Published in final edited form as:

Cogn Neurosci. 2013 ; 4(0): . doi:10.1080/17588928.2013.831820.

Relationship of Cognitive Reserve and APOE Status to the Emergence of Clinical Symptoms in Preclinical Alzheimer's Disease

Corinne Pettigrew^a, Anja Soldan^a, Shanshan Li^b, Yi Lu^b, Mei-Cheng Wang^b, Ola A. Selnes^a, Abhay Moghekar^a, Richard O'Brien^a, Marilyn Albert^a, and BIOCARD Research Team

^aDepartment of Neurology, The Johns Hopkins University School of Medicine, Baltimore, MD

^bDepartment of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Abstract

The APOE 4 allele increases the risk of developing Alzheimer's disease, whereas the APOE 2 allele reduces risk. We examined whether cognitive reserve (CR), as measured by an index consisting of education, reading, and vocabulary, modifies these associations. CR was measured at baseline in 257 cognitively normal individuals (mean age 57.2 years) who have been followed for up to 17 years (mean follow-up = 9.2 years). Cox regression models showed that CR and APOE 4 independently affected the risk of progressing from normal cognition to onset of clinical symptoms: CR reduced risk by about 50% in both 4 carriers and non-carriers, while 4 increased risk by about 150%. In contrast, APOE 2 interacted with CR, such that CR was more protective in 2 carriers than non-carriers. This suggests that individuals with an 2 genotype may disproportionately benefit from lifetime experiences that enhance cognition.

Alzheimer's disease (AD) is the most common form of dementia, with prevalence projected to increase as the U.S. population ages. While age is the largest risk factor for AD dementia, both genetic and lifestyle factors also play a role. The 4 allele of the apolipoprotein E (APOE) gene is known to be a major genetic risk factor for developing Mild Cognitive Impairment (MCI; Brainerd et al., 2013) and AD dementia (Farrer et al., 1997). The 2 allele of this same gene, on the other hand, has been shown to reduce the AD dementia risk (Corder et al., 1994). One of the major lifestyle factors associated with a lowered risk for dementia is cognitive activity. This has been measured in many ways including years of education, literacy, and occupational attainment (see Stern, 2009 for a review). The concept of cognitive reserve (CR) has been proposed to account for the protective effect of cognitive activity (Stern, 2006, 2009). CR is the notion that individual differences in lifetime experiences that enhance cognition modify the negative effects of AD brain pathology by increasing the efficiency, capacity, and flexibility of brain networks. However, high CR does not guarantee that one will remain dementia-free because genetic factors also alter one's risk for dementia.

While both APOE and CR modify risk for dementia, little is known about the degree to which CR alters the effect of APOE status on the risk of developing cognitive impairment among cognitively normal individuals. Longitudinal studies following non-demented (Ferrari et al., 2013; Ngandu et al., 2007) or normal (Hsiung, Sadovnick, & Feldman, 2004) individuals have found APOE 4 and CR independently modify risk of incident dementia.

However, no studies to our knowledge have examined the relationship between APOE 2 and CR. Furthermore, only one study has examined the degree to which CR modifies the effect of 4 during the preclinical phase of AD; this study found independent effects of 4 and CR, though its follow-up period was relatively short (Hsiung et al., 2004). Additionally, identification of midlife factors that affect risk for cognitive impairment is critically important, as the preclinical phase of AD is the ideal time for early intervention.

The current study addresses a number of issues that remain unresolved by previous studies. First, to our knowledge, no previous studies have examined the relationship between APOE genotype and CR on the risk of progressing from normal cognition to the emergence of clinical symptoms (preceding the diagnosis of MCI or AD dementia), particularly with respect to the relationship between CR and APOE 2. Second, previous longitudinal studies (Ferrari et al., 2013; Hsiung et al., 2004) report on individuals in their 70's-80's, providing little information on the relationship between APOE status and CR in midlife. The present study reports data from a cohort of individuals who were middle-aged and cognitively normal at baseline and have been followed with annual clinical and cognitive assessments. Third, previous longitudinal studies examining the relationship between APOE and CR have used education as a proxy for CR, though education is static and unlikely to change after early adulthood. In contrast, literacy may be a better reflection of reserve (Manly et al., 2003, 2005) and additionally, both literacy and vocabulary may change over time, thereby making them more sensitive CR proxies. The present study examined whether each of these indices of CR are associated with the time to onset of clinical symptoms to a similar degree.

Method

Study Design and Participant Selection

The BIOCARD study was designed to recruit and follow a cohort of cognitively normal individuals who were primarily in middle age at baseline. By design, approximately 75% of participants had a first degree relative with dementia of the Alzheimer type. The overarching goal was to identify variables among cognitively normal individuals that could predict the subsequent development of mild to moderate symptoms of AD. Subjects were administered a comprehensive neuropsychological battery annually (mean follow-up = 9.2 years). MRI scans, CSF, and blood specimens were obtained approximately every two years. The study was initiated at the NIH in 1995, and was stopped in 2005 for administrative reasons. In 2009, a research team at the Johns Hopkins School of Medicine was funded to re-establish the cohort, continue the annual clinical and cognitive assessments, collect blood, and evaluate the previously acquired MRI scans, CSF, and blood specimens.

349 individuals were initially enrolled in the study after providing written informed consent. Recruitment procedures, baseline evaluations, and annual clinical and cognitive assessments have been described elsewhere (Albert et al., submitted). Briefly, baseline evaluations included physical and neurological examinations as well as laboratory and neuropsychological testing; individuals with cognitive impairment or significant medical problems (e.g., cerebrovascular disease) were excluded from participation. Since re-establishment at Johns Hopkins, the clinical evaluation has included a physical and neurological examination, record of medication use, behavioral and mood assessments, family history of dementia, history of symptom onset, and a Clinical Dementia Rating (CDR), based on a semi-structured interview (Hughes et al., 1982; Morris, 1993).

APOE genotype was established in all but one of the study participants ($n=348$). Genotypes were determined by restriction endonuclease digestion of polymerase chain reaction amplified genomic DNA (performed by Athena Diagnostics, Worcester, MA).

Consensus Diagnoses

Each case in the study received a consensus diagnosis that was handled in a similar manner: (1) clinical data pertaining to the medical, neurologic and psychiatric status of the subject were examined, (2) reports of changes in cognition by the subject and by collateral sources were reviewed, and (3) decline in cognitive performance, based on review of longitudinal cognitive testing from multiple domains, was established (test scores were compared to standardized norms, however, cut-points were not employed). First, a determination was made concerning whether the subject was impaired. Second, if the subject was impaired, the likely etiology of the impairment was identified. These two decisions were based on the three sources of information mentioned above. Then, the age at which the clinical symptoms began was estimated, based primarily on the reports of the subject and the collateral source. This approach is comparable to the procedures used in the NIA Alzheimer's Disease Centers program.

Cognitive Reserve Composite Score

We created a CR composite score based on three measures used in previous studies to assess reserve: (1) baseline scores on the National Adult Reading Test (Nelson, 1982), (2) baseline scores on the Wechsler Adult Intelligence Scale-Revised vocabulary subtest (Wechsler, 1981), and (3) years of education. These three measures were highly correlated and loaded on a single factor in factor analysis. To calculate the composite score, these measures were z-transformed and then averaged. Due to missing values, composite scores for 16 individuals were calculated on only two of these measures, one of which was always education. CR composites such as these have been shown to have construct validity and be preferable to using a single measure (Siedlecki et al., 2009).

In addition to the composite score just described, a secondary goal of this study was to examine whether the association of CR with time to onset of clinical symptoms was equivalent for each of the three individual CR measures. To this end, we completed separate analyses for each (z-scored) CR measure.

APOE Genotype Coding

APOE $\epsilon 4$ and $\epsilon 2$ carrier status were coded by creating separate indicator variables. In one set of analyses, $\epsilon 4$ carriers were coded 1 if they had at least one $\epsilon 4$ allele and noncarriers were coded 0. A similar indicator variable was created for $\epsilon 2$ status. In another set of analyses, an indicator variable coded the number of $\epsilon 4$ alleles (0, 1, 2), in order to examine dose effects (e.g., Farrer et al., 1997), referred to here as $\epsilon 4$ load.

Statistical Methods

APOE $\epsilon 4$ and $\epsilon 2$ status in relation to baseline cognitive reserve—First, we tested whether there was an association between baseline CR and the APOE alleles of interest. To do so, linear regressions were conducted, with CR composite scores as the dependent variable and $\epsilon 4$, $\epsilon 2$, age, and gender as the independent variables. This same regression was also done for the three individual CR measures.

APOE status and baseline cognitive reserve in relation to time to onset of clinical symptoms—These analyses were designed to determine whether CR, in combination with APOE status, was associated with time to onset of clinical symptoms. Data from two groups were included: (1) subjects who were cognitively normal at their last visit ($n=202$), and (2) subjects who received a diagnosis of MCI ($n=46$) or AD dementia ($n=9$) at their last visit. A set of Cox regression analyses were performed for each set of APOE variables. These models included $\epsilon 2$ status, $\epsilon 4$ status (or load), cognitive reserve, and

the interaction (cross-product) between allele status (or load) and CR composite score as predictors, and age at onset of clinical symptoms as the outcome variable. Both 4 and 2 indicators were included in all models to test the effect of each allele independently of the other (i.e., 4 models included the 2 indicator as a covariate and vice versa, in order to use 3/ 3 status as the comparison group). These Cox regression models were also completed using the three individual CR measures. The censoring time was defined as the last date of diagnosis. Because individuals were required to be symptom free at baseline, we adjusted for left truncation in the data (Wang, Brookmeyer, & Jewell, 1993). All models included terms adjusting for baseline age and gender.

Additionally, we calculated hazard ratios (i.e., relative hazard) for each of the significant variables of interest in the Cox models. The hazard ratio (HR) indicates the change in relative risk per one unit change in the predictor. For example, if the hazard ratio is 0.46, the hazard of clinical symptom onset is reduced by a factor of 0.46 (i.e., by 54%) for each standard deviation *increase* in the measure. Likewise, if the hazard ratio is 1.51, the hazard of clinical symptom onset is increased by a factor of 1.51 (i.e., by 51%) for each standard deviation *increase* in the measure. All Cox regression models presented here used R, version 2.14.1.

Results

The data presented here pertain to 257 participants from the BIOCARD study. Table 1 displays baseline demographic characteristics for the: a) cohort as a whole, b) subjects included in the current analyses, and c) subjects in the analyses subdivided into those who remained normal and those who subsequently received a diagnosis of MCI or AD dementia. The mean time from baseline to the onset of clinical symptoms was 6.12 ($SD = 3.42$) years. The data presented here exclude subjects with a diagnosis of 'Impaired Not MCI' but results were comparable when these individuals were included in the group of normal subjects (data not shown). The reasons for the exclusion of other participants are provided in Table 1. Analyses comparing those with a family history of dementia to those without will require longer follow-up, as only one-quarter of the cohort has no family history.

Association of APOE status and baseline CR

After controlling for baseline age and gender, the linear regressions revealed no significant associations between baseline CR composite score and APOE status. Similarly, there were no associations between APOE status and the individual CR measures of education, reading, and vocabulary.

Association of APOE and baseline CR composite score in relation to time to onset of clinical symptoms

The results of the Cox regression models evaluating the CR composite, APOE status (or load), and their interactions are shown in Table 2. In all models, CR was a significant predictor of time to onset of clinical symptoms. After accounting for APOE status (or load) and adjusting for baseline age and gender, each standard deviation increase in CR was associated with a reduction in risk of approximately 50% (all HR = 0.55).

Neither 4 carrier status nor 4 load interacted with CR. In the models excluding the interaction term, CR and 4 (both carrier status and load) independently predicted time to onset of clinical symptoms, indicating additive effects on clinical outcome (see Table 2). The presence of at least one 4 allele (relative to those with no 4 allele) was associated with an increase in risk of more than 150% (HR = 2.57). Moreover, 4 homozygotes had an

additional 150% increase in risk, relative to individuals with only one $\epsilon 4$ allele, as indicated by the $\epsilon 4$ load effect (HR = 2.73).

In contrast, there was a significant interaction between CR and $\epsilon 2$ carrier status, indicating that the association between CR and time to onset of clinical symptoms is influenced by the presence of an $\epsilon 2$ allele. To interpret this interaction, we examined the effects of CR in separate Cox regressions for $\epsilon 2$ carriers and non-carriers (covarying baseline age, gender, and $\epsilon 4$, as before). These findings indicated that one standard deviation increase in CR reduced the risk of clinical symptom onset by 91% (HR = 0.09) for $\epsilon 2$ carriers, whereas the reduction in risk associated with CR was 47% (HR = 0.53) for $\epsilon 2$ non-carriers (see Table 3). This suggests that CR is more effective at reducing risk in $\epsilon 2$ carriers relative to non-carriers. (Note that the HR value associated with CR in the group of $\epsilon 2$ carriers needs to be interpreted with caution because of the small sample size of $\epsilon 2$ carriers who progressed to symptom onset.)

Association of APOE status and individual CR measures in relation to time to onset of clinical symptoms

A secondary goal of this study was to examine the predictive utility each individual CR measure. As with the CR composite score, none of the individual CR measures interacted with $\epsilon 4$ (neither the $\epsilon 4$ indicator nor $\epsilon 4$ load), suggesting CR and $\epsilon 4$ independently predict time to onset of clinical symptoms. However, the relationship of the individual CR measures with clinical symptom onset varied, as did their interaction with $\epsilon 2$ (see Table 4). The protective effects of education were only marginal, and education did not significantly interact with $\epsilon 2$. In contrast, both reading and vocabulary were associated with a reduced risk of clinical symptom onset in these models. In addition, these latter two measures interacted with $\epsilon 2$ status in a similar manner as the CR composite score, though the vocabulary interaction failed to reach significance ($p = .056$). These findings indicate that years of education was a less sensitive measure of CR in the context of these models than reading and vocabulary.

General Discussion

This study examined the association between cognitive reserve and APOE status in relation to the time to onset of clinical symptoms in a large cohort of cognitively normal, prospectively followed participants. This cohort was middle aged at baseline. There are several findings of note.

First, we found that CR and $\epsilon 4$ status incur independent risks in relation to progression from normal cognition to time to onset of clinical symptoms. Since the onset of clinical symptoms may precede the diagnosis of MCI by several years, this extends previous findings that used incident MCI as the outcome. The finding that CR, as measured by a composite score, was equally protective in both $\epsilon 4$ carriers and non-carriers is in concordance with previous longitudinal studies of non-demented individuals (Ferrari et al., 2013; Hsiung et al., 2004; Ngandu, et al., 2007) and suggests that the independent effects of CR and APOE $\epsilon 4$ status on clinical progression are evident during both the preclinical and symptomatic phases of disease. Although the present data do not speak to the mechanism by which CR reduces the effect of APOE $\epsilon 4$ on risk of clinical symptom onset, prior studies suggest that APOE $\epsilon 4$ increases the risk of AD by increasing amyloid deposition in the brain (Kim, Basak, & Holtzman, 2009), whereas CR may reduce the clinical manifestation of amyloid pathology (e.g., Yaffe et al., 2011). These results are consistent with theoretical perspectives proposing that high levels of CR allow one to better cope with brain pathology (Stern, 2009), even when brain pathology results from genetic predisposition.

The second finding of note is that higher CR was associated with a greater reduction in risk of progression from normal cognition to symptom onset in $\epsilon 2$ carriers than non-carriers. While the mechanisms through which $\epsilon 2$ alleles exert their effects are not as well understood, it has been suggested that the $\epsilon 2$ allele may reduce amyloid accumulation (e.g., Morris et al., 2010), therefore also reducing the likelihood of subsequent disease. This would suggest that individuals with an $\epsilon 2$ allele (i.e., $\epsilon 2/\epsilon 2$ or $\epsilon 2/\epsilon 3$ carriers) and higher levels of CR should have lower levels of amyloid accumulation than $\epsilon 3/\epsilon 3$ homozygotes; in addition, this latter group would be expected to have lower amyloid levels than $\epsilon 3/\epsilon 4$ and $\epsilon 4/\epsilon 4$ carriers. The risk of progression of $\epsilon 2/\epsilon 4$ individuals needs to be evaluated in future studies, as there were too few individuals with this genotype in the current study.

In contrast to some previous findings (e.g., Corder et al., 1994), we did not find an independent, protective effect of the $\epsilon 2$ allele on time to onset of clinical symptoms. It is possible that we had limited power to detect an effect of $\epsilon 2$, as only 12% of participants ($n = 30$) were $\epsilon 2$ carriers. Prior studies that have compared the effect of the $\epsilon 2$ allele independently of the effect of the $\epsilon 4$ allele (by comparing $\epsilon 2$ carriers to $\epsilon 3/\epsilon 3$ individuals) indicate that the beneficial effects of $\epsilon 2$ are relatively small (e.g., Farrer et al., 1997) and may be difficult to detect with small sample sizes.

The third finding of note concerns the comparative sensitivity of various CR measures. We found the protective effects of CR were better indicated by either: a) the entire CR composite score or b) measures of reading or vocabulary, than with years of education. Specifically, the CR composite score and reading and vocabulary measures were associated with significant reductions in risk of progression from normal cognition to the onset of clinical symptoms, whereas education alone was not significant in these analyses. The present results suggest that measures of reading or vocabulary may be more sensitive CR proxies, especially in samples with a restricted range of educational achievement (as in the present study) or in diverse ethnic and racial groups with qualitatively different educational experiences (Manly et al., 2003, 2005). Even if educational quality were constant across individuals, the number of years of schooling is likely only a rough estimate of how much one learns in school, and of cognitive activity more generally. This finding emphasizes the static nature of education, which is unlikely to change once individuals reach their mid-20's. Therefore, education may be less reflective of later life experiences, relative to vocabulary and reading ability, which may change over time. This hypothesis will need to be tested in samples with a broader range of education. Furthermore, it should be acknowledged that we cannot rule out the possibility that these language-based measures (i.e., reading, vocabulary) were more sensitive measures of CR than education alone because they are related to the outcome, given that semantic networks are often affected in AD. However, we believe this is unlikely, since our CR measures were collected at baseline, when individuals were cognitively normal.

Our findings must be interpreted in the context of their limitations. The subjects in the BIOCARD cohort are well educated, primarily Caucasian, and approximately three quarters have a family history of dementia. These cohort characteristics may limit the generalizability of these results.

In summary, our findings support and extend prior studies demonstrating that CR can reduce the risk of developing clinical symptoms during the preclinical phase of AD, even in the presence of genetic predisposition. Supporting theoretical accounts (e.g., Manly et al., 2003, 2005), these data suggest CR may be more sensitively indexed by reserve variables other than – or in addition to – education. Additionally, CR was more protective in $\epsilon 2$ carriers than non-carriers, suggesting that individuals with an $\epsilon 2$ genotype may disproportionately benefit from lifetime experiences that enhance cognition.

Acknowledgments

This study is supported in part by grants from the National Institutes of Health: U01-AG03365, and P50-AG005146. The BIOCARD Study consists of 7 Cores with the following members: (1) the Administrative Core (Marilyn Albert, Susan Larson and Nicole Favaro), (2) the Clinical Core (Ola Selnes, Marilyn Albert, Rebecca Gottesman, Ned Sacktor, Guy McKhann, Scott Turner, Leonie Farrington, Maura Grega, Irina Khurana, Daniel D'Agostino, Sydney Feagen, David Dolan, Hillary Dolan), (3) the Imaging Core (Michael Miller, Susumu Mori, Tilak Ratnanather, Timothy Brown, Hanyang Chi, Anthony Kolasny, Kenichi Oishi, Thomas Reigel, William Schneider, Laurent Younes), (4) the Biospecimen Core (Richard O'Brien, Abhay Moghekar, Ming Li), (5) the Informatics Core (Roberta Scherer, Curt Meinert, David Shade, Ann Ervin, Jennifer Jones, Matt Toepfner, Sravan Nagireddy, Alka Ahuja, Malathi Ram, April Patterson, Lisa Lassiter), the (6) Biostatistics Core (Mei-Cheng Wang, Shanshan Li, Yi Lu), and (7) the Neuropathology Core (Juan Troncoso, Barbara Crain, Olga Pletnikova, Gay Rudow, Karen Wall).

We are grateful to the members of the BIOCARD Scientific Advisory Board who provide continued oversight and guidance regarding the conduct of the study including: Drs. John Cernansky, David Holtzman, David Knopman, Walter Kukull and John McArdle, as well as Drs. Neil Buckholtz, John Hsiao, Laurie Ryan and Jovier Evans, who provide oversight on behalf of the National Institute on Aging (NIA) and the National Institute of Mental Health (NIMH), respectively. We would also like to thank the members of the BIOCARD Resource Allocation Committee who provide ongoing guidance regarding the use of the biospecimens collected as part of the study, including: Drs. Constantine Lyketsos, Carlos Pardo, Gerard Schellenberg, Leslie Shaw, Madhav Thambisetty, and John Trojanowski.

We would like to acknowledge the contributions of the Geriatric Psychiatry Branch (GPB) of the intramural program of NIMH who initiated the study (PI: Dr. Trey Sunderland). We are particularly indebted to Dr. Karen Putnam, who has provided ongoing documentation of the GPB study procedures and the data files received from NIMH.

References

- Albert, M.; Soldan, A.; Gottesman, R.; McKhann, G.; Sacktor, N.; Farrington, L.; Grega, M., et al. Cognitive changes preceding clinical symptom onset of Mild Cognitive Impairment. Submitted
- Brainerd CJ, Reyna VF, Petersen RC, Smith GE, Kenney a E, Gross CJ, Taub ES, et al. The apolipoprotein E genotype predicts longitudinal transitions to mild cognitive impairment but not to Alzheimer's dementia: Findings from a nationally representative study. *Neuropsychology*. 2013; 27:86–94. [PubMed: 23356599]
- Corder EH, Saunders AM, Risch NJ, Strittmatter WJ, Schmeddel DE, Gaskell PC, Rimmer JB, et al. Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. *Nature Genetics*. 1994; 7:180–184. [PubMed: 7920638]
- Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, Myers RH, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. *Journal of the American Medical Association*. 1997; 278:1349–1356. [PubMed: 9343467]
- Ferrari C, Xu W-L, Wang H-X, Winblad B, Sorbi S, Qiu C, Fratiglioni L. How can elderly apolipoprotein E 4 carriers remain free from dementia? *Neurobiology of Aging*. 2013; 34:13–21. [PubMed: 22503000]
- Hsiung G-YR, Sadovnick AD, Feldman H. Apolipoprotein E epsilon4 genotype as a risk factor for cognitive decline and dementia: Data from the Canadian Study of Health and Aging. *Canadian Medical Association Journal*. 2004; 171:863–867. [PubMed: 15477624]
- Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *British Journal of Psychiatry*. 1982; 140:566–572. [PubMed: 7104545]
- Kim J, Basak JM, Holtzman DM. The role of apolipoprotein E in Alzheimer's disease. *Neuron*. 2009; 63:287–303. [PubMed: 19679070]
- Manly JJ, Schupf N, Tang M-X, Stern Y. Cognitive decline and literacy among ethnically diverse elders. *Journal of Geriatric Psychiatry and Neurology*. 2005; 18:213–217. [PubMed: 16306242]
- Manly JJ, Touradji P, Tang M-X, Stern Y. Literacy and memory decline among ethnically diverse elders. *Journal of Clinical and Experimental Neuropsychology*. 2003; 25:680–690. [PubMed: 12815505]

- Morris JC, Roe CM, Xiong C, Fagan AM, Goate AM, Holtzman DM, Mintun M. a. APOE predicts amyloid-beta but not tau Alzheimer pathology in cognitively normal aging. *Annals of Neurology*. 2010; 67:122–31. [PubMed: 20186853]
- Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*. 1993; 43:2412–2414. [PubMed: 8232972]
- Nelson, HE. The National Adult Reading Test (NART): Test manual. Nfer-Nelson; Windsor, UK: 1982.
- Ngandu T, von Strauss E, Helkala E-L, Winblad B, Nissinen A, Tuomilehto J, Soininen H, et al. Education and dementia: what lies behind the association? *Neurology*. 2007; 69:1442–50. [PubMed: 17909157]
- Siedlecki KL, Stern Y, Reuben A, Sacco RL, Elkind MSV, Wright CB. Construct validity of cognitive reserve in a multiethnic cohort: The Northern Manhattan Study. *Journal of the International Neuropsychological Society*. 2009; 15:558–69. [PubMed: 19573274]
- Stern Y. Cognitive reserve and Alzheimer disease. *Alzheimer Disease and Associated Disorders*. 2006; 20:112–117. [PubMed: 16772747]
- Stern Y. Cognitive reserve. *Neuropsychologia*. 2009; 47:2015–2028. [PubMed: 19467352]
- Wang MC, Brookmeyer R, Jewell NP. Statistical models for prevalent cohort data. *Biometrics*. 1993; 49:1–11. [PubMed: 8513095]
- Wechsler, D. Wechsler Adult Intelligence Scale – Revised Manual. The Psychological Corporation; New York: 1981.
- Yaffe K, Weston A, Graff-Radford NR, Satterfield S, Simonsick EM, Yountkin SG, et al. Association of plasma β -amyloid level and cognitive reserve with subsequent cognitive decline. *Journal of the American Medical Association*. 2011; 305:261–266. [PubMed: 21245181]

Table 1

Participant characteristics at baseline for the cohort as a whole, subjects included in the analyses. Characteristics for subjects included in the analyses are also shown stratified by outcome (remained normal, progressed to MCI or AD dementia). Asterisks indicate significant differences between outcome groups.

	<u>Entire cohort</u>	<u>Subjects in analyses</u>		
		<i>All</i>	<i>Remained normal</i>	<i>Progressed to MCI or AD</i>
<i>N</i>	349	257 ^a	202	55
<i>M</i> Age (<i>SD</i>)	57.2 (10.3)	56.0 (10.3)	54.5 (9.5)	61.9 (11.3)*
Gender, females (%)	58%	61.5%	62.9%	56.4%
Education, years (<i>SD</i>)	17.0 (2.4)	17.2 (2.3)	17.3 (2.3)	16.7 (2.4)
Ethnicity, Caucasians	97.1%	97%	98.5%	92.7%*
APOE 4 carriers (%)	34%	34%	31.2%	43.6%
APOE 2 carriers (%)	15%	12%	11.9%	10.9%
<i>M</i> MMSE (<i>SD</i>)	29.5 (0.8)	29.5 (0.8)	29.6 (0.8)	29.4 (1.0)
<i>M</i> CR composite score (<i>SD</i>)	0.0 (0.8)	0.09 (0.8)	0.19 (0.7)	-0.13 (0.9)*

Abbreviations: CR = cognitive reserve

^aOf those with genotyping, 91 were excluded from the primary analyses presented here, for the following reasons: (1) clinical symptom onset was estimated to have occurred at or prior to baseline ($n = 13$), (2) withdrawn or not yet re-enrolled ($n = 39$), (3) genotype with one 2 and one 4 allele ($n = 9$), (4) missing CR variables at baseline ($n = 1$), and (5) received a consensus diagnosis of 'Impaired not MCI' ($n = 29$).

Table 2

Hazard ratio of baseline CR and APOE status in relation to time to onset of clinical symptoms. All models were adjusted for baseline age, gender, and carrier status of the other APOE allele (i.e., 4 models also included the 2 indicator as a covariate and vice versa). For models in which CR did not interact with APOE, follow-up Cox regression analyses were performed, excluding the interaction term, as shown on the right side of the table where relevant.

Variable	<u>Models with interactions</u>		<u>Models without interactions</u>	
	Hazard Ratio (95% CI)	<i>p</i> -value	Hazard Ratio (95% CI)	<i>p</i> -value
CR	0.41 (0.27 – 0.62)	< .001	0.46 (0.33 – 0.64)	< .001
4 indicator	2.67 (1.44 – 4.94)	.002	2.57 (1.40 – 4.70)	.002
Interaction	1.43 (0.70 – 2.95)	n.s.	-	
CR	0.42 (0.28 – 0.63)	< .001	0.43 (0.30 – 0.61)	< .001
4 load	2.71 (1.68 – 4.38)	< .001	2.73 (1.70 – 4.39)	< .001
Interaction	1.06 (0.59 – 1.91)	n.s.	-	
CR	0.53 (0.37 – 0.76)	.001	n/a	
2 indicator	0.75 (0.25 – 2.31)	n.s.	n/a	
Interaction	0.36 (0.15 – 0.87)	.02	n/a	

Abbreviations: CR = cognitive reserve composite score.

Table 3

Hazard ratio of baseline CR in APOE ϵ_2 carriers and non-carriers. Both models were adjusted for baseline age, gender, and ϵ_4 carrier status.

Variable	<i>N</i>	Hazard Ratio (95% CI)	<i>p</i> -value
CR in ϵ_2 carriers (ϵ_2/ϵ_2 and ϵ_2/ϵ_3)	30	0.09 (0.01 – 0.75)	.03
CR in ϵ_2 non-carriers (ϵ_3/ϵ_3)	140 [*]	0.53 (0.37 – 0.77)	.001

Abbreviations: CR = cognitive reserve composite score.

^{*} The sample size for the ϵ_2 non-carrier group represents the individuals who were ϵ_3/ϵ_3 ($n = 140$), since the model was adjusted for ϵ_4 carrier status ($n = 87$).

Table 4

Hazard ratio of individual CR proxies (education, reading, vocabulary) and their interactions with APOE $\epsilon 2$ in relation to time to onset of clinical symptoms. All models were adjusted for the $\epsilon 4$ indicator, baseline age, and gender.

Variable	Models with interactions	
	Hazard Ratio (95% CI)	<i>p</i>-value
<i>Education</i>		
Education	0.80 (0.59 – 1.03)	.084
Education $\times \epsilon 2$	0.75 (0.30 – 1.88)	.53
<i>Reading</i>		
Reading	0.62 (0.48 – 0.80)	< .001
Reading $\times \epsilon 2$	0.61 (0.37 – 1.01)	.056
<i>Vocabulary</i>		
Vocabulary	0.59 (0.37 – 0.67)	< .001
Vocabulary $\times \epsilon 2$	0.31 (0.12 – 0.80)	.015