Contents lists available at Science-Gate

International Journal of Advanced and Applied Sciences

Journal homepage: http://www.science-gate.com/IJAAS.html

The effects of age, gender, education, and APOE on the transitions from a cognitively normal state to mild cognitive impairment and dementia

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ARTICLE INFO

Article history:
Received 16 September 2020
Received in revised form
23 December 2020
Accepted 31 December 2020

Keywords:
Risk factors
Elderly
Apolipoprotein 4 allele
Cognitive impairment
Dementia

ABSTRACT

To determine the effects of a number of risk factors on the transition from a cognitively normal state to mild cognitive impairment (MCI), as transient states, and then to dementia and death, as absorbing states. The study used the data of 8,456 subjects obtained from the Uniform Data Set (UDS) conducted by the National Alzheimer Coordinating Center (NACC), and categorized them into four cognitive states; normal and MCI (transient states), dementia, and death (absorbing states). Then, statistical analysis was conducted to obtain how age, gender, educational attainment, and presence of apolipoprotein 4 allele (APOE) affect the odds of transitioning from one cognitive state to another, and to death as a competing state. Both age and APOE risk had profound effects on the cognitive transition of subjects from one state to another, and to a lesser extent, gender and education attainment. This study has contributed more evidence that risk factors like age, presence of apolipoprotein 4 allele (APOE), and to a lesser extent, education and gender have significant effects in all or some of the transitions from one cognitive state to another among elderly people.

1. Introduction

The aging of the U.S. population is projected to bring about many health problems (Knickman and Snell, 2002). One of these issues is related to the elderly's cognitive function and health. Today only, for instance, there are over 16 million individuals in the U.S. who live with some type of cognitive impairment (USDHHS, 2011). Those individuals usually suffer from multiple health problems, have longer stays in hospitals or nursing homes, and have costs that are nine times higher than the expenses of those who are at the same age but with no cognitive impairment (USDHHS, 2011).

Mild cognitive impairment (MCI) and dementia are some of those prevalent conditions among the older population (Cheng et al., 2012). MCI is known as a cognitive dysfunction that usually occurs after a normal cognitive state and before dementia (Roberts et al., 2014; Kryscio et al., 2006), whereas dementia is defined by the Alzheimer's Society as "a set of symptoms that may include memory loss and difficulties with thinking, problem-solving, or language" (ASC, 2013). It is believed that there are multiple stages or states through which an elder person with cognitive impairment go through (Bruscoli and Lovestone, 2004), and these transitions are believed to be influenced by various psychological, physical, and/or lifestyle risk factors (Cheng et al., 2012; Kryscio et al., 2006; Abner et al., 2014; Etgen et al., 2011).

For example, cardiovascular diseases have been considered as main risk factors in the development of MCI and the progression to dementia (Kivipelto et al., 2001; Luck et al., 2010), although there have been mixed results about the nature of this causality (DeCarli et al., 2004; Solfrizzi et al., 2004). Likewise, diabetes has been linked to MCI and dementia in a systematic meta-analysis study (Cheng et al., 2012).

However, there are also many other risk factors that are likely to influence the development of MCI and the transition to dementia, such as age, gender, education, and genes. A study in Germany, for instance, found that incidence rates of MCI increased with age (Luck et al., 2010); a consistent finding with another study that estimated the relative risk of age as a risk factor to be 5.93 (Solfrizzi et al., 2004). Additionally, the transition from MCI to dementia and Alzheimer disease was found to be gender-specific (Kim et al., 2015), and women with MCI showed twice as much decline as men with this condition (Alzheimer's Association, 2015). Further, a

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longitudinal study reported that higher levels of education and brain volume were strong predictors of a slow progression to cognitive impairment in later ages (ADEAR, 2012). This was also supported by another finding that showed a protective effect of education (Solfrizzi et al., 2004). Moreover, individuals who carry apolipoprotein 4 allele (*APOE* ε4 allele) were found to be at a high risk of developing MCI (Luck et al., 2010), and at a higher risk of progressing to dementia when they have both, MCI and *APOE* ε4 allele.

Although there have been many studies focusing on different risk factors affecting MCI, dementia, and the transitioning nature of them, a large body of the literature had inconclusive results, mostly due to issues related to study designs (Etgen et al., 2011). For instance, in a cross-sectional study, Lautenschlager et al. (2005) reported no difference in *APOE* ε4 distribution between the study subjects and their healthy-group counterparts. Likewise, a study of Nigerian subjects found no association between the *APOE* ε4 allele and dementia (Gureje et al., 2011). Moreover, another study was uncertain of the effect of female gender on Alzheimer disease (Launer et al., 1999), while a study in China found that developing dementia was more likely among male participants when assessing the relationship between loneliness and dementia (Zhou et al., 2017). Additionally, education was reported to have no-association, insignificant, or at the most suggestive association with dementia in three different studies (Persson and Skoog, 1996; Ochayi and Thacher, 2006; Bonaiuto et al., 1995). Those and other studies have mostly adopted similar methodological approaches and designs, such as cross-sectional surveys, case-control, and cohort study designs, where each approach has its own limitations. This study, on the other hand, adopts a different design (multistate Markov model) and utilizes a large and comprehensive data pool of subjects to explore the influence on a number of risk factors during transition states of MCI and dementia (Morris et al., 2006). The study hypothesizes that risk factors like age, gender, educational attainment, and *APOE* are associated with the transition from normal cognitive state to MCI and/or dementia and/or death.

2. Methods

2.1. Participants

The Uniform Data Set (UDS) from the National Alzheimer Coordinating Center (NACC) is a public dataset that was used to obtain the study participants (Morris et al., 2006). Using a standardized protocol, the UDS collects longitudinal data of persons with a defined set of common clinical characteristics from Alzheimer's disease centers (ADCs) across the nation (Morris et al., 2006; Spackman et al., 2012). From the December 2014 data freeze, 8,456 participants, who were 65 years or older at their first visit, and had been diagnosed with normal cognition or MCI at baseline were included in this study. Information on the participants' gender, years of education, and *APOE* status were also collected with no missing values. The UDS data and research activities were in accordance with the required research ethics standards (Morris et al., 2006).

2.2. Statistical analysis

At each visit, participants have been classified into four mutually exclusive states; two transient states: (1) normal cognition and (2) mild cognition impairment or MCI; and two absorbing states: (3) demented and (4) death. Normal cognition is the state where there is no existence of cognitive impairments and where there is a lack of any clinical diagnosis of MCI and dementia, while the state of MCI represents those who were diagnosed with MCI according to standards used by the National Alzheimer's Coordinating Center's Uniform Data Set (Abner et al., 2014; Morris et al., 2006). Dementia, on the other hand, is the state where a participant was clinically diagnosed with dementia according to the DSM-IV criteria (Abner et al., 2014). The criteria adopted to characterize each MCI and demented state ranged from clinical assessment to a standardized questionnaire and examinations designed to assess cognitive function among the subjects. More detailed information on this can be found in Morris et al. (2006).

A multistate Markov chain was fitted to the data in order to estimate the odds of transitioning from one state to another. One advantage of using the multistate Markov chain in studying transitions in cognitive status is that it takes into consideration the competing risks related to the outcome of interest, which could bias the results if not accounted for in the analysis since death or dropouts might occur before the onset of dementia (Abner et al., 2014). Any participant might have moved between transient states but once landed in absorbing states, he or she was observed in that state as the endpoint (Fig. 1). Death is considered a competing risk here due to the possibility that a participant might transition from any state directly to death without passing through MCI and/or dementia states. This study uses the terms "from state" and "to state" to describe these movements.

Odds ratios, and 95% CIs, were used to estimate the odds of each specified transition at the next assessment given the number of other risk factors. These risk factors included the participant's age (measured at the previous visit), gender (female=1 and male=0), education (none to 30 years of education), and *APOE* status (either with no risk of or with at least one ε4 allele). The analyses were performed using the SAS 9.4 software package (SAS, 2013).

3. Results

Table 1 shows the risk-factor characteristics of subjects at the baseline states of normal cognitive

state and MCI. The average age of all participants was 75.7 years, with those at the MCI state having a slightly higher age (76.4 years) than those at the baseline normal state (74.9 years).

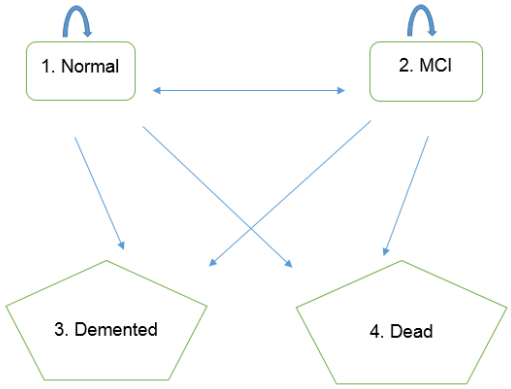

Fig. 1: Diagram of possible transitions between cognitive states and death

Also, women were over 20% more than men in the study, where most of them (44.5%) were at baseline normal cognition compared to those at baseline MCI (15.8%). Men, however, were found to be slightly more at baseline MCI (16.1%) compared to women but more men, in general, were at the baseline normal state (23.6%). The subjects' education attainment levels were almost similar to those at the normal state having 5 more months of education (15.7). But the most notable characteristic was that almost half of the subjects who were at the normal baseline state had no *APOE* Allele risk (49.2%), while the other half of subjects were distributed as follows: 18.9% had at least one *APOE* Allele at baseline normal state, 14.4% had at least one *APOE* allele at baseline MCI, and 17.5% had no APOE allele risk at baseline MCI.

Table 2 shows the effects of each of those risk factors for each transition state. Not surprisingly, age was a significant risk factor in the transition from one state to another, except for the reverse transition from MCI to normal (OR 0.96, 95% CI 0.95-0.97).

Table 1: Baseline risk-factor characteristics of the Alzheimer's disease centers participants

Characteristics	All Subjects (n=8456)	Baseline Normal (n=5759)	Baseline Mild Cognitive Impairment (n=2697)
Years of Education, Mean [95% CI]	15.5 [15.4, 15.6]	15.7 [15.6, 15.8]	15.2 [15.1, 15.3]
Gender			
Female, %	60.3%	44.5%	15.8%
Male, %	39.7%	23.6%	16.1%
apolipoprotein 4 allele *(APOE)* Risk			
At least one ε4 allele, %	33.3%	18.9%	14.4%
No ε4 allele, %	66.7%	49.2%	17.5%
Participant Age, Mean [95% CI]	75.7 [75.5, 75.8]	74.9 [74.7, 75.1]	76.4 [76.1, 76.7]

An increase in age had 1.06 (95% CI 1.05-1.07) times higher odds of moving from normal to MCI, 1.09 (95% CI 1.08-1.12) from normal to dementia, 1.13 (95% CI 1.12-1.15) from normal to death, 1.03 (95% CI 1.02-1.04) from MCI to dementia, and 1.16 (95% CI 1.13-1.18) from MCI to death, adjusting for other risk factors. Unlike age, gender had different and sometimes insignificant results. Being a woman, compared to a man, was likely to have a protective effect (OR 0.72, 95% CI 0.64-0.81) from moving from normal to MCI, and from normal to death (OR 0.67, 95% CI 0.56-0.79), and consistently had a higher effect of a reverse transition from MCI to normal (OR 1.24, 95% CI 1.09-1.42), adjusting for all covariates. The rest of the transitions had odds ratios that were insignificant. Furthermore, having a 1-year increase in education was associated with lower odds of moving from normal to MCI (OR 0.96, 95% CI 0.94-0.98), from normal to dementia (OR 0.91, 95% CI 0.86-0.96), and from normal to death (OR 0.95, 95% CI 0.92-0.97), controlling for other risk factors. The associations between education and other transitions were not significant, including reported higher odds of a reverse transition from MCI back to normal for those who had higher education attainment. However, perhaps the most significant risk factor was subjects carrying at least one apolipoprotein 4 allele. APOE risk was significantly associated with moving from a normal cognition state to dementia, compared to not having an APOE risk, with an odds ratio of 2.49 (95% CI 1.77-3.50). It also showed higher odds of transitioning from normal to MCI (OR 1.84, 95% CI 1.31-1.68), and from MCI to dementia (OR 1.95, 95% CI 1.72-2.20), and a protective effect of moving from MCI back to normal (OR 0.56, 95% CI 0.48-0.64), adjusting for the rest of the variables.

4. Discussion

In this study, both age and *APOE* risk showed profound effects on the cognitive transition of subjects from one state to another and to a lesser extent, gender and educational attainment. A one-year increase in the age of subjects affected all transitions, whether in transient or absorbing states. It also showed a protective effect in the reverse transition from an MCI state to a cognitively normal state, that is, younger subjects were more likely to go back to a normal cognitive state after being in the MCI state. Likewise, and consistent with the descriptive characteristics in Table 1 of *APOE* 4 allele as a risk factor, the presence of at least one *APOE* Allele affected 4 out of the overall 6 transitions, with the highest odds (OR 2.49) among all risk factors associated with moving from a cognitively normal state to a demented state. Being a female and having an additional one-year educational attainment, on the other hand, had protective effects on only three of all transitions.

One important observation to point out was the surprising similarity of the high magnitude in the odds of transferring from a cognitively normal state to dementia for subjects with at least one *APOE* compared to the magnitude of the odds ratio for transitioning from normal to MCI state. In the former, the odds ratio was 2.49 compared to 1.48 in the latter, which was also a highlight in the other study mentioned earlier (Kryscio et al., 2006). This implies that APOE risk is, in fact, a risk factor for dementia more than mild cognitive impairment since those who had it were reported to have an increased decline in their cognitive function to become demented without landing in the MCI state first.

Table 2: Odds ratios and the significance of the effect of risk factors on transitions between cognitive states

Parameter	Risk Comparison	Odds Ratios [a]	95% CI	p-value
	Normal → MCI [b]			
Age [c]	1-year increase in age	1.06	1.05-1.07	<0.0001
Gender	female vs. male	0.72	0.64-0.81	<0.0001
Education	1-year increase in education level	0.96	0.94-0.98	<0.0001
APOE [d] Risk	at least one ε4 allele vs. no ε4 allele	1.48	1.31-1.68	<0.0001
	Normal → Dementia			
Age [c]	1-year increase in age	1.09	1.08-1.12	<0.0001
Gender	female vs. male	0.78	0.56-1.10	0.1639
Education	1-year increase in education level	0.91	0.86-0.96	0.0006
APOE [d] Risk	at least one ε4 allele vs. no ε4 allele	2.49	1.77-3.50	<0.0001
	Normal → Death			
Age [c]	1-year increase in age	1.13	1.12-1.15	<0.0001
Gender	female vs. male	0.67	0.56-0.79	<0.0001
Education	1-year increase in education level	0.95	0.92-0.97	0.0002
APOE [d] Risk	at least one ε4 allele vs. no ε4 allele	0.89	0.72-1.12	0.3453
	MCI [b] → Normal			
Age [c]	1-year increase in age	0.96	0.95-0.97	<0.0001
Gender	female vs. male	1.24	1.09-1.42	0.0011
Education	1-year increase in education level	1.01	0.99-1.03	0.5970
APOE [d] Risk	at least one ε4 allele vs. no ε4 allele	0.56	0.48-0.64	<0.0001
	MCI [b] → Dementia			
Age [c]	1-year increase in age	1.03	1.02-1.04	<0.0001
Gender	female vs. male	1.02	0.91-1.15	0.7068
Education	1-year increase in education level	0.99	0.98-1.01	0.6317
APOE [d] Risk	at least one ε4 allele vs. no ε4 allele	1.95	1.72-2.20	<0.0001
	MCI [b] → Death			
Age [c]	1-year increase in age	1.16	1.13-1.18	<0.0001
Gender	female vs. male	0.78	0.58-1.06	0.1102
Education	1-year increase in education level	0.99	0.95-1.04	0.7193
APOE [d] Risk	at least one ε4 allele vs. no ε4 allele	1.03	0.72-1.47	0.8607

[a] Reported odds ratios after adjusting all covariates; [b] MCI = Mild cognitive state; [c] Age was centered at 75 years; [d] apolipoprotein 4 allele

These findings can be supported by fairly similar results conducted through a longitudinal study that looked at the effects of the same risk factors, in addition to family history, on the transition from the cognitively normal state to MCI and demented states (Kryscio et al., 2006). Although in Kryscio et al. (2006) study, some of these risk factors were measured differently, the overall results of that study showed that age and *APOE*, and to a lesser extent education, had significant impacts on the transition between those states. Similar to our finding, age was effective in all cognitive states, with increased age impacting both transient and absorbing states. The presence of at least one *APOE* allele had also the same effects on transitioning from normal cognitive state to MCI and to dementia. Education attainment (measured as 13-15 vs >=16) was the only significant risk factor with its effect on moving from MCI to the normal state while being a female had no significant effects like what has been obtained in this study. However, when exploring more recent literature, similar findings to our study were observed. For instance, age was found to be significantly associated with reduced performance across different cognitive tasks (Huntley et al., 2017), and with developing dementia (Wang et al., 2017). Also, the presence of the *APOE* ε4 allele was indicative of greater dementia risk in a Swedish cohort study that followed participants for nine years (Wang et al., 2017). In terms of education, Xu et al. (2016) revealed a dose-response association between educational attainment and dementia, where a one-year increase in education reduced dementia by 7%. Other studies have also demonstrated that higher education levels and performance were protective factors of dementia (Liang et al., 2020; Huntley et al., 2017; Dekhtyar et al., 2015). Finally, the female gender has also shown to be a risk factor of dementia in several studies, where being a female increased the risk of developing dementia and other cognitive decline diseases (Wang et al., 2017; Podcasy and Epperson, 2016; Chêne et al., 2015).

However, it is important to state that this study has a number of drawbacks. First, the division of the cognitive states might have neglected the presence of more than two transient states. For instance, in Kryscio et al.'s (2006) study, a transient state called mixed MCI was added as a state between MCI and dementia. The absence of such a state is likely to undermine our results since the evaluation of risk factors and especially those associated with the demented state, might not be entirely realized. Apart from the fact that UDS data does not provide an

assessment of other dementing illnesses (Morris et al., 2006), in that study, the effects of most of the risk factors on transitioning from mixed MCI were not significant, except for age (mixed MCI to dementia and to death) and to a lesser extent being a female (only significant in moving from mixed MCI to death) (Kryscio et al., 2006). Second, our study might have omitted the inclusion of some important risk factors in the analysis, such as family history. This might have changed the magnitude or even the sign of the effects of other risk factors. But again, the effect of family history was not significant as well in the Kryscio et al. (2006) study. Third, there might be a concern regarding the real effect of education and how much variation really exists in this variable. Subjects had almost the same average years of education at baseline normal and MCI states, with a difference of only five months. This might be a sign that the resulted effects of education, although not a very high impact, could be undermined. Perhaps, a better measurement of this variable is needed in order to capture its real effect on cognitive transitions. Finally, and most importantly, the utilized data in this study might have been relatively old. The reason for utilizing data of such period is that UDS has since focused on factors that are not of relevance to the purpose of this study (i.e., clinical information related to front temporal lobar degeneration and Lewy body disease), and more importantly, the collection of such data was completed on a voluntary basis (NACC, 2017), that may hinder the large dataset used in our study, which included subjects from all over the nation. However, it must be stressed that it is inaccurate to generalize these findings to other older population since the methodology of the data collection and sampling strategy in UDS is likely to suffer from a selection bias as subjects who participate in the study do so willingly and by knowing that the data are collected for academic research, which questions the lack of variation in the characteristics of those subjects, and which might explain the non-variability in their educational attainment levels, for example.

This study has contributed more evidence that risk factors like age, presence of apolipoprotein 4 allele, and to a lesser extent education and gender have significant effects in all or some of the transitions from one cognitive state to another among elderly people. It demonstrated several design and analytic strengths. First, we had a large sample size compared to the study of Kryscio et al. (2006), which gives our analysis more statistical power in order to draw more accurate findings. Second, the reliance on the UDS data as the source of the sample and the measurement of risk factors is likely to be advantageous and it certainly adds to the literature to be one of few studies using this comprehensive database. Further research can build upon these and other findings by including other risk factors, such as family history, environmental factors, and genetics, and by considering more cognitive states in order to better understand the real effects of these risk factors on cognitive transitions. Such studies would assist policymakers in tailoring public health preventive policies that detect and target populations with potential cognitive decline.

Acknowledgment

The NACC database is funded by NIA/NIH Grant U01 AG016976. NACC data are contributed by the NIA-funded ADCs: P30 AG019610 (PI Eric Reiman, MD), P30 AG013846 (PI Neil Kowall, MD), P50 AG008702 (PI Scott Small, MD), P50 AG025688 (PI Allan Levey, MD, PhD), P50 AG047266 (PI Todd Golde, MD, PhD), P30 AG010133 (PI Andrew Saykin, PsyD), P50 AG005146 (PI Marilyn Albert, PhD), P50 AG005134 (PI Bradley Hyman, MD, PhD), P50 AG016574 (PI Ronald Petersen, MD, PhD), P50 AG005138 (PI Mary Sano, PhD), P30 AG008051 (PI Thomas Wisniewski, MD), P30 AG013854 (PI Robert Vassar, PhD), P30 AG008017 (PI Jeffrey Kaye, MD), P30 AG010161 (PI David Bennett, MD), P50 AG047366 (PI Victor Henderson, MD, MS), P30 AG010129 (PI Charles DeCarli, MD), P50 AG016573 (PI Frank LaFerla, PhD), P50 AG005131 (PI James Brewer, MD, PhD), P50 AG023501 (PI Bruce Miller, MD), P30 AG035982 (PI Russell Swerdlow, MD), P30 AG028383 (PI Linda Van Eldik, PhD), P30 AG053760 (PI Henry Paulson, MD, PhD), P30 AG010124 (PI John Trojanowski, MD, PhD), P50 AG005133 (PI Oscar Lopez, MD), P50 AG005142 (PI Helena Chui, MD), P30 AG012300 (PI Roger Rosenberg, MD), P30 AG049638 (PI Suzanne Craft, PhD), P50 AG005136 (PI Thomas Grabowski, MD), P50 AG033514 (PI Sanjay Asthana, MD, FRCP), P50 AG005681 (PI John Morris, MD), P50 AG047270 (PI Stephen Strittmatter, MD, PhD).

Compliance with ethical standards

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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