caused by many different brain diseases. For example, MCI and dementia can be due to AD, cerebrovascular disease, hippocampal sclerosis, and many other underlying medical conditions. At an academic institution clinician diagnostic sensitivity is approximately 71% to 87%, and specificity is low (70.8% to 74.7%) when compared to a neuropathologic

diagnosis [18]. This is an important point because the link between one risk factor and one disease may be confounded by the presence of other disease(s) with overlapping symptoms; a given risk factor may even have different effects on different diseases. Thus it is important not to conflate our results with an implication related to a particular disease, such as AD.

Mortality as a competing risk for MCI and dementia

The data show that baseline smoking and BMI > 25 abbreviate the time from NSI to a death without serious impairment. However, smoking did decrease the odds of a transition from NSI to MCI (potentially due to cerebrovascular factors). These data on the clinical state transitions therefore indicate that the risk of death related to smoking and high body mass index (BMI) competes with the risk of progressing to mild cognitive impairment (MCI) or dementia. Therefore, the current approach appears to explain inconsistent reports of these two factors on dementia risk (cf. [16]).

Three of the four large studies reviewed in [19] showed that smoking is a significant risk factor for AD. Our study shows that baseline smoking protects against a transition into clinical MCI (OR = 0.25), but that once in the MCI state, baseline smokers have a more rapid transition to dementia as well (Table 4), which might suggest support for that hypothesis. Instead, however, smoking is a significant risk factor for the competing risk of death since a former smoker dies on average 2.8 years earlier than a never smoker while a baseline smoker dies 6.6 years earlier. Two possible explanations for these discrepant results are that the majority of our cohort (52.7% of the cohort) are former or current smokers at baseline, and that previous studies did not adjust the transition into impaired states for the effect of the competing risk of a death without a serious impairment (which was the flow of 35.8% of the cohort in the current study).

Genetic and demographic risks

A review of the literature shows generally good agreement between our results and those reported by others for genetic and demographic risks (although this is the first study to evaluate many other variables and the competing risk of death). Risks associated with APOE-ε4 carrier status, low education, family history, and gender agree with the literature. To discuss other risk variables considered here we begin by presenting Figure 2, which is a cartoon representation of our results. Our model is compatible with the hypothesis that Alzheimer's disease (AD) genetic risk factors including family history are linked to progression to MCI and dementia.

Hormonal Risks

The Women's Health Initiative Memory Study (WHIMS) [20] demonstrated in a large randomized controlled trial that post-menopausal women who took either estrogen alone or estrogen plus progesterone were more likely to incur a probable dementia or MCI (with only 68 dementia cases the authors pooled the incident events MCI and probable dementia) than women who did not take hormones (OR = 1.76; 95% CI: 1.19–2.60). Magnetic resonance images on 1,403 of these women show that cognitive decline is linked to increased brain atrophy among conjugated estrogen users [21]. Our results differ from WHIMS in that the self-reported use of hormone replacement therapy at baseline decreases the time to transition from clinical MCI into dementia but does not increase the probability of such a transition. However, it should be noted that this factor almost achieved significance in that it increases the risk that a female will transition into MCI (OR = 2.06, P = 0.073) or dementia (OR = 2.33, P = 0.082). A recent study showed that the time lapse between menopause and commencement of therapy may be critical [22], but this information is not available in our database.

Metabolic factor risks

Diabetes did not affect the risk of a transition to MCI but did abbreviate the time it takes for this transition to occur. The impact of diabetes on cognition is likely to be complex and is presently incompletely understood [23, 24]. A summary of 25 systematic reviews and 250 research studies concluded that diabetes increases the risk of both cognitive decline as well as AD, although the evidence was rated as low (e.g., OR for AD is 1.4) [25]. This is supported in [16, 19, 26]. However, a third review [19] evaluated the role of metabolic factors in promoting the incidence of AD and concluded that diabetes is not a significant risk for AD. There is only modest support for Type II diabetes as a risk for Alzheimer-type pathology since in a review of eight case-control neuropathology studies the risk of AD pathology is either not increased (4 studies) or is decreased (4 studies) among Type II diabetics when compared to controls (cf. Table 4 of [27]). However, one of these studies [28] found that diabetes does increase the risk for AD pathology among APOE- ϵ 4 carriers, a result supported by [1] in their sample of 2,547 individuals 65 years or older followed for 5.4 years on average. By contrast to the relative lack of strong support for a direct link of diabetes and AD, there are extremely strong data that suggest diabetes contributes to cerebrovascular disease [24].

In the present study, we found that diabetes shortens the time it takes to transition to clinical MCI by 7 years, but diabetes does not alter subsequent risk for dementia transition. This may relate to the specific natural history of small vessel disease linked to diabetes, which may be less likely to lead to an AD-like clinical picture [24]. Also, inclusion of an interaction term between diabetes and APOE- ϵ 4 shows that this interaction affects the time it takes to transition from NSI directly to dementia in that APOE- ϵ 4 alone has no effect on the time and diabetes alone decreases the time by 5.4 years ($P = 0.097$), while having both diabetes and APOE- ϵ 4 decreases the time from NSI to dementia by 15.5 years ($P = 0.013$).

Reviews [19] examining the role of metabolic factors as promoters of AD incidence have concluded that hypertension is not a significant risk for AD but noted the role of measurement (cutoff values for the definition of hypertension) and timing (current versus midlife) that could account for the inconsistency among results in the literature. Our current data limit our ability to test the effect of using different cutoffs for BMI and hypertension as we have too few participants that meet the definition of obesity ($BMI > 30$) and have incomplete information on baseline systolic and diastolic blood pressures. In a recent study obese individuals who expressed metabolic abnormalities in mid-life had significantly greater cognitive decline when compared to normal weight individuals [29]. Our results show that being overweight at baseline accelerates a death without a serious impairment by 2.4 years, and that baseline self-report of hypertension increases the odds of death since it is protective for all transitions into clinical MCI and/or dementia. Other studies have found that hypertension and obesity are not risks for either MCI or AD [25]. Finally, it is important to note that if we modeled the age at which a transition to clinical MCI occurred by right censoring all other competing events (deaths, direct transition into dementia) using the Cox proportional hazards model, then a $BMI > 25$ is a significant risk for such a transition ($P < 0.02$).

Modeling issues

Three issues related to the present risk model concern the method for identifying significant risk factors, the choice of a baseline age, and comparisons with more traditional models. With respect to the former we used a backwards algorithm with significance level to stay set at 0.05. Had we increased this to 0.10, then many more factors would be identified as significant. Hormone replacement therapy would be significant for the probability of a transition from NSI to either dementia or MCI (increased risk) as would baseline high blood

pressure (decreased risk). Baseline smoking would decrease the age of a transition into MCI by 6.5 years, while female gender would increase the age by 2.2 years. Hormone replacement therapy would increase the age for a dementia by 5.5 years while the presence of diabetes would decrease this age by 5.9 years. Family history would decrease the age of a death by 2.4 years. Most of the participants came to the cohort during their 60s and early 70s when the incidence of Alzheimer's-type dementia is low. Hence, excluding dementias from entering the cohort likely did not introduce significant bias as would happen had recruitment occurred at later ages [30]. Finally, use of the more traditional Cox model, which ignores mortality effects, to predict age of conversion to MCI yields a different solution. In particular, being overweight at baseline is a risk for this conversion (in addition to APOE- ϵ 4), while the model presented here finds being overweight as a risk for death instead. A Cox model to predict age of conversion to dementia, which ignores the effect of mortality as well as the possibility of first converting to MCI finds APOE- ϵ 4, family history, and baseline high blood pressure as significant risks. The model presented here finds APOE- ϵ 4 and gender as risks for direct conversion to dementia. High blood pressure and family history also affect conversion, but only through the transition into MCI. In all modeling frameworks high blood pressure at baseline is protective against the transition, which is hard to explain in the Cox model but easily explained in the semi-Markov model as it is a positive risk for death while in MCI.

Summary

In this manuscript we explored the use of a semi-Markov model to adjust for the effect of competing events (death without a dementia) and interval censoring when examining potential risk factors for transitions into clinical MCI and/or dementia. Previous work by this research group explored the use of Markov chains for this purpose (see e.g., [12, 31]). Markov models are easy to understand since they rely only on odds ratios for identifying significant risks, allow for transient impaired states between cognitively intact and clinical MCI, and allow for time dependent risk factors. The semi-Markov approach does not allow for the latter two properties but does not assume that all events are interval censored (e.g., deaths) and does not require cognitive assessments to be equally spaced. The Markov approach emphasizes odds ratios for one-step transitions (i.e., predicting the next assessment) but additional complex arithmetic is required to study the effect of a risk factor over several successive cognitive assessments [32]. The semi-Markov model uses the waiting time variables in Table 4 to assess the long term effect of a risk factor without further arithmetic and can be a valuable tool in the evaluation of dementia risk.

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References

1. Irie F, Fitzpatrick AL, Lopez OL, Kuller LH, Peila R, Newman AB, Launer LJ. Enhanced risk for Alzheimer disease in persons with type 2 diabetes and APOE epsilon4: the Cardiovascular Health Study Cognition Study. *Arch Neurol*. 2008; 65:89–93. [PubMed: 18195144]
2. Kuller LH, Lopez OL, Newman A, Beauchamp NJ, Burke G, Dulberg C, Fitzpatrick A, Fried L, Haan MN. Risk factors for dementia in the cardiovascular health cognition study. *Neuroepidemiology*. 2003; 22:13–22. [PubMed: 12566949]
3. Whitmer RA, Gustafson DR, Barrett-Connor E, Haan MN, Gunderson EP, Yaffe K. Central obesity and increased risk of dementia more than three decades later. *Neurology*. 2008; 71:1057–1064. [PubMed: 18367704]

4. Andersen PK, Geskus RB, de Witte T, Putter H. Competing risks in epidemiology: possibilities and pitfalls. *Int J Epidemiol*. 2012; 41:861–870. [PubMed: 22253319]
5. Murphy TE, Han L, Allore HG, Peduzzi PN, Gill TM, Lin H. Treatment of death in the analysis of longitudinal studies of gerontological outcomes. *J Gerontol A Biol Sci Med Sci*. 2011; 66:109–114. [PubMed: 21030467]
6. Pintile, M. Competing risks, a practical perspective. Hoboken NJ: Wiley; 2006.
7. Crowder, M. Multivariate survival analysis and competing risks. New York NY: CRC Press; 2012.
8. Castelli C, Combescure C, Foucher Y, Daures JP. Cost-effectiveness analysis in colorectal cancer using a semi-Markov model. *Stat Med*. 2007; 26:5557–5571. [PubMed: 18058847]
9. Foucher Y, Giral M, Soullillou JP, Daures JP. A semi-Markov model for multistate and interval-censored data with multiple terminal events. Application in renal transplantation. *Stat Med*. 2007; 26:5381–5393. [PubMed: 17987670]
10. Kang M, Lagakos SW. Statistical methods for panel data from a semi-Markov process, with application to HPV. *Biostatistics*. 2007; 8:252–264. [PubMed: 16740624]
11. Schmitt FA, Nelson PT, Abner E, Scheff S, Jicha GA, Smith C, Cooper G, Mendiondo M, Danner DD, Van Eldik LJ, Caban-Holt A, Lovell MA, Kryscio RJ. University of Kentucky Sanders-Brown healthy brain aging volunteers: donor characteristics, procedures and neuropathology. *Curr Alzheimer Res*. 2012; 9:724–733. [PubMed: 22471862]
12. Kryscio RJ, Schmitt FA, Salazar JC, Mendiondo MS, Markesbery WR. Risk factors for transitions from normal to mild cognitive impairment and dementia. *Neurology*. 2006; 66:828–832. [PubMed: 16567698]
13. Jicha GA, Abner E, Schmitt FA, Cooper GE, Stiles N, Hamon R, Carr S, Smith CD, Markesbery WR. Clinical features of mild cognitive impairment differ in the research and tertiary clinic settings. *Dement Geriatr Cogn Disord*. 2008; 26:187–192. [PubMed: 18724049]
14. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984; 34:939–944. [PubMed: 6610841]
15. Foucher Y, Giral M, Soullillou JP, Daures JP. A flexible semi-Markov model for interval-censored data and goodness-of-fit testing. *Stat Methods Med Res*. 2010; 19:127–145. [PubMed: 18765502]
16. Reitz C, Brayne C, Mayeux R. Epidemiology of Alzheimer disease. *Nat. Rev. Neurol*. 2011; 7:137–152. [PubMed: 21304480]
17. Mayeux R, Stern Y. Epidemiology of Alzheimer disease. *Cold Spring Harbor Perspect. Med*. 2012; 2:a006239.
18. Beach TG, Monsell SE, Phillips LE, Kukull W. Accuracy of the clinical diagnosis of Alzheimer disease at National Institute on Aging Alzheimer Disease Centers, 2005–2010. *J Neuropathol Exp Neurol*. 2012; 71:266–273. [PubMed: 22437338]
19. Purnell C, Gao S, Callahan CM, Hendrie HC. Cardiovascular risk factors and incident Alzheimer disease: a systematic review of the literature. *Alzheimer Dis Assoc Disord*. 2009; 23:1–10. [PubMed: 18703981]
20. Shumaker SA, Legault C, Kuller L, Rapp SR, Thal L, Lane DS, Fillit H, Stefanick ML, Hendrix SL, Lewis CE, Masaki K, Coker LH. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA*. 2004; 291:2947–2958. [PubMed: 15213206]
21. Espeland MA, Tindle HA, Bushnell CA, Jaramillo SA, Kuller LH, Margolis KL, Mysiw WJ, Maldjian JA, Melhem ER, Resnick SM. Brain volumes, cognitive impairment, and conjugated equine estrogens. *J Gerontol A Biol Sci Med Sci*. 2009; 64:1243–1250. [PubMed: 19729392]
22. Shao H, Breitner JCS, Whitmer RA, Wang J, Hayden K, Wengreen H, Corcoran C, Tschanz J, Norton M, Munger R, Welsh-Bohmer K, Znadi PP. For the Cache County Investigators. Hormone therapy and Alzheimer disease dementia: new findings from the Cache County Study. *Neurology*. 2012; 79:1846–1852. [PubMed: 23100399]
23. Luchsinger J, Reitz C, Patel B, Tang M, Manly JJ, Mayeux R. Relation of diabetes to mild cognitive impairment. *Archives of Neurology*. 2007; 64:570–575. [PubMed: 17420320]

24. Nelson PT, Smith CD, Abner EA, Schmitt FA, Scheff SW, Davis GJ, Keller JN, Jicha GA, Davis D, Wang-Xia W, Hartman A, Katz DG, Markesbery WR. Human cerebral neuropathology of Type 2 diabetes mellitus. *Biochim Biophys Acta*. 2009; 1792:454–469. [PubMed: 18789386]
25. Williams JW, Plassman BL, Burke J, Benjamin S. Preventing Alzheimer's disease and cognitive decline. *Evid Rep Technol Assess (Full Rep)*. 2010:1–727. [PubMed: 21500874]
26. Reitz C, Brayne C, Mayeux R. Epidemiology of Alzheimer disease. *Nat Rev Neurol*. 2011; 7:137–152. [PubMed: 21304480]
27. Nelson P, Head E, Schmitt F, Davis P, Neltner J, Jicha G, Abner E, Smith C, Van Eldik L, Kryscio R, Scheff S. Alzheimer's disease is not "brain aging": neuropathological, genetic, and epidemiological human studies. *Acta Neuropathologica*. 2011; 121:571–587. [PubMed: 21516511]
28. Peila R, Rodriguez BL, Launer LJ. Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: The Honolulu-Asia Aging Study. *Diabetes*. 2002; 51:1256–1262. [PubMed: 11916953]
29. Singh-Manoux A, Czernichow S, Elbaz A, Dugravot A, Sabia S, Hagger-Johnson G, Kaffashian S, Zins M, Brunner EJ, Nabi H, Kivimaki M. Obesity phenotypes in midlife and cognition in early old age: the Whitehall II cohort study. *Neurology*. 2012; 79:755–762. [PubMed: 22915175]
30. Yu L, T SL, Snowdon DA, Kryscio RJ. Effects of ignoring baseline on modeling transitions from intact cognition to dementia. *Computational Statistics and Data Analysis*. 2009; 53:3334–3343. [PubMed: 20161282]
31. Abner EL, Kryscio RJ, Cooper GE, Fardo DW, Jicha GA, Mendiondo MS, Nelson PT, Smith CD, Van Eldik LJ, Wan L, Schmitt FA. Mild cognitive impairment: statistical models of transition using longitudinal clinical data. *Int J Alzheimers Dis*. 2012; 2012:291920. [PubMed: 22536535]
32. Yu L, Griffith WS, Tyas SL, Snowdon DA, Kryscio RJ. A nonstationary Markov transition model for computing the relative risk of dementia before death. *Stat Med*. 2010; 29:639–648. [PubMed: 20087848]

Figure 1.
Flow diagram of transitions among states

Figure 2.
Cartoon representation of the results

Table 1

Demographic characteristics of the cohort (n = 531)

Baseline Characteristic	Percent or mean $\pm$ st. dev.
Age	73.2 $\pm$ 7.4
Education	16.0 $\pm$ 2.4
Female	63.1
APOE:	30.3
2/2	0.9
2/3	12.4
2/4	2.3
3/3	56.3
3/4	26.4
4/4	1.7
Family history of dementia	40.3
Ever smoke:	52.7
Former smoker	43.5
Baseline smoker	9.2
Type II diabetes	8.3
BMI > 25	42.7
High blood pressure	36.5
Hormone replacement therapy	18.6

Table 2

Frequency of each transition type

Transition Type	Frequency	Percent
NSI → NSI	184	35.65
NSI → MCI	19	3.58
NSI → Dementia	52	9.79
NSI → Death	190	35.78
NSI → MCI → MCI	31	5.84
NSI → MCI → Dementia	36	6.78
NSI → MCI → Death	19	3.58

Table 3

Risk factors affecting transitions among states in Figure 1. Odds ratios presented are odds of stated transition vs. odds of transition to death.

Transition	Risk factor	Odds ratio	95% C.I.	P value
NSI → MCI	APOE-ε4	2.11	1.26–3.52	0.045
	Baseline Smoker	0.25	0.07–0.83	0.024
NSI → Dementia	APOE-ε4	2.16	1.13–4.15	0.021
	Female	2.22	1.13–4.34	0.036
MCI → Dementia	High BP baseline	0.25	0.08–0.75	0.013
	Family History	3.20	1.08–9.51	0.036

Table 4

Risk factors affecting the time to a transition in Figure 1

Transition	Risk	Mean Age $\pm$ St. Dev.	P value
NSI $\rightarrow$ MCI	None	84.2 $\pm$ 6.4	
	Diabetes	77.2 $\pm$ 4.6	0.0096
NSI $\rightarrow$ Dementia	None	87.0 $\pm$ 6.9	
NSI $\rightarrow$ Death	None	90.5 $\pm$ 7.9	
	Former Smoker	87.7 $\pm$ 7.1	0.0092
	Baseline Smoker	83.9 $\pm$ 6.2	<0.0001
	BMI > 25	88.1 $\pm$ 7.3	0.027
		Mean Time (Years) $\pm$ St. Dev.	
MCI $\rightarrow$ Dementia	None	2.8 $\pm$ 1.1	
	Estrogen Replacement Therapy	1.3 $\pm$ 0.5	0.0029
	Baseline Smoker	0.66 $\pm$ 0.26	0.043
MCI $\rightarrow$ Death	None	5.9 $\pm$ 3.1	