THE ASSOCIATION BETWEEN COGNITIVE RESERVE AND TIME TO CONVERSION FROM NORMAL COGNITION TO MILD COGNITIVE IMPAIRMENT

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ABSTRACT

Mild cognitive impairment (MCI) is a subclinical cognitive decline in the elderly that increases the risk of conversion to Dementia. Delaying the onset of conversion from normal cognition to MCI has public health relevance by potentially reducing the magnitude of cognitive dysfunction related disability. It has been suggested that cognitive reserve, comprised of IQ and behaviors associated with memory facilitation and problem solving, may delay onset of MCI. Time to onset of MCI may also be associated with the risk factor of the APOE-4 allele. MCI classification criteria is inconsistent across studies, suggesting additional public health need to standardize an accurate method of screening. This study examined the association between cognitive reserve, APOE-4, and time to onset of MCI. Data from the 8 year Gingko Evaluation of Memory Study (GEM) clinical trial were used to examine these aims in a sample of n=2,284 cognitively normal individuals. The GEM MCI classification algorithm was extended over 8 years to examine normal cognition survival. Indicators of cognitive reserve were IQ, average monthly frequency of cognitive reserve behaviors, and number of different cognitive reserve behaviors engaged in each month. APOE-4 presence was defined as having at least one copy of the APOE-4 allele. N=1,226 (53.68%) individuals remained cognitively normal over the eight year followup compared to n=1,058 (46.32%) who developed incident MCI over eight year followup. Incident MCI individuals had significantly higher age ($p<0.0001$) and education ($p=0.0320$) at entry and were more likely to be male ($p=0.0497$), Asian/Pacific Islander, Black,

or “Other” identified race (p=0.0078). Incident MCI individuals had significantly lower frequency of reading newspapers (p=0.0228) and solving crosswords (p=0.0301), as well as IQ (p=0.0002). Neither the average monthly frequency of cognitive reserve behaviors (p=0.6662) nor the number of different cognitive reserve behaviors engaged in each month were significantly associated with MCI onset (p=0.7809). Age (p<0.0001), education (p<0.0001), IQ (p<0.0001), and APOE-4 presence (p<0.0001) were significantly associated with time to MCI onset in a Cox proportional hazard model adjusted for age, education, IQ, APOE-4 presence, cognitive reserve behavior frequency, and number of different cognitive reserve behaviors engaged in each month.

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PREFACE

I'd like to thank Dr. Joyce Bromberger for advising M.S-Epidemiology education, and the progress on this thesis. I'd also like to extend my gratitude to Dr. Tina Costacou, Dr. John Shaffer and Dr. Beth Snitz of the University of Pittsburgh. Dr. Tina Costacou was an invaluable asset in both my education, as well as helping with the data management of this thesis. Dr. John Shaffer provided me knowledge in the class of human population genetics during my tenure at the University of Pittsburgh's Graduate School of Public Health, and served as an expert reference for this thesis. Lastly I'd like to thank Dr. Beth Snitz of the University of Pittsburgh Medical Center's Department of Neurology, in connection with the Gingko Evaluation of Memory (GEM) study, both for providing me access to GEM data and providing insight into the topic of cognitive decline while writing my thesis.

1.0 BACKGROUND

A general decline in cognitive and executive function is expected as a product of the natural aging process in human beings. Extremely fast or profound deterioration may instead be the result of an underlying progression of neurodegenerative illness. Clinicians and researchers have identified a subclinical state that shows a substantial association with the risk of developing age related neurodegenerative illness[1, 2, and 3]. This stage known as Mild Cognitive Impairment (MCI) is comprised of a mix of symptoms similar to dementia- memory decline, difficulty with language, problems with planning and executive function- but at lower levels which are not easily diagnosed and do not meet clinical thresholds for dementia[1,2,3,4]. The affected individual likely has inhibited planning, speed of recall, and may even be aware of slight memory deficits. These deficits may go unnoticed and persist for many years before obvious progression to clinical dementia occurs[5]. A potential intervention to prevent an individual's cognition from deteriorating from normal to MCI would theoretically also reduce the number of people who progress to clinical Dementia and Alzheimer's[5, 6]. Such an intervention would greatly reduce the health related, social, and economic costs that this aging population faces by delaying the onset of MCI[8.9].

MCI identification is complex and often unreliable due to inconsistent diagnostic criteria. A major source of this unreliability comes from the difficulty in characterizing accurate criteria for MCI diagnosis[3, 7.9]. Research has shown that within one clinic, estimated frequencies of MCI

varied significantly across the same sample of patients (n=676) simply by altering the method of assessment. Using one summarized test score yielded an estimate of 84.3% of patients meeting MCI criteria, whereas a mixed methods diagnostic approach yielded a much lower estimate of 39.5% [7]. Other papers support this idea by showing that using a single score testing for diminished verbal memory is biased against people with low education[10]. This variability in sensitivity suggests the need for a more systematic method of identifying MCI. There is also a relative lack of studies examining MCI screening methods when adjusting for modifiable behaviors such as education[14]. These factors suggest a need to more accurately characterize MCI and to identify more elements that may potentially modify the progression from normal cognition to MCI.

Past studies have shown that certain behaviors can increase the speed of problem solving and facilitate memory formation. Behaviors such as choosing a cognitively difficult occupation, obtaining higher education, and solving puzzles are components of the cognitive reserve hypothesis, which postulates that mitigation of cognitive decline can occur as a result of participation in activities which stimulate thought[11,12,13,14,15,16,17]. This provides evidence to suggest that if cognitive reserve is modifiable, an intervention utilizing cognitive reserve to delay MCI may be applied to a target population at risk for cognitive decline, such as the elderly[11, 12, 13, and 14]. Another population at risk for MCI may include those who have a genetic pre-disposition for accelerated cognitive decline, such as individuals carrying the risk allele of Apolipoprotein E-4 (APOE-4). Unlike the other variants of APOE-2 or APOE-3, APOE-4 has been shown to be a significant risk factor for dementia and Alzheimer's disease as well as earlier onset Parkinson's disease based on longitudinal studies[17, 18.19,20,21]. The exact mechanism by which APOE-4 increases these risks is unknown at the moment, yet population cohort studies

note that E4's effect size is significantly associated with increasing age, suggesting it may be related to MCI dysfunction in the elderly[18, 22].

It is important in this study to examine if components of cognitive reserve can significantly moderate the time to onset of symptoms of MCI. We aim to **1.) Examine whether or not the average monthly participation of modifiable cognitive reserve behaviors and the number of different types of cognitive reserve behaviors is inversely related to MCI onset**. We will also **2.) Examine APOE-4 heterozygous and homozygous genotypes to determine whether or not this genetic factor affects time to appearance of MCI.** Lastly, we will 3.) **Examine if the average monthly participation of modifiable cognitive reserve behaviors and the number of different types of cognitive reserve behaviors are significant upon adjusting for age at entry, IQ, years of education, and APOE-4 presence**. Data from an 8 year longitudinal study of a subset of individuals from the Gingko Evaluation of Memory Study (GEM) were analyzed to determine these aims[3 and 23]. The GEM study's Gingko Biloba intervention was determined to be insignificant, therefore the entire sample can be observed free of interference[23].

2.0 METHODS

2.1.1 Subjects and Procedures

All participant data were collected as part of the Gingko Evaluation of Memory Study (GEM) -a randomized clinical trial investigating the hypothesis that Gingko Biloba supplementation may lower incidence of dementia. Subjects were recruited from the period of 2000-2002 and followed over a period of eight years. Details about recruitment locations and methods have been published previously[26]. Subjects were pre-screened via the Telephone Interview for Cognitive Status (TICS) psychological battery and individuals who were determined to not have dementia, not taking Warfarin or Gingko Biloba, and did not have liver or kidney issues were invited for full neuropsychological and physical testing including a blood draw[23]. Cognition was measured with the Modified Mini-Mental State Examination (3MSE), clinical dementia rating (CDR), Alzheimer's disease assessment-cognitive portion (ADAS-cog), and a proprietary neuropsychological battery[3 and 23]. Participants who had a CDR of 0, completed at least 6 out of 10 GEM neuropsychological tests, and scored in the age by education stratified lowest 10^{th} percentile on <2 tests were grouped as "normal"[3]. Participants who were determined to have undiagnosed dementia were excluded from further participation. Participants who had a CDR of 0.5, completed at least 6 out of 10 GEM neuropsychological tests, and scored in the age by education stratified lowest 10^{th} percentile on ≥2 tests were included and grouped as "MCI"[3].

Subjects were included only if they did not have any pre-existing neurodegenerative disease or bleeding/clotting disorder, and did not use cholinesterase inhibitors, Gingko Biloba, Vitamin E, or anticoagulants. Follow up consisted of 6 month checkups involving the 3MSE, CDR, and ADAS-cog, with annual examinations including the proprietary neuropsychological battery[23]. 6 month checkups showing significant decrease in the 3MSE, CDR, and ADAS-cog necessitated inclusion of the proprietary neuropsychological battery, followed by neurological examination and imaging if abnormalities remained. The maximum number of visits in the study that any participant could achieve was 16. In 2004, the study design changed to include the full neuropsychological battery at each annual visit for every participant regardless of performance on the 3MSE, CDR, or ADAS-cog[23]. The current study examined the subsample of participants without MCI at baseline and followed their cognitive function longitudinally.

2.1.2 Determining Mild Cognitive Impairment

Baseline cognition and MCI were determined using a data driven algorithm based on a compilation of individually validated test scores[3 and 23]. Domains tested included verbal memory (California Verbal Learning Test), visual memory (24 point modified Rey-Osterrieth figure), construction (24 point modified Rey-Osterrieth figure-copy condition and 24 point modified WAIS-R Block Design), language (30 item Boston Naming Test and Animal Fluency Test), psychomotor Speed/attention (Trail-Making Test A and WAIS-R Digit Span Forward) and executive functions (Trail-Making Test B and Stroop color/Word Test)[3]. A complementary CDR-a battery designed to diagnose the presence and severity of dementia symptoms- was also utilized. MCI diagnosis was based upon a global CDR score of 0.5 as well as testing below the age by education stratified 10th percentile on 2 or more of the neuropsychological battery tests as

previously determined by the Cardiovascular Health Study's (CHS)[3 and 23]. This was also the criteria for diagnosing MCI during the current study.

2.1.3 Defining Cognitive Reserve

At baseline, the frequency and diversity of everyday behaviors that reflected cognitive reserve were measured. These behaviors (reading a book, reading a newspaper, talking about local/national problems with someone, doing crossword puzzles, the ability to use a computer, balancing a checkbook, and taking classes to learn a new subject) were obtained using the Lifestyle Activity Questionnaire (LAQ) [25]. The subjects were then asked to quantify the average monthly time spent on each activity on a Likert scale ranging from 0-"Never/less than once a month" to 5-"everyday". Based on existing literature suggesting a more easily interpretable summary score, 0-5 scores were changed to 0= "not at all", 1 = "once a month", 2.5 = "two to three times a month", 4 = "once a week", 10 = "2 to three times a week", and 30 = "everyday"[25]. The average frequency of participation in cognitive reserve behaviors was estimated by creating a summary score adding the new 30 day scaled scores and dividing by the number of behaviors comprising cognitive reserve[25]. Diversity of cognitive reserve behaviors was defined as the total number of different cognitive reserve behaviors that an individual participated in at least once a month[25]. Premorbid IQ (National Adult Reading Test-American Version, Ravens Colored Progressive Matrices) was collected at baseline as well. For the current study, these 3 components (IQ, summary score of the frequency of cognitive reserve behaviors, number of different cognitive reserve behaviors engaged in) comprise cognitive reserve.

2.1.4 APOE-4 Genotyping

A blood draw was collected at baseline from the participants and used for laboratory analysis, which included the genotyping of the risk allele APOE4. For the purposes of the current study, individuals with genotypes 24, 34(heterozygotes), and 44(homozygotes) will be termed "APOE-4 present". All other genotypes (22, 23, and 33) will be termed "APOE-4 absent".

2.1.5 Statistical Analysis

An a priori significance level of $\alpha=0.05$ was used to determine statistical significance in all tests. Descriptive statistics were compared for the subgroup of participants who did not have MCI at baseline and never developed it during the study, with the subgroup of participants who did not have MCI at baseline yet were diagnosed at a later visit. The distribution of continuous independent variables was assessed using the Kolmogorov-Smirnov test of normality. Statistically significant differences in characteristics between the 2 subgroups was assessed using a Wilcoxon Man-Whitney test on continuous independent variables due to all variables being non-normally distributed. Differences in distribution of categorical variables (race, gender, and APOE-4 presence) were assessed using Chi-Squared Tests, and Fishers Exact Test when sufficiently small. A Hardy-Weinberg Equilibrium table displaying genotype and allele frequencies based on a 3 allele expansion equation ($p^2+2pq+q^2+2qr+r^2$) was constructed, using a Chi-Squared Test to determine statistical significance. A Spearman correlation matrix containing all independent variables was created to examine any relationship between variables. A product limit survival table showing normal cognition/at-risk individuals and MCI diagnosed

individuals by visit number was constructed as part of a survival analysis. A Kaplan-Meier survival curve was created and stratified by APOE-4 presence and analyzed using a log-rank statistic and Chi-Squared Test. As part of the survival analysis examining time to diagnosis of MCI, Cox proportional hazard regression models were constructed, censoring for death, dementia, dropout, and having <6 of 10 completed neuropsychological tests and/or no CDR. Univariate Cox proportional hazard regressions were constructed for age at entry (years), education at entry (years), and IQ. Cox proportional hazard regressions for APOE-4 presence, the summary score for frequency of engagement in cognitive reserve behaviors, and the summary score for diversity of cognitive reserve behaviors were constructed, adjusting for the primary predictors of age at entry (years), education at entry (years), and IQ. Lastly, a full model was constructed incorporating age at entry (years), education at entry (years), IQ, APOE-4 presence, the summary score for frequency of engagement in cognitive reserve behaviors, and the summary score for diversity of cognitive reserve behaviors. The Akaike Information Criterion (AIC) model fit statistic will also be included in the Cox proportional hazard models to help assess model fit before and after adjustment.

3.0 RESULTS

Table 1 describes the demographics of the subset of the sample who did not have MCI at baseline and never developed it (n=1,226, 53.68%), as well as the individuals who did not have MCI at baseline but developed incident MCI later on in the study (n=1,058, 46.32%). Independent variables were all non-normally distributed according to the Kolmogorov-Smirnov test ($p<0.0001$). Both groups' median age upon entry into the study were below 80 but significantly differed ($p<0.0001$). MCI group median quartile age was 77 years (75, 79) and the incident MCI group median quartile was 78 years (76, 81). Both groups were predominantly Caucasian (97.72% No MCI vs. 95.46% incident MCI) with Black (1.63% vs. 2.46%), Asian/Pacific Islander (0.24% vs. 1.23%), and "Other" (0.41% vs. 0.85%) being significantly overrepresented in the group developing incident MCI ($p=0.008$). The distribution of gender between groups significantly differed, with a greater proportion of men observed in the incident MCI group (52.61% Male No MCI and 56.71% Male incident MCI, $p=0.0497$). Both groups were highly educated. The median number of years of education in both groups was 14 (12, 16 No MCI and 12, 17 incident MCI) was similar to that of the group developing incident MCI but still significantly differed ($p=0.0320$). The two groups also differed in IQ ($p=0.0002$), newspaper reading frequency ($p=0.02$), crossword puzzle solving frequency ($p=0.03$), all being lower among incident cases, and APOE-4 presence ($p<.0001$), with a greater proportion of cases carrying at least one APO-4 allele.

As shown in Table 2, the genotypic frequency of the entire sample without MCI at baseline and the subset who never develop MCI were both in Hardy-Weinberg Equilibrium. This examination also revealed that the allele frequency-determined from the genotype frequency of the entire sample without MCI at baseline (2=8.03%, 3=79.89%, 4=12.08%) and the subset who never develop MCI (2=8.58%, 3=81.08%, 4=10.34%) - were in Hardy Weinberg Equilibrium as well.

Spearman correlations comparing relationships between variables showed several significantly associated independent variables in Table 3, though the size of the correlations was small. The smallest significant correlation was between IQ and the frequency of taking classes/courses ($r=0.042$, $p=0.0428$), while the largest correlation was between the frequency of using a computer and the frequency of taking classes/courses ($r=0.207$, $p<0.0001$). The presence of APOE-4 was not significantly correlated with any cognitive reserve behavior.

A similar Spearman correlation matrix in Table 4 compared the independent variables used in the Cox proportional hazards model. Larger significant correlations were seen in this table, ranging from ($r=-0.045$, $p=0.029$) to ($r=0.678$, $p<0.0001$).

The product limit survival table seen in Table 5 shows that of the group of participants who did not have baseline MCI (n=2,284), only 53.93% (n=1,123) remained cognitively normal until the end of the study after censoring for death, dementia, dropout, and having <6 neuropsychological battery tests completed. Incidence rates of MCI were proportionately lowest at visit 3 (0.22%) and proportionately highest at visit 9 (8.38%), staying high at visits 10 (7.36%), 11 (5.495), 12 (7.45%), and 13 (7.85%) until they started to decrease dramatically afterwards. The resulting curve in Figure 1 shows the steep decline. The Kaplan Meier survival curve stratified by Apoe-4 presence, reveals a better survival (56.2%) in those with no copies of

APOE-4 compared to those with at least one copy of APOE-4 (44.47%, log-rank p-value <0.0001).

Univariate Cox proportional hazard models for age at entry (HR=1.098, 95% CI=1.077-1.120) and IQ (HR=0.985, 95%CI=0.977-0.992) were significant predictors of MCI onset, while education was not. Table 6 shows Cox proportional hazard model results for the summary score of cognitive reserve behavior frequency, the number of different cognitive reserve behaviors, and APOE-4 presence, unadjusted and after adjusting for age at entry, years of education at entry and IQ. Neither the unadjusted nor the adjusted models for the summary score of cognitive reserve behavior frequency and the number of different cognitive reserve behaviors were significant. APOE-4 was a significant predictor of time to MCI onset (HR=1.421, 95%CI=1.220-1.654, p<0.0001), becoming larger after adjustment (HR=1.470, 95%CI 1.261-1.713, p=<0.0001). In Table 7's full model of all independent variables, only age at entry, education at entry, IQ, and APOE-4 presence were significant predictors of time to MCI onset.

4.0 DISCUSSION

This study examined the association between behaviors comprising cognitive reserve and whether or not they affect time to conversion from normal cognition to MCI. Another aim of this study was to examine whether cognitive reserve was associated with the presence of at least one copy of APOE-4, and if this genetic factor affected time to conversion from normal cognition to MCI as well. By utilizing the GEM data driven algorithm designed for MCI screening at baseline and extending it longitudinally, time to MCI can be determined.

Significant between group differences were observed in the frequency of reading a newspaper and the frequency of solving crossword puzzles in individuals never developing MCI versus those who developed incident MCI. Despite many of the cognitive reserve behaviors being correlated to each other, neither the summary score of cognitive reserve behavior frequency nor the summary score of cognitive reserve behavior diversity was significant in the fully adjusted Cox proportional hazard model. However, it was discovered that IQ, age upon study entry, and APOE-4 presence were consistently significant predictors of MCI incidence. In the fully adjusted model (Table 7), each unit increase in an individual's IQ was associated with a 0.033% reduction in the risk of developing MCI. The fully adjusted Cox proportional hazard model also suggested that carrying at least one copy of the APOE-4 gene increased the risk of MCI by 44%. Age is likely a very large factor in this disease, as adjustment did not appear to

alter its effect on MCI incidence. For each additional year of age, the risk of MCI increased by 10%.

Interestingly, the examination of years of education at entry found between group differences showed that the incident MCI group was significantly more educated. Table 7 supports this finding by showing that as years of education increase, MCI hazard increases (after adjusting for IQ, APOE-4 presence, average frequency of cognitive reserve behaviors, and number of different cognitive reserve behaviors). These findings are antithetical to the cognitive reserve hypothesis, as previous literature strongly suggests that increasing years of education decreases risk of cognitive decline[14 and 30]. Further analysis will need to be conducted in order to observe why this finding was present, as it is possible that an unaccounted for confounder or bias is present, but outside the scope of this study. One possible explanation may be that a survival bias is present. A study by Meara et al. showed that education is significantly positively associated with life expectancy[31]. Due to the advanced age (75+ as per GEM protocol) and the level of education being high in the sample, it may be that more participants were able to live longer, but progressed to MCI as a result of progressive aging.

Significantly more Black, Asian, and "Other" racially classified individuals were present in the incident MCI group than statistically expected, which is consistent with previous studies on race/ethnicity and cognitive decline[27]. Another expected result was that there appeared to be an effect based on sex since a statistically significant proportion of men developed MCI rather than their female peers. This is similar to modern research as it has been shown that in prior epidemiological studies, males proportionally develop MCI more often than women[28].

The analysis of genotypes both in the entire subset of individuals without baseline MCI and in the subset of the sample who never develop incident MCI showed that the frequencies did

not deviate from expected proportions and were in Hardy-Weinberg Equilibrium. Since it is not statistically significant, certain assumptions can be made. The first assumption is that the quality of the actual genotyping was reliably performed, since the allele frequencies roughly match background population frequencies[29]. The second assumption is that the acquisition of subjects upon recruitment and study was sufficiently random and there was no environmental or biological selection for a specific allele. These findings increase the validity of the genetic results in the study.

The product limit survival table allowed for a condensed view of the proportion of the sample with normal cognition versus MCI over the course of the study. No diagnoses were made without a CDR, as this was an integral component of the original GEM MCI diagnosis, however a total of 11 individuals (8 diagnosed MCI, 3 diagnosed normal) were made with <6 out of 10 completed neuropsychological tests. The protocol for the GEM study at baseline cognitive determination mandated that individuals needed to complete ≥6 of 10 neuropsychological tests, but did not drop participants over the course of the study for not completing <6 tests at any visit. Therefore these 11 individuals who were categorized by the longitudinal application of the GEM MCI algorithm were inconsistent with the baseline criteria for MCI versus normal cognition, and censored. It is worth mentioning that the current study is novel in extending the GEM data driven algorithm longitudinally.

The current study has many strengths by borrowing from the GEM data. This study has a large sample size enabling ample power for calculations used. Another strong point this study has is the 8 year follow up time, allowing for the novel use of the GEM MCI classification algorithm to be applied longitudinally. The algorithmic diagnosis utilized by GEM helps solve the issue of inconsistency in MCI diagnosis by systematically using a series of individually

validated standardized tests, as well as modifying the impairment cutoff to the lower 10th percentile whereas some studies typically use the lower 8th percentile. Lastly, the pooled data is extensive and incorporates detailed information on participant cognition through many different validated psychological batteries.

Limitations of the current study include external validity, effectiveness, and bias concerning the GEM data. Though the recruitment for the GEM study was conducted at 4 locations- University of Pittsburgh, UC Davis/Sacramento, Johns Hopkins University, and Wake Forest University-the sample is both highly educated and overwhelmingly Caucasian, limiting its generalizability[26]. Secondly, though the GEM MCI classification algorithm's strength is its systematic diagnosis and multi-domain psychological analysis, more data would be needed to assess its effectiveness in the general public as a clinical screening tool rather than under experimental conditions. Recall bias may be present, as the LAQ questionnaire that GEM subjects participated in prior to enrollment served as the basis for this study's cognitive reserve related behavior frequency variables and was based on participant recall of the prior month[25]. Another limitation of the study occurred due to the GEM study design changing in 2004 to include the full neuropsychological battery for every participant annually regardless of performance on the 3MSE, CDR, or ADAS-cog, whereas previously the battery was only necessary if a participant tripped the preliminary battery[3]. For this reason, inclusion of n=303 cognitively normal subjects at baseline was not possible due to an inability to match multiple CDR scores to neuropsychological test scores that did not continue past visit 1. Further study may be necessary, requiring methods to impute missing data.

5.0 CONCLUSION

In summation, this study was not able to observe an association between time to event of MCI and the frequency of cognitive reserve behaviors or time to event of MCI and the diversity of cognitive reserve behaviors. Adjusting for the frequency of cognitive reserve behaviors, the diversity of cognitive reserve behaviors, APOE-4 presence, IQ, education, and age, higher IQ was significantly associated with increased time to MCI, yet increased age, education, and APOE-4 presence were significantly associated with decreased time to MCI. While not part of the cognitive reserve hypothesis, the significant effect that age and APOE-4 have on time to MCI suggests that individuals 75 years of age and older as well as those with the genetic risk factor of APOE-4 may want to be proactive and request more frequent standardized cognitive screening similar to the GEM method. Though IQ is a part of the cognitive reserve hypothesis it is largely not modifiable and thus cannot be operationalized to attempt to delay onset of MCI. Future longitudinal studies should seek to determine exactly which modifiable activities comprising the cognitive reserve hypothesis are most significant, and systematically test them similar to what has been done in this study. Overall, more research needs to take place on the behavioral, neurobiological, and pathological basis of cognitive decline in order to delay the onset of cognitive dysfunction in aging.

APPENDIX: TABLES

Table 1: Characteristics of Participants without Baseline MCI at Visit 1, N=2,284

	Never Develop MCI (N=1,226, 53.68%)	**Develop MCI** (N=1,058, 46.32%)
Age at entry (Median, 25th percentile, 75th percentile)	77 (75-79)	78 (76-81)±
Race White Black Asian/Pacific Islander Other	 N=1,198 (97.72%) (N=20, 1.63%) (N=3, 0.24%) (N=5, 0.41%)	 (N=1,010, 95.46%) (N=26, 2.46%) ± (N=13, 1.23%) ± (N=9, 0.85%) ±
Gender Male Female	 (N=645, 52.61%) (N=581, 47.39%)	 (N=600, 56.71%) ± (N=458, 43.29%)
Education (Median, 25th percentile, 75th percentile)	14(12-16)	14 (12-17)±
IQ (Median, 25th percentile, 75th percentile)	120(113-124)	117(111-123)±
Reading a Book (Median, 25th percentile, 75th percentile **)**	10(2.5-30)	10(2.5-30)
Reading a Newspaper (Median, 25th percentile, 75th percentile)	30(30-30)	30(10-30)±
Talking about local/national Issues (Median, 25th percentile, 75th percentile)	10(4-30)	10 (2.5-30)
Crossword Puzzles (Median, 25th percentile, 75th percentile)	0(0-10)	0 (0-10)±
Balancing Checkbook (Median, 25th percentile, 75th percentile)	1(1-2.5)	1(1-2.5)
Taking Courses/Classes (Median, 25th percentile, 75th percentile)	0 (0-0)	0 (0-0)
Using a Computer (Median, 25th percentile, 75th percentile)	0 (0-10)	0(0-10)
APOE-4 Present	N=176 (17.76%)	N=222 (25.64%) ±

± signifies statistical significance of $p<0.05$

Table 2: Distribution of APOE Genotypes and Alleles

		Genotype Frequency						**Allele Frequency**			**p=**
		22	**23**	**24**	**33**	**34**	**44**	**2**	**3**	**4**	
Baseline	N=2,074	0.87%	12.25%	2.07%	63.98%	19.58%	1.25%	8.03%	79.89%	12.08%	0.3867
Never MCI	N=991	0.71%	13.82%	1.92%	65.79%	16.75%	1.01%	8.58%	81.08%	10.34%	0.9829

Table 3 Spearman Correlation Matrix, N=2,284

	IQ	Books	Newspaper	Issues	Crossword	Checkbook	Classes	Computer	APOE-4
IQ	____	**0.106** **P=<0.0001**	0.005 P=0.8268	0.031 P=0.1375	**0.066** **P=0.0015**	0.034 P=0.1006	**0.042** **P=0.0428**	**0.121** **P=<0.0001**	-0.032 P=0.1225
Books	____	____	-0.0001 P=.9982	**0.089** **P=<0.0001**	**0.122** **P=0.0014**	**0.052** **P=0.0127**	**0.060** **P=0.0037**	**0.125** **<0.0001**	0.005 0.8024
Newspaper	____	____	____	**0.218** **P=<0.001**	**0.066** **P=<0.0014**	0.027 P=0.1907	**0.055** **P=0.0084**	**0.078** **P=.0002**	0.026 P=.2037
Issues	____	____	____	___	0.022 P=0.2836	0.037 P=0.0782	**0.091** **P=<0.0001**	**0.096** **P=<0.0001**	0.025 P=0.2253
Crossword	____	____	____	____	___	**0.047** **P=0.0253**	-0.002 P=0.9278	0.039 P=0.0625	-0.040 P=0.0522
Checkbook	____	____	____	____	____	____	0.032 P=0.1251	**0.066** **P=0.002**	-0.006 P=.7677
Classes	____	____	____	____	____	____	____	**0.207** **P=<0.0001**	-0.011 P=0.5850
Computer	____	____	____	____	____	____	____	____	-0.025 P=0.2277
APOE-4	____	____	____	____	____	____	____	____	____

Bold signifies statistical significance of $p<0.05$

Table 4: Spearman Correlation Matrix of Cox Model Variables, N=2,284

	IQ	APOE-4	Age	Education	Cognitive Reserve Behavior Frequency	Cognitive Reserve Behavior Diversity
IQ	---	-0.032 p=0.122	**-0.045 p=0.029**	**0.678 P=<0.0001**	**0.129 p<0.0001**	**0.141 p<0.0001**
APOE-4	----	----------	**-0.053 p=0.011**	-0.002 p=0.923	-0.0007 p=0.975	-0.037 p=0.073
Age	----	----------	------	-0.022 p=0.275	-0.037 p=0.075	**-0.049 p=0.0180**
Education	----	----------	------	------	**0.084 p<.0001**	**0.119 p<.0001**
Cognitive Reserve Behavior Frequency	----	----------	------	------	----------	**0.621 p<.0001**
Cognitive Reserve Behavior Diversity	----	----------	------	------	----------	----------

Bold signifies statistical significance of p<0.05

Table 5: Incident MCI by Visit, N=2,284

Visit	Number at Risk	MCI	Survival	Failure	Total MCI	Normal Cognition	# Normal Cognition With >4 Missing Tests	# MCI With >4 Missing Tests
3	2,284	5	0.9978	0.00219	5	2,279	0	1
4	2,278	8	0.9943	0.00569	13	2,270	0	0
5	2,270	12	0.9891	0.0109	25	2,258	0	0
6	2,258	18	0.9812	0.0188	43	2,240	0	0
7	2,240	33	0.9667	0.0333	76	2,207	0	0
8	2,207	143	0.9041	0.0959	219	2,064	0	0
9	2,064	173	0.8283	0.1717	392	1,891	0	3
10	1,888	139	0.7673	0.2327	531	1,749	0	2
11	1,747	96	0.7252	0.2748	627	1,651	0	0
12	1,651	123	0.6711	0.3289	750	1,528	0	0
13	1,528	120	0.6184	0.3816	870	1,408	0	1
14	1,407	80	0.5833	0.4167	950	1,327	0	0
15	1,327	63	0.5556	0.4444	1013	1,264	0	1
16	1,263	37	0.5393	0.4607	1050	1,223	3	0

Table 6: Cox Proportional Hazard Models 1-6

	Predictor	**HR**	**95% CI**	**P=**
Model 1	Cognitive Reserve Behavior Frequency	0.992	0.977- 1.007	0.2827
Unadjusted AIC= 11836.905				
Model 2 **(Adjusted for age, education, and IQ)**	Cognitive Reserve Behavior Frequency	0.999	0.984- 1.015	0.9013
Adjusted AIC= 11838.674				
Model 3	Cognitive Reserve Behavior Diversity	0.986	0.929-1.045	0.6300
Unadjusted: AIC= 11836.905				
Model 4 **(Adjusted for age, education, and IQ)**	Cognitive Reserve Behavior Diversity	1.002	0.943-1.064	0.9518
Adjusted: AIC=11687.611				
Model 5±	Apoe-4 Presence	1.421	1.220-1.654	<0.0001
Unadjusted: AIC=12648.344				
Model 6± **(Adjusted for age, education, and IQ)**	Apoe-4 Presence	1.470	1.261-1.713	<0.0001
Adjusted: AIC=12466.997				

Table 7: Cox Proportional Hazard Model 7

Model 7				
		Hazard Ratio	**95% CI**	**P=**
Age		1.100	1.077-1.123	<.0001
Education		1.084	1.049-1.120	<.0001
IQ		0.967	0.957-0.978	<.0001
APOE4	E4 Present	1.441	1.229-1.690	<.0001
Cognitive Reserve Behavior Frequency		0.996	0.976-1.015	0.6662
Cognitive Reserve Behavior Diversity		1.011	0.937-1.091	0.7809
AIC	11548.413			

APPENDIX: FIGURES

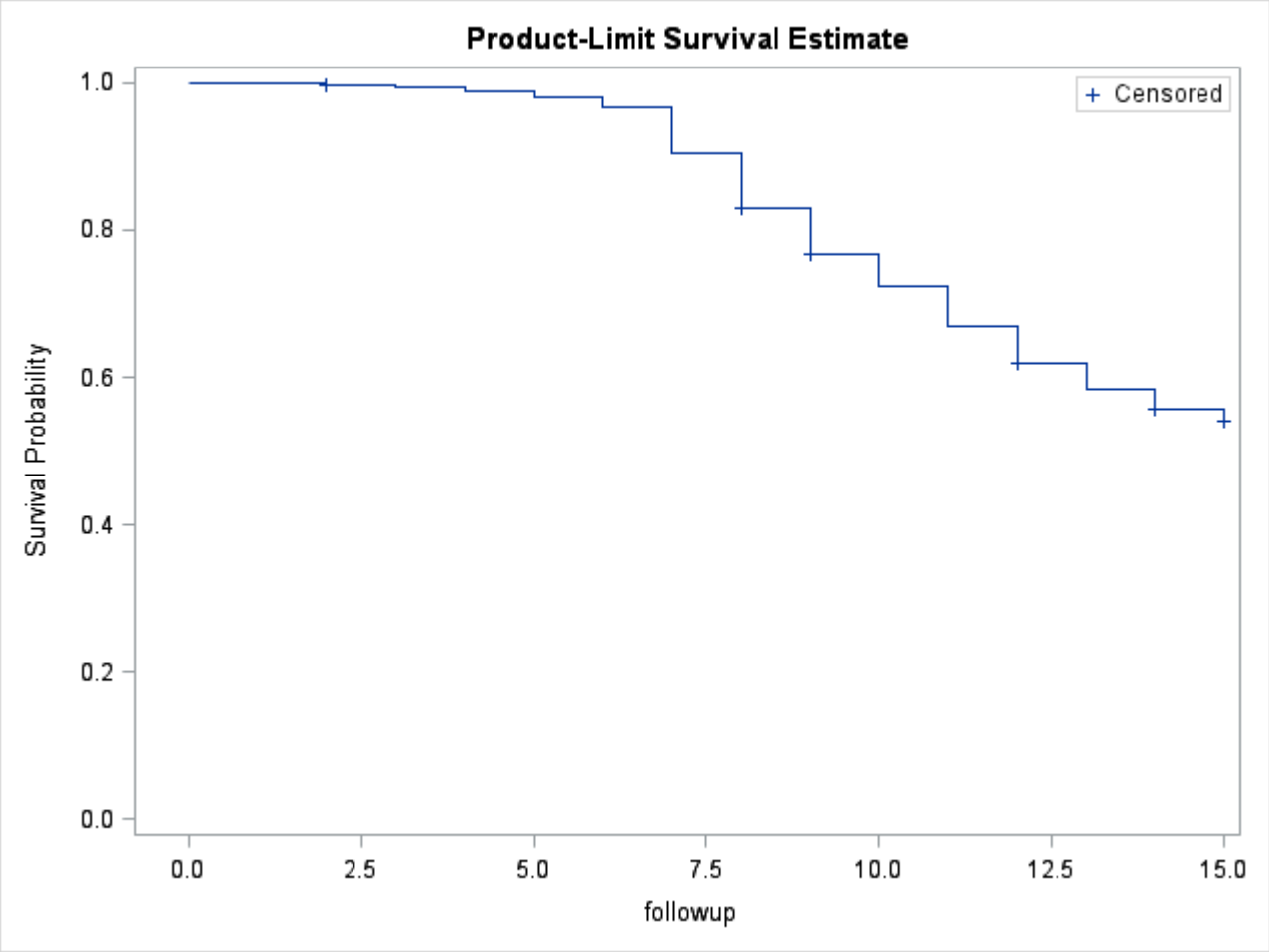

Figure 1: Product Limit Survival Curve of normal cognition visits 3-16

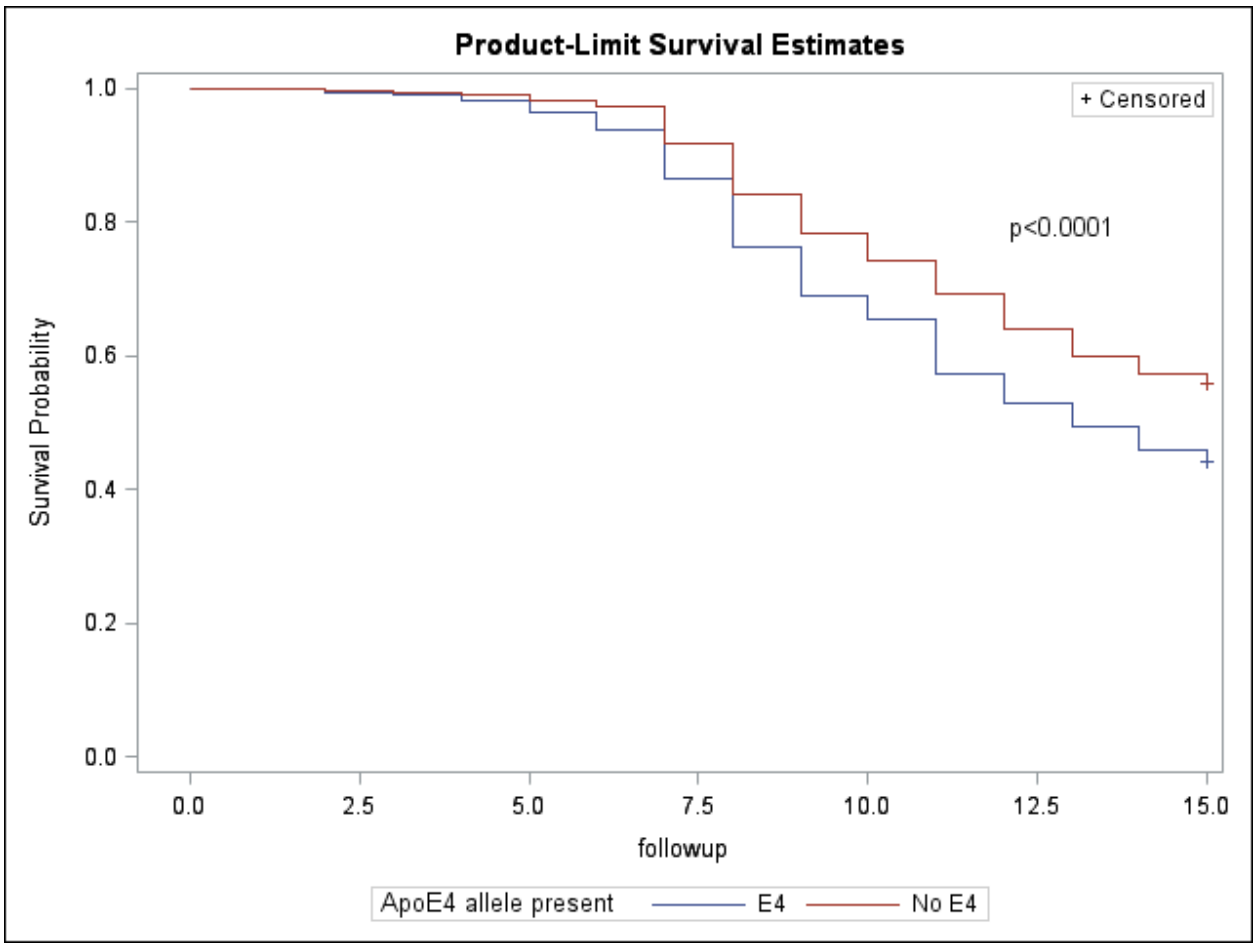

Figure 2: Kaplan Meier Survival Curve stratified by APOE-4 Presence for visits 3-16

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