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The Effects of Cognitive Reserve on the Rate of Cognitive Decline in Persons with Mild Cognitive Impairment

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The Effects of Cognitive Reserve on Cognitive Decline in Patients with Mild Cognitive Impairment

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ABSTRACT

BACKGROUND: The cognitive reserve theory posits that innate intelligence or certain aspects of life experiences may provide a reserve against Alzheimer's disease (AD) development. The theory hypothesizes that when dementia symptoms emerge in people with high cognitive reserve, disease pathology is at its severe stages. Clinical progression will be more rapid in these individuals than those with low cognitive reserve. OBJECTIVE: To examine the influence of education and occupation on the rate of cognitive decline in older adults with MCI over a two-year period. HYPOTHESIS: Older adults with MCI who have higher education and occupation levels will display a more rapid cognitive decline over a two-year span than those with lower education and occupations. PARTICIPANTS: Two-hundred and sixty-one MCI participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI). METHODS: The independent variables were years of education and occupation during most of working career. Gender, age, and marital status were utilized as covariates. Scores from the screening/baseline, 6-month, and 24-month Mini-Mental Status Examinations (MMSE) and Alzhemer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog) were used to assess cognition. MAIN ANALYSIS: Orthogonal contrasts in a repeated measures (RM) multivariate ANOVA (MANOVA) and multivariate analysis of covariance (MANCOVA) were performed to determine the extent of cognitive decline. RESULTS: Highly educated MCI participants had slower rates of cognitive decline on the MMSE than persons with medium ($F(1,255) = 4.395$, $p = .037$) and low ($F(1,255) = 4.430$, $p = .036$) education. A faster cognitive decline occurred on the MMSE in the high than the low occupation category over a two-year period ($F(1,252) = 3.886$, $p = .050$). Education and occupation levels had no effect on ADAS-Cog performance during the same time ($p > .05$). CONCLUSION: Higher education may have a protective effect against cognitive decline in MCI while high occupation may have a reverse effect. These effects are test dependent and data limitations significantly limit the generalizability of the findings.

Introduction

Mild cognitive impairment (MCI) represents a transitional state between normal, age-related cognitive changes and the possible early stages of AD (Petersen et al., 1999). Persons with MCI experience persistent deficits in memory or other cognitive functions that are not severe enough to meet the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Revised* (DSM-IV-R) criteria for dementia (Petersen, 2004). The condition's symptoms are sufficiently mild so that social and occupational activities remain undisturbed (Petersen, 2004). As the cognitive and behavioral symptoms grow more severe, a large proportion of MCI patients convert to AD. Between 10% and 15% of MCI cases each year develop AD (DeCarli, 2003; Luis et al., 2003; Petersen et al., 2001). With the current prevalence of AD (5.3 million cases) expected to more than double by 2030 (Alzheimer's Association, 2010), MCI and AD present significant public health problems. Isolating methods that may delay disease symptoms, reduce the use of health-related services, and decrease the need for long-term care is imperative. One proposed strategy is to build brain resiliency against disease by encouraging people to lead mentally stimulating lives.

Cognitive reserve theory posits that innate intelligence or certain aspects of life experiences, such as education and adult occupation, may provide a reserve against brain pathology (Scarmeas & Stern, 2004; Stern, 2006; Stern, 2009; Stern, Albert, Tang, & Tsai, 1999). Individuals with high education and occupational attainment may have preexisting brain networks that are less susceptible to, or compensate for, disease disruption than persons with low levels of education and occupation (Stern, 2006). In other words, people with greater cognitive reserve may process tasks in ways that allow

them to cope better with brain damage. The cognitive reserve theory may explain why some elders with clinically normal neuropsychological testing during their lives have full AD neuropathology at autopsy (Bennet et al., 2006; Hulette et al., 1998; Katzman et al., 1988; Knopman et al., 2003).

Figure 1 illustrates the theoretical association of cognitive reserve on the rate of cognitive decline in persons with cognitive impairment. The model suggests that disease pathology slowly increases over time and that cognitive reserve levels influence when the initial cognitive changes are clinically expressed (Stern 2006; Stern 2009; Stern, Albert, Tang, & Tsai, 1999). Symptoms of pathologic disruption will take longer to become evident in high reserve individuals than persons with low reserve. When the clinical manifestations of the disease do emerge in high reserve patients, the degree of brain damage is quite severe. The time between the first symptoms of cognitive deterioration and mortality in these people is likely to be shorter than those with less reserve (Stern 2006; Stern 2009; Stern, Albert, Tang, & Tsai, 1999).

Stern (2006; 2009) proposes two possible subcomponents of cognitive reserve to explain the theory: neural reserve and neural compensation. Neural reserve refers to the efficiency, capacity, and flexibility of existing brain networks underling task performance. People whose neural networks are highly efficient, have significant capacity, and greater flexibility may be more able to endure disruptions caused by disease pathology. Neural compensation is the brain's ability to utilize additional networks not normally implemented by cognitively healthy people. Individuals who are highly educated and work in mentally challenging environments are likely to have significant neural reserve and/or compensation (Stern, 2009). Although beyond the scope of the

present investigation, several neuroimaging studies show that the brains of people with high cognitive reserve are more efficient and often process tasks differently than those with lower reserve (Bosch et al., 2010; Springer, McIntosh, Wincour, & Grady, 2005; Scarmeas et al., 2003; Solé-Padullés et al., 2009; Stern et al., 2005). High cognitive reserve patients should have more disease pathology upon the initial expression of the cognitive symptoms. The cognitive reserve theory hypothesizes that a fast cognitive decline will follow since these individuals' brains are at the advanced pathologic stages of the disease (Stern, 2006; Stern, 2009).

Most investigations have examined the association of cognitive reserve and the incidence of dementia. Valenzuela and Sachez (2005) performed a systematic review of the literature that reported the effects of education and occupation on incident dementia. The researchers found that 10 of the 15 studies demonstrated a significant protective effect of education, while the remaining five had no effect. Nine out of 12 studies showed a significant protective effect for occupation, while three had no effect. A meta-analysis of the data revealed that higher education decreased the risk of developing dementia by 47% while higher occupational attainment reduced the risk by 44%. Thus, high levels of education and occupation may delay the onset of dementia symptoms in some people. Disease pathology, however, will most likely continue to run its course.

Table 1 summarizes epidemiological investigations examining the association between cognitive reserve and the rate of cognitive decline. All of the studies reviewed with AD participants found that high levels of cognitive reserve resulted in faster cognitive declines. In contrast, longitudinal studies assessing normal aging found slower cognitive declines in people with higher educational attainment. While this may appear

counterintuitive at first, it is consistent with the cognitive reserve hypothesis. Studies investigating normal aging will likely see a slow cognitive decline in people with higher cognitive reserve since they can tolerate more disease pathology. There is a "point of inflection," however, when the brain exhausts all of its neural reserve and compensating strategies (Stern 2006; Stern 2009). A swift decrease in cognition over time will ensue, as seen in the AD studies. An important question remaining is whether these results can be applied to people with mild cognitive impairment.

Only one study was uncovered which examined the effects of cognitive reserve on the rate of cognitive decline in the MCI population. Based in Sweden, Rolstad et al. (2009) investigated whether education had an impact on the pathology and neuropsychological test performance in MCI participants over time. Persons with MCI received cognitive tests and underwent neuroimaging at baseline and a two-year follow-up. Years of education was used as a proxy for cognitive reserve and categorized into low ($\leq$ 9 years), medium (10 to 14 years), and high ($\geq$ 15 years). The researchers found no association between the level of cognitive reserve and the rate of cognitive decline. However, neuroimaging revealed that highly educated MCI participants had more dementia pathology compared to medium and low educated people (Rolstad et al., 2009). The study's small sample size (n = 66) significantly limits its generalizability.

The objective of the current investigation is to examine the influence of education and occupation on the rate of cognitive decline in older adults with MCI over a two-year period. Since it is known that being female (Artero et al., 2008), older (Petersen, 2000), and unmarried (Håkansson, 2009) may decrease the time to dementia development, the study's main analyses will control for these variables (Figure 2). Dementia symptoms in

African Americans and Latinos may progress slower than other races and ethnicities (Mehta et al., 2008). These two variables, however, will not be considered due to the study sample's minimal racial and ethnic diversity. The hypothesis is that older adults with MCI who have higher education and occupational levels will display a more rapid cognitive decline over a two-year span than those with lower education and occupations. The results could be beneficial in identifying effective strategies to minimize the burden of cognitive disease.

Method

Data

Data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu\ADNI) was obtained on January 17th, 2010. The Principle Investigator of this initiative is Michael W. Weiner, M.D., at the University of California, San Francisco. The ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and participants have been recruited from over 50 sites across the United States and Canada. The investigation was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, five-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessments can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific

markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

Local institutional board reviews at each participating ADNI site approved the study. The present investigation was approved by the University of Connecticut Health Center's Institutional Review Board.

Participants

The original ADNI screening sample consisted of 397 MCI participants recruited between 2005 and 2007. Enrolled participants passed a thorough screening examination that required medical, physical, and neurological tests. A 1.5T MRI was conducted to detect infarctions. MCI participants' cognitive abilities were tested using neuropsychological assessments at the screening, baseline, and subsequent 6- to 12-month study intervals for up to three years. Detailed information regarding the ADNI protocol and procedures can be found at www.loni.ucla.edu\ADNI.

Inclusion criteria required participants to be between the ages of 55 and 90 (inclusive), English or Spanish speaking, and have an informant who could provide an independent evaluation of functioning. MCI participants had to have a total score on the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) between 24 and 30, a memory complaint, objective memory loss measured by the Weschler Memory Scale Logical Memory II (Wechsler, 1987), a Clinical Dementia Rating (Morris, 1993) of 0.5, significant cognitive impairment in other non-memory domains, essentially preserved activities of daily living, and no evidence of dementia. Women had to be

sterile or at least two years past child-bearing potential. Other inclusion criteria included a Hachinski ischemic score (Hachinski et al., 1975) of four or less, a Geriatric Depression Scale (Sheikh & Yesavage, 1986) score of less than six, visual and auditory acuity adequate for neuropsychological testing, at least six grades of education or work history, general health with no diseases precluding enrollment, and an agreement to undergo DNA (Apolipoprotein E), blood, and urine testing.

Participants were excluded from the ADNI if they did not meet the above inclusion criteria or took an excluded medication (Appendix A) within four weeks of the screening visit. Excluded medications included those with significant central nervous system anti-cholinergic activity, narcotic analgesics, Anti-Parkinsonian drugs, diuretics, and investigational medications. Cholinesterase inhibitors, memantine, vitamin E, estrogen, estrogen-like compounds, and some antidepressants and neuroleptics were permitted if the doses were stable for four weeks prior to screening (Appendix B).

Of the 397 MCI participants enrolled in the ADNI, 261 (66%) were included in the present investigation's analysis sample. The repeated measures analysis plan (described later in detail) required every participant to have a dependent measure at each time interest. As a result, one hundred thirty-five persons with MCI were excluded due to incomplete dependent measures at the screening, baseline, 12-month, or 24-month visits. One participant was excluded because of a reported stroke at the 12-month interval.

Independent Variables – Education & Occupation

Education and occupation information for each participant was collected at the screening visit. The "years of education" variable was trichotomized into low (≤ 12

years), medium (≥13 and ≤ 16 years), and high (≥17 years) categories. Open-ended responses to "primary occupation during most of working career" first were categorized according to the United States Equal Employment Opportunity (EEO-1) Job Classification Guide (United States Equal Employment Opportunity Commission, 2006a). The EE0-1 Job Classification Guide serves as a bridge between the 2000 Census job codes and the 10 job categories on the Employer Information Report EE0-1. The categories are based on the average skill level, knowledge, and responsibility involved in performing each job's duties. The EE0-1 job classifications were categorized further into high (Executive/Senior/First/Mid Level Officials and Managers; Professionals; Technicians) and low (Sales Workers; Administrative Support Workers; Craft Workers; Operatives; Laborers and Helpers; Service Workers) occupational groups for ease of presenting and interpreting the findings. An intermediate occupational level was not used because a clear distinction of such a category could not be made using the EEO-1 Job Classification Manual (United States Equal Employment Opportunity Commission, 2006b). Homemakers/housewives (n = 22) were coded as missing due to the varying level of skills, knowledge, and responsibilities necessary to perform the jobs' activities.

Covariates – Gender, Age, & Marital Status

Demographic information was collected at the screening visit. Gender, age, and marital status were controlled for in the final analyses. Age remained a continuous variable. The screening marital status ("married" or "other") was treated as a time-invariant factor since few (n = 2) participants reported a change in marital status between the screening and 24-month visits.

Dependent Variables – MMSE & ADAS-Cog

Cognitive severity was characterized using total scores from the MMSE and the Alzhemer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog; Rosen, Mohs & Davis, 1988). The MMSE is a brief screening test of mental status and cognitive functioning. It is useful in estimating the severity of cognitive impairment and tracking cognitive changes in an individual over time (Folstein, Folstein, & McHugh, 1975). Cognitive areas assessed include orientation, attention, immediate recall, short-term recall, language, and constructional praxis. Total MMSE scores range from zero to 30 with lower scores indicating worse cognitive functioning. The MMSE was administered at the screening, 12-month, and 24-month visit.

The ADAS-Cog is a global rating scale used to determine the level of cognitive dysfunction and is more comprehensive than the MMSE (Rosen, Mohs, & Davis, 1988). The ADAS-Cog assesses areas such as language, recall, word-finding ability, naming, constructional praxis, ideational praxis, orientation, word recall, and word recognition. The assessment has shown sufficient sensitivity and specificity in discriminating between cognitively impaired patients and healthy controls (Schwarb, Koberle, & Spiegel, 1988). The ADAS-Cog scores range from zero to 70 with lower scores indicating better cognitive status. The ADAS-Cog was administered at baseline, 12-month, and 24-month visit.

Analysis

As appropriate, frequencies and descriptive statistics were run on the demographic and cognitive test scores. Differences in demographics between the included and

excluded groups were calculated using Pearson chi-square (χ^2) or Fisher's exact tests for categorical variables and independent t-tests were used for continuous variables. Demographic differences between the education and occupation categories in the analysis sample were performed using χ^2 and One-Way Analysis of Variance (ANOVA). Correlations between the independent and dependent variables were conducted using Spearman's rank-order (r_s; one rank-order and one continuous variable), Pearson product-moment (r; two dichotomous variables), and point-biserial (rpb; one dichotomous and one continuous variable) correlations.

Separate repeated measures (RM) multivariate ANOVA (MANOVA) and multivariate analysis of covariance (MANCOVA) tests were performed. In each model, the between-subject factors were education and occupation. The within-subject factors were total MMSE scores at the screening, 12-month, and 24-month intervals and total ADAS-Cog scores at baseline, 12-month, and 24-month visits. Gender, age, and marital status were included as covariates in the RM MANCOVA. Post-hoc pairwise comparisons, with Bonferroni adjustments, were performed on the ADAS and MMSE scores. Univariate tests from orthogonal contrasts in the RM MANCOVA were used to determine mean differences on cognitive tests scores each time point. Univariate tests results from orthogonal contrasts in the RM MANOVA and RM MANCOVA were conducted to determine which groups had faster rates of cognitive decline between points of interest. All analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 17.0.

Results

Demographics

Table 2 illustrates the demographic characteristics of the sample. The sample was mostly white (95%) and not Hispanic or Latino (97%). A large proportion of MCI participants were males (68%), married (83%), high (43%) and medium (40%) educated, and worked in high-level occupations (64%) during most of their working career.

Comparisons of the analysis sample and excluded groups revealed no significant differences in occupation ($\chi^2(1, n = 397) = 1.1, p = .294$), age ($t(397) = .547, p = .585$), marital status ($\chi^2(1, n = 397) = 3.377, p = .066$), race ($\chi^2(1, n = 397) = 1.748, p = .186$), or ethnicity ($p = .251$, Fisher's exact test). There was a significant difference, however, between the two groups in education ($\chi^2(1, n = 397) = 7.254, p = .027$) and gender ($\chi^2(1, n = 397) = 4.593, p = .032$). The excluded MCI group had more females (43%) and a higher proportion of low (25%) and medium (45%) educated participants than the included group.

Demographic characteristics of the low- ($n = 44$), medium- ($n = 105$), and high- ($n = 112$) education groups are presented in Table 3. The only significant difference identified between the three groups was their occupation ($\chi^2(2, n = 261) = 71.145, p = .000$). People with high education worked in higher occupations than those with low education. No statistically significant differences existed for gender ($\chi^2(2, n = 261) = .436, p = .804$), age ($F(2,211) = 1.973, p = .141$), race ($\chi^2(2, n = 261) = .306, p = .858$), ethnicity ($\chi^2(2, n = 261) = .614, p = .736$), or marital status ($\chi^2(2, n = 261) = 1.667, p = .434$).

Table 4 displays the demographics of the low- (n = 94) and high- (n = 167) occupation categories. There were significantly more males in the high-occupation group than the low-occupation group ($\chi^2(2, n = 261) = 6.359, p = .012$). No differences existed for age ($t(259) = 1.088, p = .277$), race ($\chi^2(2, n = 261) = 1.366, p = .243$), ethnicity ($\chi^2(2, n = 261) = .189, p = .667$), or marital status ($\chi^2(2, n = 261) = .375, p = .540$).

Correlations

Bivariate analyses are displayed in Table 5. A moderate positive relationship existed between education and occupation whereby people with higher education worked in higher occupations ($r_s = .513, p = .000$). MMSE and ADAS-Cog were negatively correlated, indicating that MCI participants who performed poorly on one cognitive measure also performed poorly on the other. MMSE and ADAS-Cog scores were not correlated with education at any interval. The small positive relationship between MMSE and occupation at the screening ($r_s = .204, p = .001$), 12-month ($r_s = .150, p = .015$), and 24-month assessments ($r_s = .134, p = .030$) suggested that higher occupations predicted better MMSE outcomes. ADAS-Cog and occupation were negatively correlated at the 12-month ($r_s = -.167, p = .007$) and 24-month intervals ($r_s = -.151, p = .015$). These negative relationships revealed that low occupations performed worse on the ADAS-Cog than individuals with high occupations. No significant correlation existed, though, between ADAS-Cog and occupation at baseline ($r_s = -.100, p = .107$). Gender, age, and marital status were not associated with MMSE and ADAS-Cog outcomes.

MMSE Scores

The median time between the screening and 12-month MMSE was 403 days. The median time from the 12-month to the 24-month MSSE was 370 days. There was a significant overall worsening of MMSE scores over time based on the RM MANOVA ($F(2,510) = 46.389, p = .000$) and RM MANCOVA ($F(2,504) = 46.436, p = .000$) models. Pairwise comparisons of the MMSE totals in both general linear models revealed significant differences between all three time points ($p \leq .05$).

MMSE and Education

Table 6 provides the mean MMSE scores for the education groups at the screening, 12-month, and 24-month visits. The significance levels between the education groups at each time are presented in Table 7. At baseline, the low-educated group had significantly higher mean MMSE scores than the medium-educated group ($p = .008$). The high-educated participants, though, did not significantly differ from the low- ($p = .190$) or medium- ($p = .143$) education groups. No significance differences were noted in MMSE performance at the 12-month interval for any education category ($p > .05$). At the 24-month visit, people with high education had significantly better scores on the MMSE than persons with medium education ($p = .028$). The low-education group did not significantly differ from the medium- or high-education categories at this time ($p > .05$).

Table 8 displays the univariate test results from orthogonal education contrasts in the RM MANOVA and MANCOVA when the dependent measures were MMSE scores.

Figure 3 presents the education plots from the RM MANCOVA analysis. Unexpectedly, high-educated people with MCI had slower cognitive declines between the screening and 24-month visit than the low-educated participants ($F(1,255) = 4.430$, $p = .036$). The significance remained even when gender, age, and marital status were controlled for ($F(1,255) = 5.692$, $p = .018$). Mean MMSE scores for medium-educated participants did not decline more rapidly than high-educated people during this time ($F(1,255) = 3.104$, $p = .079$) until the covariates were included in the analysis ($F(1,255) = 4.395$, $p = .037$). No significant differences in the decline of MMSE scores were detected between the screening and 12-month visit for any education level. Low-educated participants had a faster cognitive decline between the 12-month and 24-month visits ($F(1,255) = 4.38$, $p = .038$). The medium-education group also declined faster than the high-education group during this period ($F(1,255) = 4.78$, $p = .030$).

MMSE and Occupation

Mean MMSE scores for the low- and high-occupation categories (Table 6) were significantly different at the screening visit ($p = .004$; Table 7). MCI participants with high occupations started the study with better MMSE scores. No significant differences were found at the 12-month ($p = .133$) or 24-month ($p = .838$) visits.

Table 9 provides the univariate test results from occupation contrasts in the RM MANOVA and RM MANCOVA. No statistically significant differences in MMSE performance over time were found between the occupation levels in the RM MANOVA. Controlling for gender, age, and marital status resulted in a faster cognitive decline for persons in high occupations between the screening and 24-month visit (Figure 4.;

$F(1,252) = 3.886, p = .050$). The RM MANCOVA showed no distinctions in the decline of cognition between the two groups from screening to the 12-month visit $F(1,252) = .273, p = .602$). MMSE means scores did decrease more rapidly in high-occupation group than the low occupation members between the 12-month and 24-month visits ($F(1,252) = 4.013, p = .046$).

ADAS-Cog Scores

The median time between the baseline and 12-month ADAS-Cog was 365 days. Between the 12-month and 24-month visits the median time was 370 days. A significant overall decline in ADAS-Cog performance occurred during the two-year period based on the RM MANOVA ($F(1,504) = 45.823, p = .000$) and RM MANCOVA ($F(2,504) = 45.823, p = .000$) findings. Pairwise comparisons showed a trend in the decline of MMSE scores from baseline to 12-months (p=.056). All other time-point comparisons were highly significant ($p = .000$).

ADAS-Cog and Education

Each education group's mean ADAS-Cog scores for the baseline, 12-month, and 24-month study visits are presented in Table 10. Table 11 displays the significance levels between the education groups at each time. No statistically significant differences existed between the groups at the baseline and 12-month assessments ($p > .05$). At the 24-month visit, lower-educated MCI participants had worse mean ADAS-Cog scores than MCI participants with high education ($p = .049$). The middle-educated group also had worse mean ADAS-Cog scores than the high-educated group ($p = .033$). No

difference was detected at this time between the low- and middle-educated people (p = .635)

Table 12 shows the results from the education contrasts in the RM MANOVA and MANCOVA when the dependent measures were ADAS-Cog scores. Figure 5 presents the education plots from the RM MANCOVA analysis. No significant differences were detected in the rate of cognitive decline between people with low, medium, and high education at any time. Entering gender, age, and marital status into the RM general linear model had little effect. Contrasts in the RM MANCOVA revealed only a trend between the 12-month and 24-month visits whereby the low-educated group had a faster decline than the high-educated group ($F(1,252) = 3.661, p = .057$).

ADAS-Cog and Occupation

Mean ADAS-Cog scores for the occupation categories (Table 10) were not significantly different at the baseline, 12-month, or 24-month period ($p > .05$; Table 11).

Univariate findings from the orthogonal occupation contrasts in the RM MANOVA and RM MANCOVA are displayed in Table 13. Figure 6 displays the plots from the RM MANCOVA analysis. Even when the covariates were included, the low- and high-occupational groups did not differ in their cognitive decline from the baseline to 24-month visit ($F(1,252) = .018, p = .892$). The two groups also had similar declines in cognition between the baseline and 12-month ($F(1,252) = .651, p = .421$) as well as the 12-month and 24-month visits ($F(1,252) = .744, p = .389$).

Discussion

Cognitive reserve theorizes that disease pathology begins many years before symptoms emerge and progresses slowly over time. The model predicts that certain life experiences, such as greater years of education and working in a mentally stimulating environment, may provide a protective effect against the expression of dementia symptoms (Scarmeas & Stern, 2004; Stern, 2006; Stern, 2009; Stern, Albert, Tang, & Tsai, 1999). These symptoms will be displayed later in individuals with high cognitive reserve since their brains are able to cope with more damage. When the brain's cognitive reserve is exhausted, though, clinical progression will be more rapid (Stern, 2006; Stern, 2009).

The current investigation explored the impact of cognitive reserve on the rate of cognitive decline in patients with MCI. Since MCI may represent initial stages of dementia (Petersen et al., 1999; Petersen et al., 2001), it was hypothesized that older adults with MCI who have higher education and occupational attainment would display a more rapid cognitive decline over a two-year period than those with lower education and occupations.

Contrary to previous AD studies (Andel et al., 2006; Braundet et al., 2008; Hall et al., 2007; Hanyu et al., 2008; Roselli et al., 2009; Scarmeas, Albert, Manly, & Stern, 2006; Stern, Albert, Tang, & Tsai, 1999; Wilson et al., 2004) the investigation found that high education slowed the rate of cognitive decline in people with MCI. High-educated MCI participants had slower declines on the MMSE than persons with low education. When gender, age, and marital status were controlled for in the analyses, high-educated MCI participants had a less rapid decline on the MMSE over two years than individuals with

medium education. Significant education distinctions in MMSE performance were not detected one year into the study. Between the first and second study years, low- and medium-educated people with MCI had more accelerated cognitive declines than high-education people. These effects, however, were only detected when the MMSE was used to measure cognition. Education level had no effect on the rate of cognitive decline on the ADAS-Cog.

Occupation analyses had reverse effects. When the covariates were controlled, people who worked in high occupations during most of their working career declined faster on the MMSE than those in lower occupations. No differences in the speed of decline existed for the occupation group during the first study year. The high-occupation group's cognition deteriorated much faster between the first and second years. Mean scores on the ADAS-Cog showed no significant occupation effects on the rate of cognitive decline.

Drug studies with Alzheimer's disease patients reveal performance differences over time on the MMSE and ADAS-Cog (Vellas et al., 2005; Jones et al., 2009). These studies show that MMSE scores decrease faster than ADAS-Cog tests. Although the authors do not suggest a reason for this discrepancy, it is likely due to differences in what each test measuremes. For example, the MMSE's measure of memory is entirely based on verbal memory (Folstein, Folstein, & McHugh, 1975). The ADAS-Cog, however, assesses both verbal and visual memory (Rosen, Mohs & Davis, 1988). If a person with dementia has extensive disease pathology in the brain networks controlling verbal memory (but not visual memory), he or she could score slightly worse on the MMSE than the ADAS-Cog. The 70-item ADAS-Cog ultimately is a more comprehensive measure

than the 30-item MMSE. Such discrepancies in these screening tools may have caused the different test results.

The findings that high education may have a protective effect against cognitive decline while higher occupation may have a reverse effect in people with MCI are difficult to interpret. Several data limitations may explain the contrasting results. First, a positive correlation existed between education and occupation. People with higher education worked in higher occupational levels. However, the high-education and high-occupation group represented a disproportionate number of MCI participants in the study. A slower cognitive decline may have resulted in the lower-educated group if more people were included in that category. Second, low-educated persons started the study with significantly better MMSE scores. Higher numbers of low-educated participants could potentially reduce this gap and result in a less dramatic decline in MMSE scores. Third, it is assumed that there is a distinction between the occupation categories regarding job skills, knowledge, and responsibility. This differentiation may not truly exist, though, since job titles were used to classify participants. Without knowing the precise requirements of each person's job, high- and low-occupation groups may be inaccurately categorized. Fourth, participants were exposed to the same cognitive assessments at each visit. A learning or carryover effect may have occurred in the higher educated participants whereby some outcomes were related to the group learning the measure. The possibility of this effect, though, is diminished considerably in the ADNI study design (participants were tested no earlier than every six months and the majority have memory problems). Fifth, almost half (44%) of the original MCI participants were excluded because they were either lost to follow-up or did not complete a screening/baseline, 12-

month, or 24-month cognitive assessment. Gender and education differences existed between the analysis and excluded sample. This difference increases the chances that those excluded may have performed differently on the cognitive measures. Sixth, the date of MCI onset is unknown. It cannot be determined if the cognitive declines are due to the duration of the condition or some other factor(s). Finally, changes in medications during the course of the study, which could affect cognitive test performance, were not considered in the final analyses.

Despite these limitation, there are also several strengths to this investigation. First, the repeated measures design is useful because individual differences are controlled for, ultimately reducing the error term and increasing power. Second, the design allows for changes in the same individuals over time to be examined - strengthening cause and effect relationships. Third, the sample consisted of a large, well-defined sample of MCI participants. Participants were recruited from several sites across the United States and Canada and strict inclusion and exclusion criteria were enforced. It is highly likely that this sample represents a "pure" MCI group.

This study provides support that education may reduce rate of cognitive decline in MCI and, ultimately, dementia development. Encouraging people to perform brain-stimulating activities throughout their adult life may delay symptom onset of AD (Farmer et al., 1995; Stern, 2006; Stern 2009). This delay is critical considering the prevalence of AD in the United States is expected to more than double in the next 20 years (Hebert et al., 2003). The increase in the number of people with AD will dramatically augment the national healthcare system's financial burdens. Isolating methods that delay the onset of AD symptoms could ease much of the future financial and caregiver burden.

Strengthening the promotion of higher education may be an alternative to pharmacological approaches for reducing the risk of AD development. However, future investigations must explore the effects of this and other lifestyle variables further in MCI patients before program and policy recommendations can be made.

TABLES

Table 1. Summary of Reviewed Studies Investigating the Association of Cognitive Reserve (i.e. Education and/or Occupation) on the Rate of Cognitive Decline in Normal Aging and Alzheimer's Disease

Author(s)	*N*	Subjects	Time Studied	Cognitive Reserve Variables	Measures of Cognitive Decline	Main Analyses	Findings
Andel et al. (2006)	171	AD	Longitudinal, Semi-annually for 2.5 years	Education: Low (≤ 12 years) High (> 12 years) Occupation: Low/High categories based on complexity scores derived 1970 occupational census data	MMSE	MEM with RM	High education and high levels of occupational complexity were associated with a faster rate of decline on the MMSE.
Braundet et al. (2008).	670	AD	Longitudinal, Baseline and every 6 to 12 months for 3 years	Education: Low (≤ 8 years) Intermediate (9 to 12 years) High (> 12 years)	MMSE, DRS	MEM with RM	Annually adjusted DRS rate and MMSE decline over 3.5 years were higher for the patients in the high and intermediate than in the low education groups.

AD = Alzheimer's Disease, ARCD = Age-Related Cognitive Decline, BDAE = Boston Diagnostic Aphasia Examination, BNT = Boston Naming Test, BVRT = Benton Visual Retention Test, DRS = Dementia Rating Scale, DS = Digit Span, FRT = Figural Recognition Test, GEE = Generalized Estimated Equations, Lin R = Linear Regression, Log R = Logistic Regression, MEM = Mixed Effects Models, MMSE = Mini-Mental State Examination, *N* = Sample Size, OR = Pdss Ratio, PtT = Paired t Tests, REM = Random Effects Models, RM = Repeated Measures, SPMSQ = Pfeiffer Short Portable Mental-Status Questionnaire, SPM = Standard Progressive Matrices, SRT = Selective Reminding Task, SS = Short Story, STD = Standard Deviation, WAIS-R = Wechsler Adult Intelligence Scale-Revised, WMS-R = Wechsler Memory Scale-Revised

Table 1 (Continued). Summary of Reviewed Studies Investigating the Association of Cognitive Reserve (i.e. Education and/or Occupation) on the Rate of Cognitive Decline in Normal Aging and Alzheimer's Disease

Author(s)	*N*	Subjects	Time Studied	Cognitive Reserve Variables	Measures of Cognitive Decline	Main Analyses	Findings
Butler et al. (1996)	678	NL Aging (Nuns)	Cross-Sectional, Baseline and 18 months	Education: Low (< 16 years) High (≥ 16 years)	MMSE	Log R	Having at least a Bachelors degree was associated with a slower cognitive decline on the MMSE than a lesser (or no) degree (mean age = 83)
Chodosh et al. (2002)	684	NL Aging	Longitudinal, Baseline and 7th-year	Education: Low (<12 years) High (≥ 12 years)	SPMSQ	Log R	Having less than a 12th grade education was risk of cognitive impairment (OR = 1.8). Twelve or more years of education was strongly associated with a slower rate of overall cognitive decline (mean age = 74)
Christensen et al. (1997)	644	NL Aging	Longitundal, Baseline and 4th year	Education: Low (≤ 9 years) Intermediate (10 to 13 years) High (≥ 14 years)	MMSE	Log R	Low educational attainment was associated with greater decline on the MMSE. (mean age = 77)

AD = Alzheimer's Disease, ARCD = Age-Related Cognitive Decline, BDAE = Boston Diagnostic Aphasia Examination, BNT = Boston Naming Test, BVRT = Benton Visual Retention Test, DRS = Dementia Rating Scale, DS = Digit Span, FRT = Figural Recognition Test, GEE = Generalized Estimated Equations, Lin R = Linear Regression, Log R = Logistic Regression, MEM = Mixed Effects Models, MMSE = Mini-Mental State Examination, *N* = Sample Size, OR = Pdss Ratio, PtT = Paired t Tests, REM = Random Effects Models, RM = Repeated Measures, SPMSQ = Pfeiffer Short Portable Mental-Status Questionnaire, SPM = Standard Progressive Matrices, SRT = Selective Reminding Task, SS = Short Story, STD = Standard Deviation, WAIS-R = Wechsler Adult Intelligence Scale-Revised, WMS-R = Wechsler Memory Scale-Revised

Table 1 (Continued). Summary of Reviewed Studies Investigating the Association of Cognitive Reserve (i.e. Education and/or Occupation) on the Rate of Cognitive Decline in Normal Aging and Alzheimer's Disease

Author(s)	*N*	Subjects	Time Studied	Cognitive Reserve Variables	Measures of Cognitive Decline	Main Analyses	Findings
Farmer et al. (1995)	14,883	NL Aging	Longitudinal, Baseline and 1 year	Education: Low (≤ 9 years) Intermediate (10 to 12 years) High (≥ 13 years)	MMSE	Log R	In people ≥ 64 and < 64 years of age, higher education showed a protective effect for cognitive decline. (mean age in ≥ 64 = 71 and < 64 = 29)
Hall et al. (2007)	117	AD	Longitudinal, 12- to 18-month intervals	Education: Low (≤ 7 years) Intermediate (8 to 11 years) High (≥ 12 years)	SRT	REM	Higher education delays the onset of accelerated cognitive decline; once it begins it is more rapid in persons with more education.
Hanyu et al. (2008)	53	AD	Longitudinal, Baseline, 6-months, and 24-month	Education: Low (< 12 years) High (≥ 12 years)	MMSE	PtT	The high education group had a faster cognitive decline then the low education group.

AD = Alzheimer's Disease, ARCD = Age-Related Cognitive Decline, BDAE = Boston Diagnostic Aphasia Examination, BNT = Boston Naming Test, BVRT = Benton Visual Retention Test, DRS = Dementia Rating Scale, DS = Digit Span, FRT = Figural Recognition Test, GEE = Generalized Estimated Equations, Lin R = Linear Regression, Log R = Logistic Regression, MEM = Mixed Effects Models, MMSE = Mini-Mental State Examination, *N* = Sample Size, OR = Pdss Ratio, PtT = Paired t Tests, REM = Random Effects Models, RM = Repeated Measures, SPMSQ = Pfeiffer Short Portable Mental-Status Questionnaire, SPM = Standard Progressive Matrices, SRT = Selective Reminding Task, SS = Short Story, STD = Standard Deviation, WAIS-R = Wechsler Adult Intelligence Scale-Revised, WMS-R = Wechsler Memory Scale-Revised

Table 1 (Continued). Summary of Reviewed Studies Investigating the Association of Cognitive Reserve (i.e. Education and/or Occupation) on the Rate of Cognitive Decline in Normal Aging and Alzheimer's Disease

Author(s)	*N*	Subjects	Time Studied	Cognitive Reserve Variables	Measures of Cognitive Decline	Main Analyses	Findings
Lyketsos et al. (1999)	1,488	NL Aging	Longitudinal, Baseline and 11.5-year follow-up	Education: 1. ≤ 8 years 2. 9 to 11 years 3. 12 years 4. 13 to 15 years 5. ≥ 16 years	MMSE	Log R	Cognitive decline occurred in all age groups. Having > 8 years of education was associated with less decline. % of sample for each age groups (18-30 (29%), 31-40 (16%), 41-50 (9%), 52-60 (13%), 61-70 (17%), ≥ 71 (15%)
Roselli et al. (2009)	162	AD	Longitudinal, Baseline and 6-Month	Education: Low (< 8 years) High (≥ 8 years)	MMSE	GEE with RM	Patients with education ≥8 years showed a faster cognitive decline.
Scarmeas et al. (2006)	312	AD	Longitudinal, Semi-annually for 5 years	Education: Continuous	Composite Score from SRT, BVRT, WAIS-R, DRS, BNT, BDAE	Lin R	Each additional year of education there was 0.3% STD lower composite cognitive performance for each year of follow up. Higher education led to faster cognitive declines.

AD = Alzheimer's Disease, ARCD = Age-Related Cognitive Decline, BDAE = Boston Diagnostic Aphasia Examination, BNT = Boston Naming Test, BVRT = Benton Visual Retention Test, DRS = Dementia Rating Scale, DS = Digit Span, FRT = Figural Recognition Test, GEE = Generalized Estimated Equations, Lin R = Linear Regression, Log R = Logistic Regression, MEM = Mixed Effects Models, MMSE = Mini-Mental State Examination, *N* = Sample Size, OR = Pdss Ratio, PtT = Paired t Tests, REM = Random Effects Models, RM = Repeated Measures, SPMSQ = Pfeiffer Short Portable Mental-Status Questionnaire, SPM = Standard Progressive Matrices, SRT = Selective Reminding Task, SS = Short Story, STD = Standard Deviation, WAIS-R = Wechsler Adult Intelligence Scale-Revised, WMS-R = Wechsler Memory Scale-Revised

Table 1 (Continued). Summary of Reviewed Studies Investigating the Association of Cognitive Reserve (i.e. Education and/or Occupation) on the Rate of Cognitive Decline in Normal Aging and Alzheimer's Disease

Author(s)	*N*	Subjects	Time Studied	Cognitive Reserve Variables	Measures of Cognitive Decline	Main Analyses	Findings
Stern et al. (1999)	177	AD	Longitudinal, Annually for 4 years	Education: Low (≤ 12 years) High (> 12 years) Occupation: Low (unskilled, semiskilled, skilled trade or craft, and clerical/office worker) High (manager Business / government and professional / technical) Categories based 1990 census data	SRT	RA with RM	Memory declined more rapidly in AD patients with higher educational and occupational attainment.
Wilson et al. (2004)	494	AD	Longitudinal, Annually for 3 years	Education Continuous	Composite Score from MMSE, WMS-R, BNT, DS, SPM, FRT	MEM with RM	Higher educational attainment is associated with an faster cognitive decline in AD

AD = Alzheimer's Disease, ARCD = Age-Related Cognitive Decline, BDAE = Boston Diagnostic Aphasia Examination, BNT = Boston Naming Test, BVRT = Benton Visual Retention Test, DRS = Dementia Rating Scale, DS = Digit Span, FRT = Figural Recognition Test, GEE = Generalized Estimated Equations, Lin R = Linear Regression, Log R = Logistic Regression, MEM = Mixed Effects Models, MMSE = Mini-Mental State Examination, *N* = Sample Size, OR = Pdss Ratio, PtT = Paired t Tests, REM = Random Effects Models, RM = Repeated Measures, SPMSQ = Pfeiffer Short Portable Mental-Status Questionnaire, SPM = Standard Progressive Matrices, SRT = Selective Reminding Task, SS = Short Story, STD = Standard Deviation, WAIS-R = Wechsler Adult Intelligence Scale-Revised, WMS-R = Wechsler Memory Scale-Revised

Table 2. Demographic Characteristics of Sample

Variable	MCI (N = 261)
Gender, %	
Male	68%
Female	32%
Race, %	
White	95%
Other	5%
Ethnicity, %	
Not Hispanic or Latino	97%
Hispanic or Latino	3%
Age, mean (SD)	74.95 (± 7.43)
Marital Status, %	
Married	83%
Other	17%
Education, %	
High	43%
Medium	40%
Low	17%
Occupation, %	
High	64%
Low	36%

SD = Standard Deviation

Table 3. Demographics of the Low, Medium, and High Education Groups (N = 261)

Variables	*Low Education* (n = 44)	*Medium Education* (n = 105)	*High Education* (n = 112)
Gender, %			
Male	66%	70%	67%
Female	34%	30%	33%
Race, %			
White	96%	95%	94%
Other	4%	5%	6%
Ethnicity, %			
Not Hispanic or Latino	98%	98%	97%
Hispanic or Latino	2%	2%	3%
Age, mean (SD)	75.09 (± 6.53)	75.93 (± 7.86)	73.96 (± 7.99)
Marital Status, %			
Married	77%	82%	86%
Other	23%	18%	14%
Occupation, %*			
Low	82%	43%	36%
High	18%	57%	64%

p = Significance Level

* = Significant at the alpha .05 level

SD = Standard Deviation

Table 4. Demographics of the High and Low Occupation Groups (N = 261)

Variables	*Low Occupation* (n = 94)	*High Occupation* (n = 167)
Gender, %*		
Male	59%	74%
Female	41%	26%
Race, %		
White	97%	93%
Other	3%	7%
Ethnicity, %		
Not Hispanic or Latino	97%	97%
Hispanic or Latino	3%	3%
Age, mean (SD)	74.29 (± 7.14)	75.32 (± 7.45)
Marital Status, %		
Married	81%	84%
Other	19%	16%

p = Significance Level

* = Significant at the alpha .05 level

SD = Standard Deviation

Table 5. Bivariate Correlations at Screening/Baseline, 12-Month, and 24-Month Time Points ($N = 261$)

Variables	*Time*					
	Screening/Baseline		12-Month		24-Month	
	r	*p*	*r*	*p*	*r*	*p*
Education x Occupation[¥]	.513	.000*				
MMSE x ADAS-Cog[€]	-.320	.000*	-.611	.000*	-.786	.000*
Education x MMSE[¥]	.067	.284	.097	.120	.078	.206
Occupation x MMSE[¥]	.204	.001*	.150	.015*	.134	.030*
Gender x MMSE[¤]	-.048	.439	-.050	.417	-.095	.128
Age x MMSE[€]	.-088	.158	-.005	.938	.040	.516
Marital Status x MMSE[¤]	-.023	.709	.-068	.273	-.028	.685
Education x ADAS-Cog[¥]	-.078	.208	-.086	.166	-.081	.194
Occupation x ADAS-Cog[¥]	-.100	.107	-.167	.007*	-.151	.015*
Gender x ADAS-Cog[¤]	-.063	.311	.121	.051	.118	.057
Age x ADAS-Cog[€]	.044	.481	.078	.212	.000	.990
Marital Status x ADAS-Cog[¤]	.106	.088	.000	.995	-.013	.840

r = Correlation Coefficient

p = Significance Level

x = Variables are being compared

[¥] = Spearman's Rank-Order Correlation

[€] = Pearson's Product-Moment Correlation

[¤] = Point-Biserial Correlation

N/A = Not Applicable (Screening/Baseline measures only)

* = Significant at the alpha .05 level

Table 6. Mean MMSE Scores and Standard Deviations for the Education and Occupation Levels at Each Time ($N = 261$)

Variables	*Time*					
	Screening		12-Month		24-Month	
	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD
Education						
Low	27.72	± 0.65	26.94	± 1.08	24.95	± 1.51
Medium	26.75	± 0.32	26.34	± 0.54	24.69	± 0.76
High	27.18	± 0.49	26.79	± 0.81	26.22	± 1.14
Occupation						
Low	26.79	± 0.39	26.32	± 0.65	25.36	± 0.94
High	27.65	± 0.43	27.06	± 0.71	25.21	± 1.01

$\bar{x}$ = Mean

SD = Standard Deviation

Table 7. Univariate Test Results (Significance Levels) of the Orthogonal Contrasts Comparing the Mean MMSE Scores at Each Time ($N = 261$)

Variable Contrasts	*Time*		
	Screening	12-Month	24-Month
	p	*p*	*p*
Education			
Low vs Medium	.008*	.320	.757
Medium vs High	.143	.363	.028*
Low vs High	.190	.818	.188
Occupation			
Low vs High	.004*	.133	.838

p = Significance Level

* = Significant at the Alpha .05 Level

Table 8. MMSE Scores: Orthogonal Contrasts (Education Level) in the Repeated Measures MANOVA and MANCOVA ($N = 261$)

RM Model & Education Level Contrasts	*Intervals*					
	Screening - 12 Month		12-Month - 24-Month		Screening - 24-Month	
	F	*p*	*F*	*p*	*F*	*p*
RM MANOVA						
Low vs Medium	.547	.500	.317	.574	.858	.355
Medium vs High	.001	.973	4.780	.030*	3.104	.079
Low vs High	.395	.530	4.359	.038*	4.430	.036*
RM MANCOVA						
Low vs Medium	.541	.463	.308	.580	.933	.335
Medium vs High	.082	.755	5.619	.019*	4.395	.037*
Low vs High	.742	.390	4.928	.027*	5.692	.018*

F = F Statistic

p = Significance Level

* = Significant at the Alpha .05 Level

Table 9. MMSE Scores: Orthogonal Contrasts (Occuppation Level) in the Repeated Measures MANOVA and MANCOVA ($N = 261$)

RM Model & Occupation Level Contrasts	*Intervals*					
	Screening - 12 Month		12-Month - 24 Month		Screening - 24-Month	
	F	*p*	*F*	*p*	*F*	*p*
RM MANOVA						
Low vs High	.078	.780	3.227	.074	2.644	.105
RM MANCOVA						
Low vs High	.273	.602	4.013	.046*	3.886	.050*

F = F Statistic

p = Significance Level

* = Significant at the alpha .05 level

Table 10. Mean ADAS Scores and Standard Deviations for the Education and Occupation Levels at Each Time ($N = 261$)

Variables	*Time*					
	Baseline		12-Month		24-Month	
	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD
Education						
Low	12.37	± 1.71	12.66	± 2.26	16.07	± 2.82
Medium	11.51	± 0.86	12.89	± 1.13	15.31	± 1.42
High	10.41	± 1.30	11.38	± 1.72	12.50	± 2.16
Occupation						
Low	11.47	± 1.05	12.66	± 1.38	14.60	± 1.72
High	11.39	± 1.14	11.94	± 1.51	14.65	± 1.88

$\bar{x}$ = Mean

SD = Standard Deviation

Table 11. Univariate Test Results (Significance Levels) of the Orthogonal Contrasts Comparing the Mean ADAS Scores at Each Time ($N = 261$)

Variable Contrasts	*Time*		
	Baseline	12-Month	24-Month
	p	*p*	*p*
Education			
Low vs Medium	.382	.860	.635
Medium vs High	.167	.153	.033*
Low vs High	.075	.375	.049*
Occupation			
Low vs High	.912	.504	.970

p = Significance Level

* = Significant at the Alpha .05 Level

Table 12. ADAS Scores: Orthogonal Contrasts (Education Level) in the Repeated Measures MANOVA and MANCOVA ($N = 261$)

RM Model & Education Level Contrasts	*Intervals*					
	Baseline - 12 Month		12-Month - 24-Month		Baseline - 24-Month	
	F	*p*	*F*	*p*	*F*	*p*
RM MANOVA						
Low vs Medium	1.543	.215	1.057	.305	.005	.943
Medium vs High	.345	.557	1.577	.210	2.301	.131
Low vs High	.469	.494	3.346	.069	1.071	.302
RM MANCOVA						
Low vs Medium	1.342	.248	.860	.355	.005	.942
Medium vs High	.276	.600	2.235	.136	2.838	.093
Low vs High	.474	.519	3.661	.057	1.352	.247

F = F Statistic

p = Significance Level

* = Significant at the Alpha .05 Level

Table 13. ADAS Scores: Orthogonal Contrasts (Occuppation Level) in the Repeated Measures MANOVA and MANCOVA ($N = 261$)

RM Model & Occupation Level Contrasts	*Intervals*					
	Baseline - 12 Month		12-Month - 24 Month		Baseline - 24-Month	
	F	*p*	*F*	*p*	*F*	*p*
RM MANOVA						
Low vs High	1.378	.242	.570	.451	.064	.801
RM MANCOVA						
Low vs High	.651	.421	.744	.389	.018	.892

F = F Statistic

p = Significance Level

* = Significant at the alpha .05 level

FIGURES

Figure 1. Theoretical Illustration of the Impact of Cognitive Reserve on Cognitive Test Performance Over Time

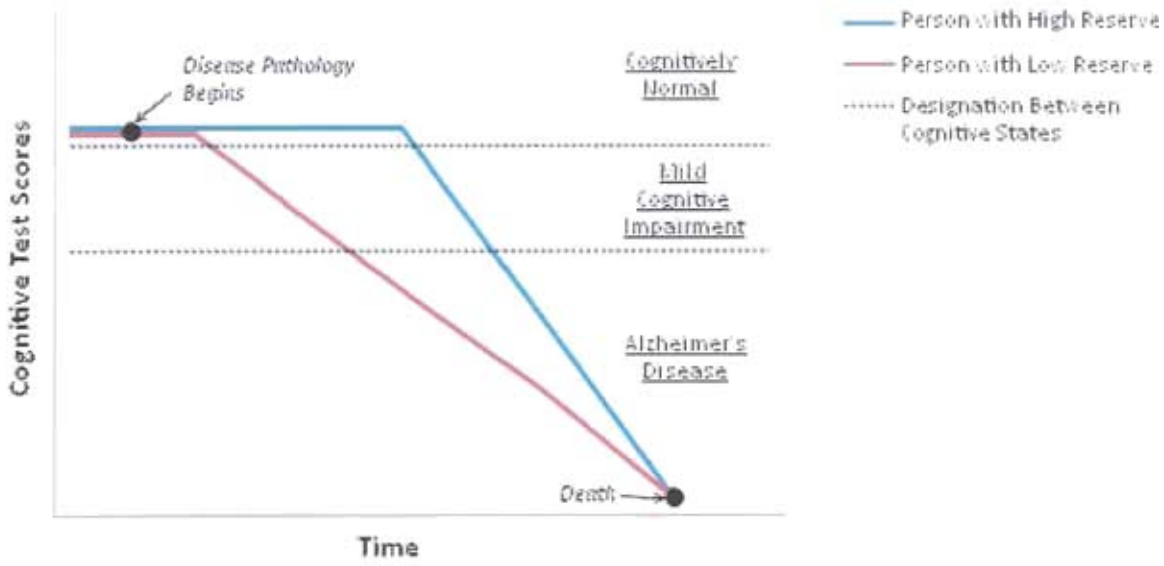


Figure 2. Logical Model: Association Between Cognitive Reserve and Cognitive Decline with Mediating Covariates

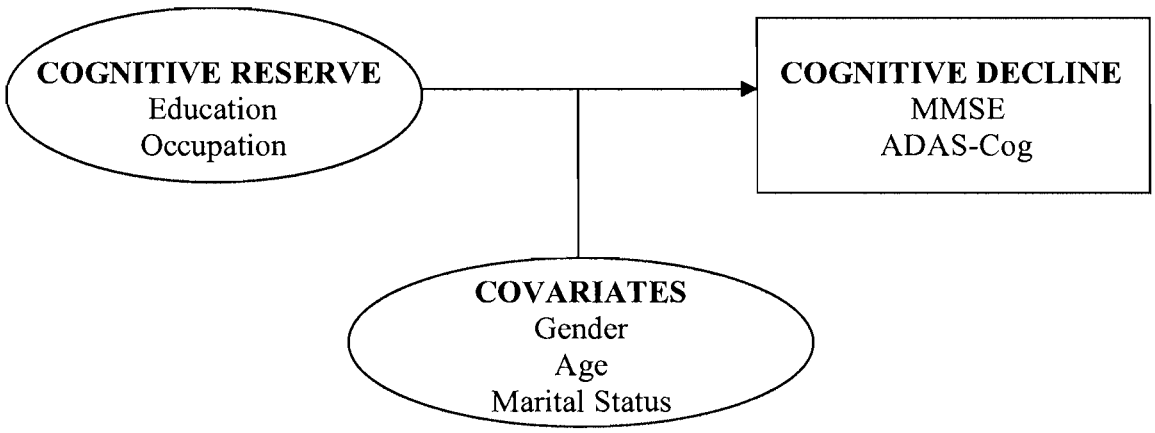
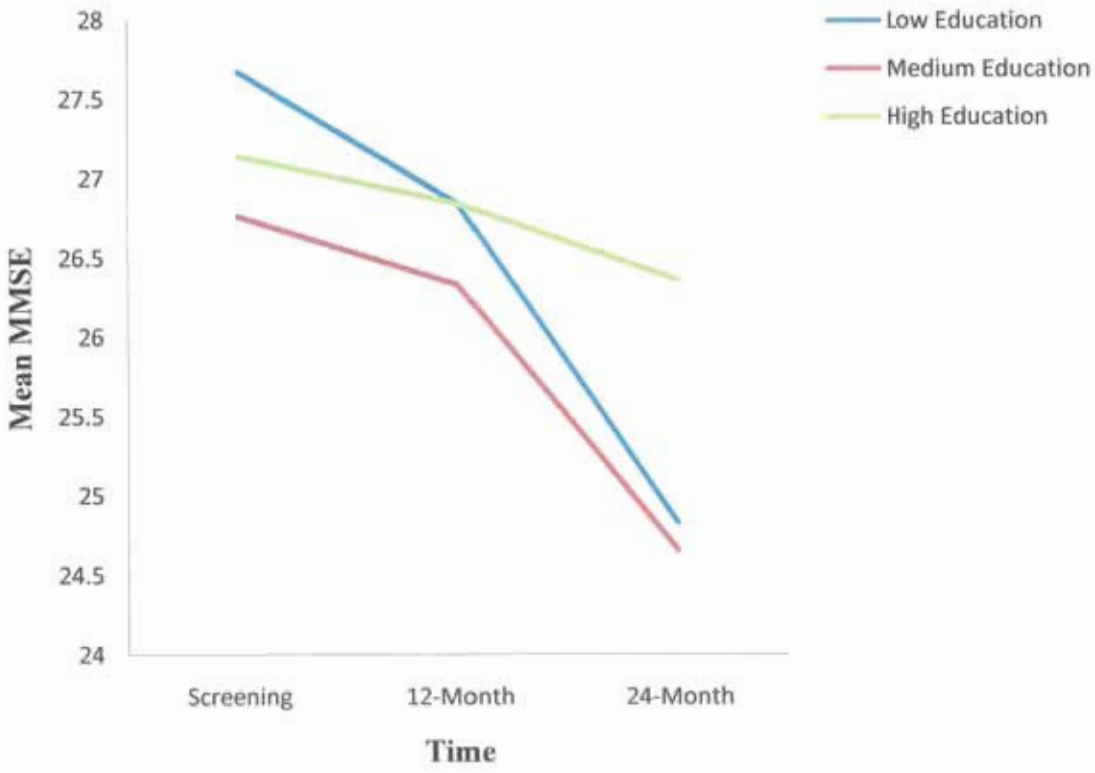


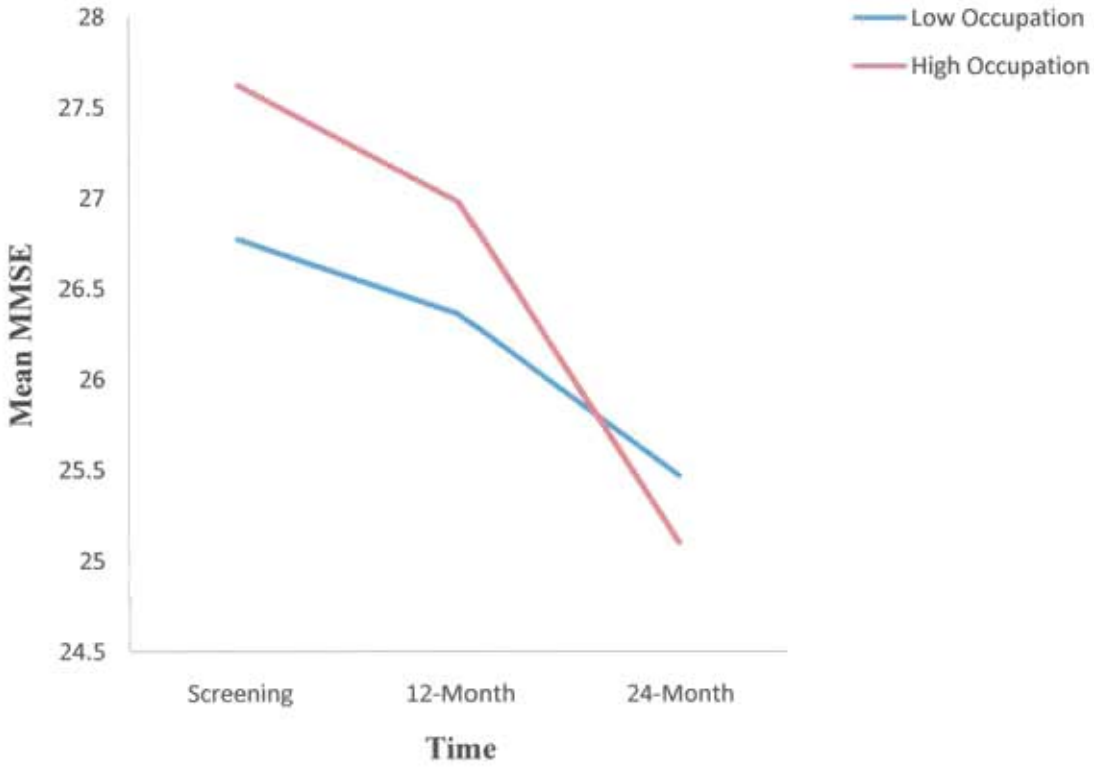
Figure 3. Low, Medium, and High Education: Mean MMSE Scores over Time (Plots from RM MANCOVA)



L. Covariates appearing in the model are evaluated at the following values:

Gender = 1.32, Age = 74.95, and Marital Status = .83

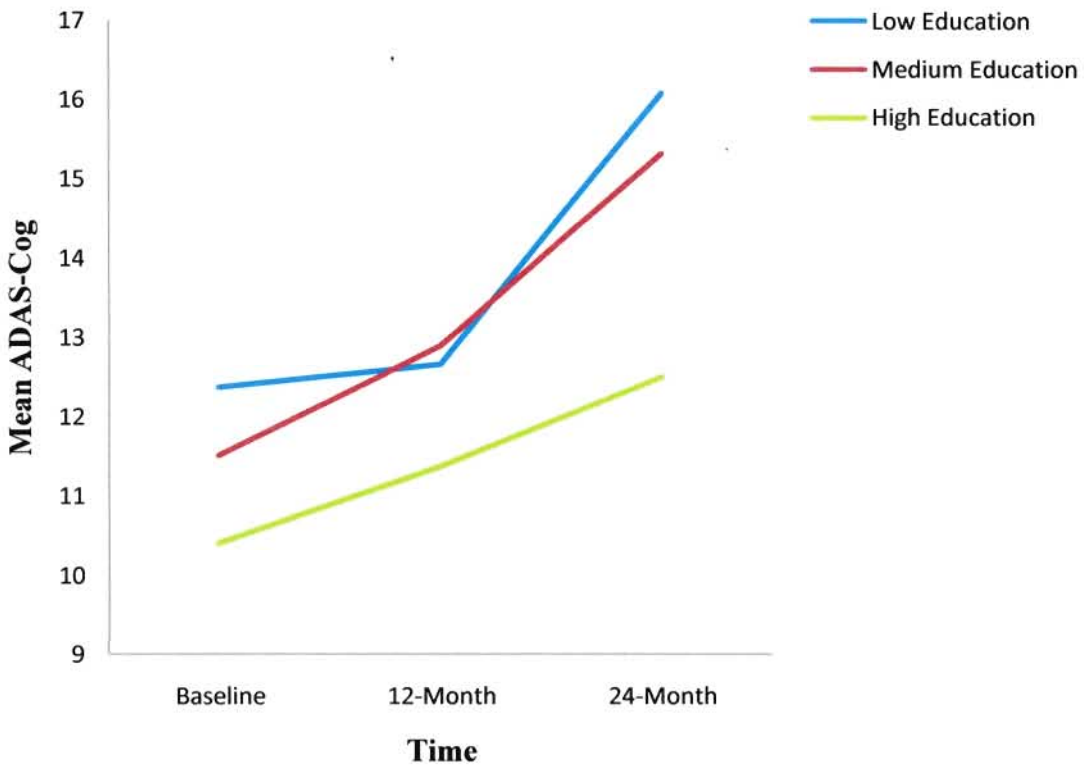
Figure 4. Low and High Occupation: Mean MMSE Scores over Time (Plots from RM MANCOVA)



2. Covariates appearing in the model are evaluated at the following values:

Gender = 1.32, Age = 74.95, and Marital Status = .83

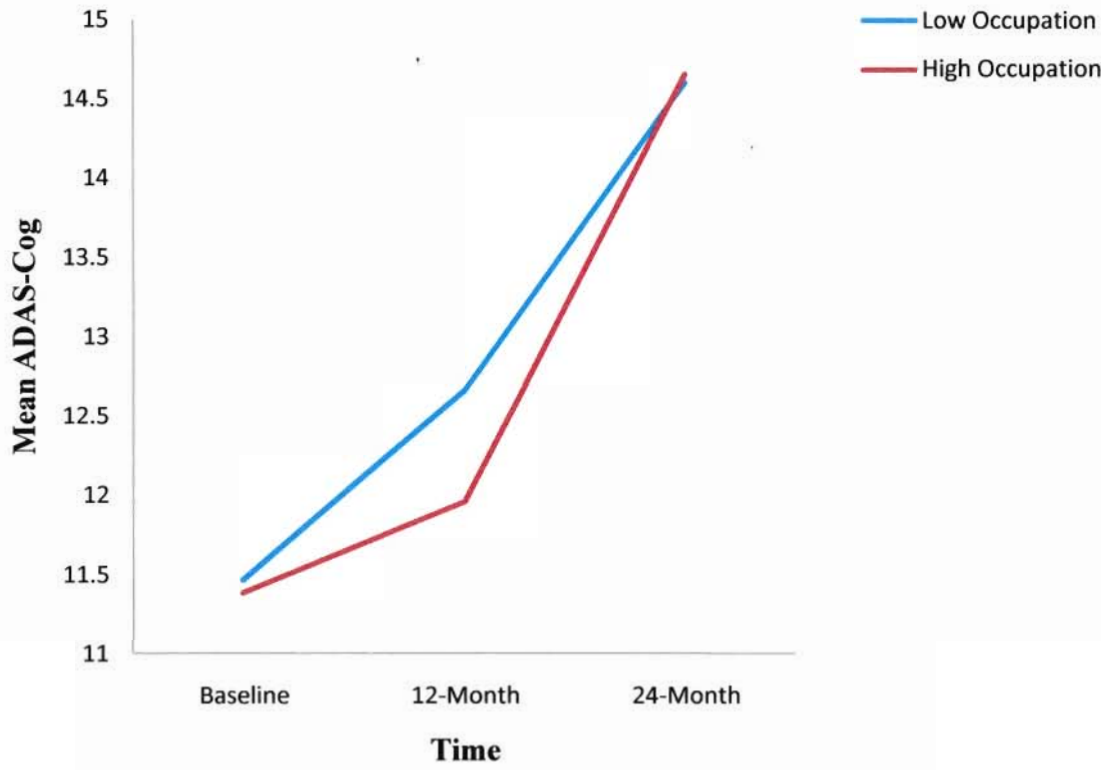
Figure 5. Low, Medium, and High Education: Mean ADAS-Cog Scores over Time (Plots from RM MANCOVA)



3. Covariates appearing in the model are evaluated at the following values:

Gender = 1.32, Age = 74.95, and Marital Status = .83

Figure 6. Low and High Occupation: Mean ADAS Scores over Time (Plots from RM MANCOVA)



4. Covariates appearing in the model are evaluated at the following values:

Gender = 1.32, Age = 74.95, and Marital Status = .83

APPENDIX

Appendix A. Excluded Medications Not Allowed within 4 Weeks Prior to Screening*

	General Name
Narcotic Analgesics	Hydromorphone
	Oxycodone/Acetaminophen
	Oxycodone/Aspirin
	Propoxyphene Darvon and its variations
	Narcotics that contain codeine or morphine
Neuroleptics	Chlorpromazine
	Fluphenazine
	Loxapine
	Perphenazine
	Thioridazine
	Thiothixene
	Trifluoperazine
	Clozapine
	Haloperidol
Anti-Cholinergics	Amantadine l
	Benztropine
	Cyproheptadine
	Dicyclomine
	Diphenhydramine
	Diphenoxylate with atropine Lomotil
	Hydroxyzine
	Hyoscyamine
	Meclizine
	Prochlorperazine
	Trihexyphenidyl
	Trimethobenzamide
Anti-Parkinsonian Drugs	Bromocriptine
	Deprenyl/Selegiline
	Levodopa
	Pergolide
	Pramipexole
Sedatives/Benzodazapines	Chlordiazepoxide

Appendix A (Continued). Excluded Medications Not Allowed within 4 Weeks Prior to Screening*

	General Name
Sedatives/Benzodazapines	Diazepam
	Flurazepam
	Meprobamate
	Triazolam
Anti-Hypertensives	Clonidine
Anti-Depressants	Amitriptyline
	Amoxapine
	Clomipramine
	Desipramine
	Doxepin
	Imipramine
	Isocarboxazide
	Lithium
	Maprotiline
	Nortriptyline
	Phenelzine
	Protriptyline
	Tranylcypromine
	Trimipramine

*Not an exhaustive list of excluded medications

Appendix B. Permitted Medications Allowed if Dose was Stable for 4 Weeks Prior to Screening*

	General Name
Neuroleptics	Aripiprazole
	Olanzapine
	Quetiapine
	Risperidone
	Ziprasidone
Sedatives/Benzodazapines	Alprazolam
	Buspirone
	Chloral Hydrate
	Lorazepam
	Oxazepam
	Temazepam
	Trazodone
	Zaleplon
	Zolpidem
Anti-Depressants	Bupropion
	Citalopram
	Escitalopram
	Fluoxetine
	Mirtazapine
	Nefazodone
	Paroxetine
	Sertraline
	Trazodone
	Venlafaxine

*Not an exhaustive list of permitted medications.

REFERENCES

Alzheimer's Association. (2010). 2010 Alzheimer's disease facts and figures. *Alzheimer's & Dementia, 6,* 158-194.

Andel, R., Vigen, C., Mack, W.J., Clark, L.J., & Gatz, M. (2006). The effect of education and occupational complexity on rate of cognitive decline in Alzheimer's patients. *Journal of the International Neuropsychological Society, 12,* 147-152.

Artero, S., Ancelin, M.L., Portet, F., Dupuy, A., Berr, C., Dartigues, J.F., Tzourio, C., Rouaud, O., Poncet, M., Pasquier, F., Auriacombe, S., Touchon, J., & Ritchie, K. (2008). Risk profiles for mild cognitive impairment and progression to dementia are gender specific. *Journal of Neurology, Neurosurgery, and Psychiatry, 79,* 979-984.

Bennett, D.A., Schneider, J.A., Arvanitakis, Z., Kelly, J.F., Aggarwal, N.T., Shah, R.C., & Wilson, R.S. (2006). Neuropathology of older persons without cognitive impairment from two community-based studies. *Neurology, 66,* 1837-1844.

Bosch, B., Bartrés-Faz, D., Rami, L., Arenaza-Urquijo, E.M., Fernández-Espejo, D., Junqué, C., Solé-Padullés, C., Sánchez-Valle, R., Bargalló, N., Falcón, C., Molinuevo, J.L. (2010). Cognitive reserve modulates task-induced activations and deactivations in healthy elders, amnestic mild cognitive impairment and mild Alzheimer's disease. *Cortex, 46,* 451-461.

Bruandet, A., Richard, F., Bombois, S., Maurage, C.A., Masse, I., Amouyel, P., & Pasquier, F. (2008). Cognitive decline and survival in Alzheimer's disease

according to education level. *Dementia and Geriatric Cognitive Disorders, 25,* 74-80.

Butler, S.M., Ashford, J.W., & Snowdon, D.A.. (1996). Age, education, and changes in the mini-mental state exam scores of older women: findings from the Nun study. *Journal of the American Geriatrics Society, 44,* 675-681.

Chodosh, J., Reuben, D.B., Albert, M.S., & Seeman, T.E. (2002). Predicting cognitive Impairment in high-functioning community-dwelling older persons: MacArthur studies of successful aging. *Journal of the American Geriatrics Society, 50,* 1051-1060.

Christensen, H., Korten, A.E., Jorm, A.F., Henderson, A.S., Jacomb, P.A., Rodgers, B., & Mackinnon, A.J. (1997). Education and decline in cognitive performance: compensatory but not protective. *International Journal of Geriatric Psychiatry, 12,* 323-330.

DeCarli, C. (2003). Mild cognitive impairment: diagnosis, prognosis, aetiology, and treatment. *Lancet Neurology, 2,* 15−21.

Farmer, M.E., Kittner, S.J., Rae, D.S., Bartko, J.J., & Regier, D.A. (1995). Education and change in cognitive function. The Epidemiologic Catchment Area Study. *Annals of Epidemiology,* 5, 1-7.

Folstein, M.F., Folstein, S.E., & McHugh, P.R. (1975). "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12,* 189-198.

Hachinski, V. C., Iliff, L. D., Phil, M., Zilhka, E., DuBoulay, G. H., McAllister, V. L., Marshall, J., Russell, R. W. R., & Symon, L. (1975). Cerebral blood flow in dementia. *Archives of Neurology, 32*, 632–637.

Hall, C.B., Derby, C., LeValley, A., Katz, M.J., Verghese, J., & Lipton, R.B. (2007). Education delays accelerated decline on a memory test in persons who develop dementia. *Neurology*, 69, 1657-1664.

Håkansson, K., Rovio, S., Helkala, E.L., Vilska, A.R., Winblad, B., Soininen, H., Nissinen, A., Mohammed, A.H., & Kivipelto, M. (2009). Association between mid-life marital status and cognitive function in later life: population based cohort study. *British Medical Journal, 339*, 1-8.

Hanyu, H., Sato, T., Shimizu, S., Kanetaka, H., Iwamoto, T., & Koizumi, K. (2008). The effect of education on rCBF changes in Alzheimer's disease: a longitudinal SPECT study. *European Journal of Medicine and Molecular Imaging, 35*, 2182-2189.

Hebert, L.E., Scherr, P.A., Bienias, J.L., Bennett, D.A., & Evans, D.A. (2003). Alzheimer's disease in the U.S. population; Prevalence estimates using the 2000 census. *Archives of Neurology, 60*, 1119–1122.

Hulette, C.M., Welsh-Bohmer, K.A., Murray, M.G., Saunders, A.M., Mash, D.C., McIntyre, L.M. (1998). Neuropathological and neuropsychological changes in "normal" aging: evidence for preclinical Alzheimer disease in cognitively normal individuals. *Journal of Neuropathology and Experimental Neurology, 57,* 1168-1174.

Jones, R.W., Schwam, E., Wilkinson, D., Waldemar, G., Feldman, H.H., Zhang, R., Albert, K., & Schindler, R. (2009). Rates of cognitive change in Alzheimer disease: Observations across a decade of placebo-controlled clinical trials with donepezil. *Alzheimer's Disease and Associated Disorders*, *23*, 357-364.

Katzman, R., Terry, R., DeTeresa, R., Brown, T., Davies, P., Fuld, P., Renbing, X. & Peck, A. (1988). Clinical, pathological, and neurochemical changes in dementia: a subgroup with preserved mental status and numerous neocortical plaques. *Annals of Neurology, 23*, 138−144.

Knopman, D.S., Parisi, J.E., Salviati, A., Floriach-Robert, M., Boeve, B.F., Ivnik, R.J., Smith, G.E., Dickson, D.W., Johnson, K.A., Petersen, L.E., McDonald, W.C., Braak, H., & Petersen, R.C. (2003). Neuropathology of cognitively normal elderly. *Journal of Neuropathology and Experimental Neurology, 62,* 1087-1095.

Luis, C.A., Loewenstein, D.A., Acevedo, A., Barker, W.W., & Duara, R. (2003). Mild cognitive impairment. Directions for future research. *Neurology, 61*, 438–444.

Lyketsos, C.G., Chen, L.S., & Anthony, J.C. (1999). Cognitive decline in adulthood: an 11.5-year follow-up of the Baltimore Epidemiologic Catchment Area study. *The American Journal of Psychiatry*, 156, 58-65.

Mehta, K.M., Yaffe, K., Pérez-Stable, E.J., Stewart, A., Barnes, D., Kurland, B.F., & Miller, B.L. (2008). Race/ethnic differences in AD survival in US Alzheimer's Disease Centers. *Neurology, 70,* 1163-1170..

Mohs, R.C. & Cohen, L. (1988). Alzheimer's Disease Assessment Scale (ADAS). *Bulletin, 24*, 458-462

Morris JC. (1993). The Clinical Dementia Rating (CDR): current version and scoring

rules. *Neurology, 43*, 2412-2414.

Peterson, R.C. (2000). Mild cognitive impairment or questionable dementia? *Archives of Neurology, 57*, 643-644.

Petersen, R.C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine, 256*, 183-194.

Petersen, R.C., Smith, G.E., Waring, S.C., Ivnik, R.J., Tangalos, E.G., & Kokmen, E. (1999). Mild cognitive impairment: Clinical characterization and outcome. *Archives of Neurology, 56*, 303-308.

Petersen, R.C., Stevens, J.C., Ganguli, M., Tangalos, E.G., Cummings, J.L., & DeKosky, S.T. (2001). Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). *Neurology, 56,* 1133-1142.

Rolstad, S., Nordlund, A., Eckerström, C., Gustavsson, M.H., Zetterberg, H., & Wallin, A. (2009). Cognitive reserve in relation to abeta42 in patients converting from MCI to dementia - a follow-up report. *Dementia and Geriatric Cognitive Disorders, 28,* 110-115.

Roselli, F., Tartaglione, B., Federico, F., Lepore, V., Defazio, G., & Livrea, P. (2009). Rate of MMSE score change in Alzheimer's disease: influence of education and vascular risk factors. *Clinical Neurology and Neurosurgery, 111*, 327-330.

Rosen, W.G., Mohs, R.C., & Davis, K.L. (1988). A new rating scale for Alzheimer's disease. *American Journal of Psychiatry, 141*, 1356-1364.

Scarmeas, N., Albert, S.M., Manly, J.J., & Stern, Y. (2006). Education and rates of cognitive decline in incident Alzheimer's disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 77*, 308-316.

Scarmeas, N. & Stern, Y. (2004). Cognitive reserve: Implications for diagnosis and prevention of Alzheimer's disease. *Current Neurology and Neuroscience Reports, 4*, 374-80.

Scarmeas, N., Zarahn, E., Anderson, K.E., Habeck, C.G., Hilton, J., Flynn, J., Marder, K.S., Bell, K.L., Sackeim, H.A., Van Heertum, R.L., Moeller, J.R., & Stern, Y. (2003). Association of life activities with cerebral blood flow in Alzheimer disease: implications for the cognitive reserve hypothesis. *Archives of Neurology, 60,* 359-365.

Schwarb, S., Koberle, S., & Spiegel, R. (1988). The Alzheimer's Disease Assessment Scale (ADAS): an instrument for early diagnosis of dementia. *International Journal of Geriatric Psychiatry, 3*, 45-53.

Sheikh, J.I. & Yesavage, J.A. (1986). Geriatric Depression Scale (GDS)' Recent evidence and development of a shorter version. *Clinical Gerontologist, 5,* 165-173.

Solé-Padullés, C., Bartrés-Faz, D., Junqué, C., Vendrell, P., Rami, L., Clemente, I.C., Bosch, B., Villar, A., Bargalló, N., Jurado, M.A., Barrios, M., & Molinuevo, J.L. (2009). Brain structure and function related to cognitive reserve variables in normal aging, mild cognitive impairment and Alzheimer's disease. *Neurobiology of Aging, 30*, 1114-1124.

Springer, M.V., McIntosh, A.R., Wincour, G., & Grady, C.L. (2005). The relation between brain activity during memory tasks and years of education in young and older adults. *Neuropsychology, 19*, 181-192.

Stern, Y.S. (2006). Cognitive reserve and Alzheimer's disease. *Alzheimer Disease & Associated Disorders, 20*, S69-S74 .

Stern, Y.S. (2009). Cognitive reserve. *Neuropsycholgia, 47*, 2015-2028.

Stern, Y.S., Albert, S., Tang, M.X., & Tsai, W.Y. (1999). Rate of memory decline in AD is related to education and occupation: cognitive reserve? *Neurology, 53,* 1942-1947.

Stern, Y.S., Habeck, C., Moeller, J., Scarmeas, N., Anderson, K.E., Hilton, H.J., Flynn, J., Sackeim, H., & van Heertum, R. (2005). Brain networks associated with cognitive reserve in healthy young and old adults. *Cerebral Cortex, 15*, 394-402.

United States Equal Employment Opportunity Commission. (2006a). EEO-1 job classification guide: A guide which maps 2000 census job codes and titles into the ten (10) EEO-1 survey job categories. Washington, D.C.. Retrieved on January 28th, 2010 from http://www.eeoc.gov/employers/eeo1survey/upload/jobclassguide.pdf.

United States Equal Employment Opportunity Commission. (2006b). EEO-1 instruction booklet. Washington, D.C.. Retrieved on January 28th, 2010 from http://www.eeoc.gov/employers/eeo1survey/upload/instructions_form.pdf.

Valenzuela, M.J. & Sachev, P. (2005). Brain reserve and dementia: A systematic review. *Psychological Medicine, 35*, 1-14.

Vellas, B., Lauque, S., Gillette-Guyonnet, S., Andrieu, S., Cortes, F., Nourhashémi, F., Cantet, C., Ousset, P.J., & Grandjean, H. (2005). Impact of nutritional status on the evolution of Alzheimer's disease and on response to acetylcholinesterase inhibitor treatment. *Journal of Nutrition, Health, and Aging, 9*, 75-80.

Wechsler, D. (1987). *Manual for the Wechsler Memory Scale-Revised.* The Psychological Corporation, San Antonio; 1987.

Wilson, R.S., Li, Y., Aggarwal, N.T., Barnes, L.L., McCann, J.J., Gilley, D.W., & Evans, D.A. (2004). Education and the course of cognitive decline in Alzheimer disease. *Neurology, 6*3, 1198-1202.