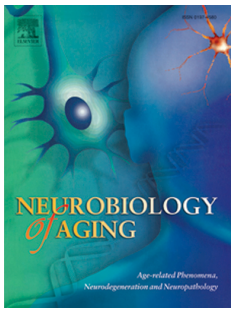

Education does not Protect Cognitive Function from Brain Pathology in the ADNI 2 Cohort

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Education does not Protect Cognitive Function from Brain Pathology in the ADNI 2 Cohort

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Abbreviations: Alzheimer's Disease Neuroimaging Initiative (ADNI), Alzheimer's Disease (AD), Mild Cognitive Impairment (MCI), Cognitive Reserve (CR), Magnetic Resonance Imaging (MRI), Memory (MEM), Executive Function (EF), Cerebrospinal Fluid (CSF), Amyloid-Beta 42 ($A\beta_{42}$), Intracranial Volume (ICV), Linear Mixed Models (LMM)

Keywords: Education, Cognitive Reserve, Alzheimer's Disease, Cognition, Biomarkers

Abstract

Educational attainment is widely accepted as a cognitive reserve variable. However, few studies have demonstrated that education statistically moderates the effects of pathology on cognition. Here, we explored this issue in a sample of 441 Alzheimer's disease (AD) and mild cognitive impairment (MCI) participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI2) cohort who had AD markers ($A\beta_{42}$, tau, structural brain volumes) at baseline and underwent cognitive testing at baseline and at 6-month, 12-month, and 24-month timepoints. An AD-related biomarker (atrophy/pathology) composite at baseline was developed using stepwise backward linear regression. Potential moderation effects of education on the relationship between AD biomarkers and memory and executive function were explored using linear mixed models. Education was positively correlated with cognition, and biomarkers were negatively correlated with cognition, across domains and diagnostic groups. However, education generally did not moderate the effects of biomarkers on baseline or longitudinal cognition. Our results do not support the hypothesis that education protects cognitive function from brain pathology in the ADNI 2 cohort, questioning its accepted status as a reserve variable.

1. Introduction

Educational attainment and its correlates have positive effects on cognitive performance across the lifespan (Brewster et al., 2014; Salthouse, 1991a, 1991b). Such findings have raised the possibility that education may promote cognitive reserve (CR)(Stern, 2002). A number of studies have provided apparent support for education as a CR variable, reporting more severe AD pathology in those with higher versus lower education (Garibotto et al., 2008; Kemppainen et al., 2008). However, new consensus guidelines concerning CR research (Stern et al., 2018) suggest that conclusions concerning CR variables should be based on statistical moderation between pathology and clinical/cognitive status variables. That is, cognitive performance should be predicted by the interaction between a purported CR variable and brain status.

Only a few studies with large sample sizes have reported such statistical moderation (Bennett et al., 2005, 2003, Stern et al., 1995, 1992). Further, these findings are counterbalanced by several null results (Koepsell et al., 2008; Roe et al., 2007; Stern et al., 1999). Potential discrepancies between previous results could include the clinical status of participants, the cognitive domain tested and the use of cross-sectional versus longitudinal designs. Here, we comprehensively explored these possibilities by examining if education moderates the effects of pathology on either baseline or longitudinal memory and/or executive function in MCI and/or AD clinical groups.

2. Materials and Methods

We accessed data from 441 participants with MCI or AD from Alzheimer's Disease Neuroimaging Initiative 2 (ADNI2) that had summary measures of MRI regional volumes, CSF AD pathology (n=426), composite scores of memory (Crane et al., 2012) and EF (Gibbons et al., 2012), and basic demographic information (Table 1) at baseline (Figure S1). Composite measures of baseline atrophy/pathology were derived empirically based on their association with scores per cognitive domain. Baseline composite measures of atrophy/pathology here included both structural volumes and concentration ratio of tau/$A\beta_{42}$ in the CSF (Bakkour et al., 2009; Fagan et al., 2007; Shaw et al., 2009). Individual structures were ICV-normalized, and both structural volumes and tau/$A\beta_{42}$ ratio were z-scored relative to the group mean before they were entered into the composites. Backward elimination was used to remove the least significant predictor one at a time until only z-scored predictors with $p < 0.05$ were remaining which were averaged to form the cognitive domain specific composites.

Insert Table 1 about Here

Using SPSS, linear mixed models were then used to determine if baseline pathology and education predict cognitive scores at baseline and longitudinally for both MCI and AD groups at $p<0.05$, with MEM or EF scores as the dependent variables. Models included all possible interactions excluding age and gender (pathology × time, education × time, pathology × education, and pathology × education × time).

3. Results

There was a main effect of education on both cognitive domains in the AD and MCI groups (Tables 2, 3). There were no significant education x time interactions in either cognitive domain, for either group (Tables 2, 3).

Insert Tables 2 & 3 about Here

The specific pathology variables predictive of each cognitive composite variable are listed in Table S1. The MEM and EF pathology composite measures were highly significant predictors of their respective baseline cognitive domain scores as listed in Tables 2, 3 (all p values ≤ 0.001).

There were no significant education x pathology or education x pathology x time interactions in either cognitive domain for either diagnostic group (Tables 2, 3). Further investigation using an age median split yielded the same conclusion for memory (Tables S2, S3) with a mixed conclusion for EF (Tables S2, S3; Figure S2).

4. Discussion

Our results indicate that higher educational attainment was associated with better cognitive functioning in MCI and AD, in both MEM and EF domains. However, education generally did not moderate the effects of atrophy/pathology, time or their interaction on cognitive function. Only in a subgroup of younger AD participants was a moderating effect of education observed and this effect was selective to EF. These results are consistent with other studies with large samples (Koepsell et al., 2008; Roe et al., 2007; Vemuri et al., 2011). Overall, our results suggest that education is an insufficient proxy for cognitive reserve. However, the selective CR effect we observed in a younger AD subgroup leaves open the possibility that education may protect EF against significant pathology prior to additional brain declines associated with advanced aging (See Supplementary Material for the complete version of this manuscript).

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144 *****Supplementary*****

145 ## 1. Introduction

146 Educational attainment and its correlates such as literacy and knowledge have been
147 shown to have positive effects on cognitive performance across the lifespan (Brewster
148 et al., 2014; Salthouse, 1991a, 1991b). In addition education has been shown to be
149 predictive of cognitive performance longitudinally in older adults (Jefferson et al., 2011;
150 Le Carret et al., 2003; Singh-Manoux et al., 2011). These findings suggest that
151 education may have protective effects against age-related cognitive declines. Early
152 evidence for this possibility came from findings that lower educational attainment was
153 associated with higher prevalence of Alzheimer's disease (AD) (Prencipe et al., 1996;
154 Stern, 2002) and incidence (Letenneur et al., 1994; Stern et al., 1994).

155 Such findings raised the possibility that education may promote cognitive reserve (CR).
156 The theory of CR arose as an explanation for the mismatch between brain health and
157 cognitive status (Stern, 2002). For example, early evidence came from results showing
158 that a significant number of individuals who meet criteria for pathological AD
159 nevertheless remain cognitively normal (Mortimer, 1997; Shaw et al., 2009; Valenzuela
160 and Sachdev, 2006). CR theory holds that that certain lifestyle variables are responsible
161 for attenuation of the effects of brain pathology or injury on cognitive function (Stern,
162 2002).

163 A number of studies have provided apparent support for education as a CR variable,
164 reporting more severe pathology in AD or mild cognitive impairment (MCI) groups with
165 high education relative to their lower educated peers (Garibotto et al., 2008;

Kemppainen et al., 2008). Recently, however, new consensus guidelines concerning CR research have been proposed by a workgroup of 30 researchers in the field (Stern et al., 2018). The new guidelines suggest that CR research should include three key components: the status of the brain (reflecting brain structure and/or pathology), clinical or cognitive performance outcomes, and a putative CR measure (i.e. a positive lifestyle variable). Further, the new criteria suggest that conclusions drawn from a putative CR variable should be based on statistical moderation effects of the variable in the relationship between brain structure/pathology and clinical/cognitive status. That is, cognitive performance should be predicted by the interaction between a purported CR variable and brain status.

Only a few studies with large sample sizes have reported statistical moderation effects of education on the relationship between brain status and cognition (Bennett et al., 2005, 2003, Stern et al., 1995, 1992). However, positive findings from these studies are counterbalanced by the results from several well-powered studies reporting that education did not moderate the effects of brain status on cognition (Koepsell et al., 2008; Roe et al., 2007; Stern et al., 1999). Collectively, the mixed findings suggest that although there is some evidence that education may be a proxy of CR, the evidence is not as strong as is often assumed in the literature.

Potential discrepancies between previous results could include the clinical status and age of participants, the cognitive domain tested and the use of cross-sectional versus longitudinal designs. Here we were able to address these issues via the use of baseline and longitudinal data of both MCI and AD participants from the Alzheimer's Disease Neuroimaging Initiative 2 (ADNI2; NIH U01 AG0204904). ADNI provides access to

validated cognitive composites of memory and executive function in participants over a 24-month period. We focused on MCI and AD participants as cognitively impaired participants are more likely to have AD pathology, maximizing power to find CR effects. Composites measures of pathology associated with MEM and EF were developed from ADNI measures of cerebrospinal fluid (CSF) markers of AD and magnetic resonance imaging (MRI)-derived structural brain volumes as predictive utility of AD-related cognitive declines have been demonstrated for both CSF-related measures (e.g. Tau/$A\beta_{42}$ ratio (Blennow et al., 2015; Shaw et al., 2009)), and brain structural volumes (Bakkour et al., 2009; Devanand et al., 2012; Mouton et al., 1998).

We hypothesized that educational level would be positively associated with MEM and EF performance and that pathology would be negatively associated with performance in each cognitive domain. Further, we predicted that education would moderate the associations between pathology and cognitive performance, with potential group differences in the strength of statistical moderation. Specifically, we expected that moderation effects may be most pronounced in the MCI group as reserve processes may remain more viable due to less advanced neurodegeneration and cognitive impairment compared to AD group.

2. Materials and Methods

2.1 Participants

Research described in this manuscript was conducted under an approved University of Kentucky Institutional Review Board protocol. We accessed publicly available participant data from the Alzheimer's Disease Neuroimaging Initiative 2 (ADNI2) for all

participants with a diagnosis of MCI or AD. Clinical diagnosis of MCI or AD following standardized ADNI procedures and criteria detailed elsewhere (Petersen, 2008; Petersen et al., 2010)

2.2 Composite Measures of Cognition

Composite measures of memory (MEM (Crane et al., 2012)) and executive function (EF (Gibbons et al., 2012)) were provided by the University of Washington through ADNI 2. These composites consider a range of neurocognitive measures provided by ADNI and are normalized over the entire sample. The memory composite included the Rey Auditory Verbal Learning Test (RAVLT), elements of the Alzheimer's disease assessment schedule cognition subscale (ADAS-Cog), recall elements of the Mini-Mental State Examination (MMSE), and logical memory neurocognitive tests, while the executive function composite included the Clock Drawing test, Trail Making test, animal and vegetable Category Fluency, Digit Span test and Digit Symbol test, and the Wechsler Adult Intelligence Scale-Revised Digit Symbol Substitution. The MEM and EF composites were calculated based on neurocognitive scores collected at baseline, 6 months, 12 months, and 24 months (the final available AD timepoint) after imaging and CSF collection. Sample sizes for each timepoint are reported in Table S4.

2.3 Composite Measures of Pathology

Composite measures of pathology relevant to each cognitive domain were derived empirically based on their strength of association with scores in that cognitive domain. The empirical construction of custom measures of pathology for each cognitive domain has the advantage of improving the interpretability of potential moderation effects (i.e.

protective effects) as the pattern of pathology is known to negatively affect that cognitive domain. The composite measures of pathology here can be broadly classified as structural volume and concentration ratio of tau/$A\beta_{42}$ in the CSF, as both of these are specific, sensitive measures of AD (Bakkour et al., 2009; Fagan et al., 2007; Mouton et al., 1998; Shaw et al., 2009).

Measures of structural brain volume were provided by the University of California San Francisco through ADNI 2. These measurements were obtained from 3 dimensionally acquired T1-weighted scans. Additional parameters have been published previously (Jack et al., 2008). Structural volumes were computed through FreeSurfer 5.1 segmentation using a standardized ADNI protocol (Fischl et al., 2004; Reuter et al., 2012). Images were automatically segmented, although a visual quality control check was performed.

Measures of CSF protein levels were provided by the University of Pennsylvania through ADNI 2. Participants underwent lumbar sampling of CSF, which was analyzed for amyloid-beta 42 ($A\beta_{42}$), tau, and phosphorylated tau (p-tau) content using the Inno-BIA xMAP Luminex platform (Olsson et al., 2005). The tau/$A\beta_{42}$ ratio was z-scored and used within each composite measure of pathology (described below) as it provides a sensitive and specific measure for AD (Fagan et al., 2007; Shaw et al., 2009).

Pathology models were run separately for MEM and EF cognitive domains using backward elimination, and there was no requirement that predictors be unique to either cognitive domain. Instead, the final pathology models reflect the most predictive combination of pathology measures for each cognitive domain.

2.4 Statistical Analyses

All statistical analyses were performed using SPSS (version 24). Potential statistical outliers were identified as participant mean scores 3 standard deviations from their group mean and the effects of these outliers on statistical models were tested. All variables were initially screened to test the assumption of normal distribution. Error residuals for education as a predictor of memory and EF were normally distributed. Independent t-tests and chi square at $p < 0.05$ were initially used to compare between diagnostic groups (Table 1). Linear mixed models were then used to determine if pathology and education predict cognitive scores at baseline and longitudinally.

3. Results

3.1 Participant Characteristics

Participants were individuals with MCI (N=313) or AD (N=128). As a whole, participants were 72.5 ± 7.7 years old (range: 55-91), were 43.3% female, and had 16.2 ± 2.6 years of education (range: 9-20). A total of 4 data outlier scores were detected (1 in the memory cognitive composite, 2 in the memory pathology composite, and 1 in the EF pathology composite). Exclusion of these outlier scores did not alter the significance of any of the models and these scores were thus retained to increase sample size. Both cognitive composites as well as pathology composites followed a normal distribution. When comparing between groups (Table 1), there was no significant difference in gender ($p = 0.347$). The MCI group was younger ($p = 0.001$), more educated ($p = 0.021$), had a significantly lower Tau/$A\beta_{42}$ ratio ($p < 0.001$), and significantly greater

performance on both the memory ($p < 0.001$) and EF composites ($p < 0.001$), as expected.

3.2 Effect of Age, Gender, and Education on MEM/EF Scores

There were no main effects of age or gender on either memory or executive function in the AD group (Table 2), but there was a main effect of age on executive function ($p < 0.001$) and gender on memory ($p = 0.001$) in the MCI group (Table 3).

There was a main effect of education on both cognitive domains in the AD and MCI groups (Tables 2, 3). There were no significant education x time interactions in either cognitive domain for either group, although there was a trend toward an interaction on memory ($p = 0.078$) in the AD group (Table 2).

3.3 Effect of Pathology on MEM/EF Scores

MEM and EF pathology composite measures consisted of a combination of pathology variables that predict scores on their respective (MEM or EF) cognitive composites (Table S1). Pathology variables which commonly predicted both MEM and EF cognitive domain scores included the Tau/$A\beta_{42}$ ratio and hippocampal volume while there were also regional brain volume predictors unique to each cognitive domain (e.g., MEM; entorhinal cortex, EF; supramarginal gyrus). The MEM and EF pathology composite measures were highly significant predictors of their respective baseline cognitive domain scores as listed in Tables 2, 3 (all p values ≤ 0.001). The pathology composite measures also predicted longitudinal decline on their respective cognitive domain scores (all p values ≤ 0.003), with the exception of EF scores in the AD group, which showed only a slight trend.

3.4 Effect of Education × Pathology × Time on MEM/EF Scores in AD Group

There were no significant education x pathology or education x pathology x time interactions in either cognitive domain. After dividing the AD group into younger and older age groups using a median split (younger: 55-74.9 years old and older: 75-90 years old), both the education × pathology term and the education × pathology x time term remained non-significant for memory (Table S2). Similarly, the education × pathology term also remained non-significant for EF. However, there was an education x pathology x time interaction on EF scores in the younger group (Figure S2).

3.5 Effect of Education × Pathology × Time on MEM/EF Scores in MCI Group

The education x pathology and education x pathology x time terms were not significant for MEM or EF. There was a marginally significant pathology x education interaction on EF scores ($p = 0.054$). However, this interaction was in the opposite direction than that expected by cognitive reserve theory: baseline EF scores were more negatively affected by pathology in MCI participants with higher education than those with lower education. Dividing the MCI group into younger and older age group using a median split (younger: 55-71.9 years and older: 72-91 years) did not alter the non-significant pathology x education or the pathology x education x time terms in either cognitive domain (Table S3).

3.6 Power Analysis

A retrospective power analysis was conducted to determine if our null findings were the result of insufficient power. G*power (version 3.1.9.2) was used with post-hoc F-tests parameters selected, with effect size, total sample size, numerator degrees of freedom,

and covariates specified. Using a small mean effect size (0.4) taken from studies which have published previously on an interaction between brain pathology and education on cognition in AD (Alexander et al., 1997; Bennett et al., 2005, 2003; Stern et al., 1992) we had over 99% power in each group (Figure S3). Therefore, we were well-powered to detect cross-sectional brain pathology x education interactions in both the MCI and AD groups.

A power analysis for the three-way (longitudinal) interaction (brain pathology x education x time) using the same small (0.4) mean effect size from the cross-sectional analysis yielded at least 70% power in the AD group and 99% power in the MCI group. To achieve 80% power in the AD group, a medium (0.5) or larger effect size would be required. Therefore, we were well-powered to detect a three-way interaction in both groups for medium or larger effect sizes but slightly underpowered to detect a three-way interaction in the AD group in the case of a small effect size.

4. Discussion

We tested whether educational attainment moderates the effects of AD-related pathology on cognition in a large multicenter (ADNI2) data set. Potential effects of education on memory (MEM) and executive function (EF) were explored in groups of individuals with mild cognitive impairment (MCI) and Alzheimer's disease (AD). Our results indicate that higher educational attainment was associated with better cognitive functioning in MCI and AD, in both MEM and EF domains. However, education generally did not moderate the effects of pathology, time or their interaction on cognitive function. Only in a subgroup of younger AD participants was a moderating effect of

education observed and this effect was selective to EF. Our results are consistent with a view that education is an insufficient proxy for cognitive reserve.

Consistent with previous results, we found that educational attainment was positively associated with cognitive performance at baseline (Brewster et al., 2014; Le Carret et al., 2003; Singh-Manoux et al., 2011). In the present study, greater educational attainment was associated with better baseline cognitive performance in both the MCI and AD groups, within each of the cognitive (EF and MEM) domains tested. These findings are in line-with the notion that positive effects of higher educational attainment on multiple cognitive domains remain into older adulthood (Christensen et al., 2001; Stern, 2002).

The main question we addressed here was whether education protects against the typical negative effects of time, pathology, and/or their potential interaction, on cognition. To test for such potential moderation effects, we developed composite measures of pathology that were negatively associated with scores in each of the MEM and EF cognitive domains. The composite measures included the CSF tau/$A\beta_{42}$ ratio and regional measures of brain volume, both of which have been strongly linked with AD-related cognitive decline pathology (Devanand et al., 2012; Fagan et al., 2007; Martin et al., 2010; Shaw et al., 2009; Vos et al., 2013).

As expected, scores on each of the MEM and EF pathology composite measures were negatively associated with their respective cognitive composite scores at baseline (all p values ≤ 0.001). Further the pathology composite measures strongly predicted cognitive

363 decline over time in each case (all p values ≤ 0.003), with the exception of EF change
364 which showed only a slight trend (p = 0.10).

365 *4.1 Education does not Moderate the Effects of Pathology on Baseline MEM or EF*
366 *Function in MCI or AD Groups*

367 Contrary to our hypotheses, in the present ADNI cohort of AD and MCI participants,
368 education generally did not moderate the effects of pathology on baseline MEM or EF
369 scores. We did observe one marginally significant education by pathology interaction on
370 baseline EF scores in MCI group only but was in the opposite expected direction for
371 cognitive reserve. Specifically, baseline EF scores were more negatively affected by
372 pathology in MCI participants with higher education than those with lower education. No
373 other interactions were observed on baseline MEM scores for the MCI group or either
374 MEM or EF scores in the AD group.

375 Our baseline results are inconsistent with those of several studies reporting that
376 education moderates the effects of pathology on baseline cognitive scores (Bennett et
377 al., 2005, 2003; Kemppainen et al., 2008; Scarmeas et al., 2003; Stern et al., 1992), but
378 are consistent with several previously reported null findings at baseline (Koepsell et al.,
379 2008; Roe et al., 2007; Stern et al., 1999; Vemuri et al., 2011). It remains possible that
380 education may only selectively moderate the effects of certain kinds of pathology,
381 perhaps only on specific cognitive measures. In the present study, composite
382 neuropsychological and pathology scores were used, which reduce the need for testing
383 multiple hypotheses/comparisons and minimize measurement errors due to
384 idiosyncratic single measure results (Crane et al., 2008). Our study was well-powered to

find potential moderation effects using composite measures. Reporting null results from well-powered studies is important in order to avoid confirmation bias in the literature.

4.2 Education Only Selectively Moderates the Effects of Pathology on Longitudinal Declines in EF Scores

Turning to our longitudinal results, none of our models demonstrated a significant education by time interaction on cognition. In other words, having a higher education was not protective for EF or MEM functioning over time in either the MCI or AD groups. These results are in-line with several other well powered studies which failed to find protective effects of education on cognitive decline (Christensen et al., 2001; Tucker-Drob et al., 2009; Zahodne et al., 2011).

In the present study, the availability of measures of pathology and longitudinal cognitive scores allowed for the gold-standard test of a cognitive reserve variable: whether the variable interacts with levels pathology to influence cognitive decline (Stern et al., 2018). Results from our three-way interaction models indicated that education did not protect against MEM or EF declines in either the MCI or AD group. None of these four main models approach significance despite the relatively large sample size and high power of the present study.

A final set of analyses were conducted to address the possibility that a three-way interaction between education, pathology and time may be age-dependent. For these analyses, the MCI and AD groups were each divided into younger and older subgroups. Results from these analyses were generally similar to the analyses conducted across the full age ranges with one exception: a three-way interaction was observed in the

younger AD group. The basis of this interaction was that younger AD participants with higher education showed less decline in EF function than their less educated peers harboring similar levels of pathology (Figure S2).

This moderation effect does provide limited support for education as a cognitive reserve variable. The presence of this moderation effect in the younger AD subgroup, but not the older AD subgroup, could be seen as consistent with a view that compensation/reserve processes remain more viable until some threshold of age-related neurodegeneration is reached, at which time reserve may become exhausted (Stern, 2009). In support of this view, several studies have reported that, in AD participants, higher education was related to steeper cognitive declines over time than those with lower education (Andel et al., 2006; Teri et al., 1995; Tucker-Drob et al., 2009). In the present study, older AD participants with higher education did not show steeper cognitive declines than their age-matched peers with lower education. However, it remains possible that reserve may have already been exhausted at baseline in the older AD group. While not providing direct evidence, the relatively steep cognitive decline seen in the younger AD with high education and high pathology between year 1 and year 2 (Figure S2) is consistent with this possibility.

Overall, the highly selective moderation effect we observed in the context of a larger set of null findings, including the majority of models involving younger and older subgroups, suggest that education appears to be insufficient as a stand-alone cognitive reserve variable. Education is a static variable typically completed in younger adulthood but serves as a proxy for many more dynamic later-life healthy lifestyle variables. For example, higher education is associated with greater physical activity level and physical

health (Ho et al., 2011; Schnohr et al., 2004; Shaw and Spokane, 2008), higher social engagement (Glass et al., 2006; Krueger et al., 2009), and increased cognitive activity (Krueger et al., 2009), which could be promoting CR in some previous education studies. Similarly, it has been reported that neither education nor occupational complexity alone was associated with dementia incidence (Valenzuela et al., 2011).

Methodologically, this study benefits from an appropriately large sample size that includes both AD and MCI participants and tests both EF and MEM functions. Our test for moderation, the pathology x education interaction is also the strong-form test of a cognitive reserve variable (Stern et al., 2018). The wide range of ages in our sample allowed for additional exploration of age-dependent CR effects.

This study has limitations. First, although we view our use of a composite measure of atrophy/pathology measure to be a strength, the specific individual component biomarkers used in the composite may not be the most sensitive available. Other biomarkers using PET tracers can detect and localize AD pathology (amyloid plaques or tau tangles) in specific areas of the brain, while fluorodeoxyglucose PET can provide a metabolic/functional measure, but were not used here. These measures may be more sensitive in detecting some longitudinal cognitive changes, such as possibly EF declines, which were not predicted in the AD group by our pathology composite.

A second limitation of the present study was that participant dropout was significant in the AD group at the 2-year point, leaving a relatively small sample size in the AD group at 2-year follow-up. While this study was generally well-powered to detect most potential CR effects, even with small effect sizes, it was slightly under-powered to detect a

longitudinal CR effect with a small effect size in the AD group. Interestingly, though, the one protective effect of education against pathology observed in this study was a selective CR effect against EF declines in a younger AD sub-group (Table S2). This selective CR effect in a younger AD subgroup leaves open the possibility that education may protect EF against significant pathology prior to additional brain declines associated with advanced aging.

5. Conclusion

Education was associated with better cognitive functioning in the ADNI 2 cohort. However, education was generally not protective against the effects of time or AD-related pathology on cognition. Education alone may be an insufficient proxy for cognitive reserve. More dynamic proxies of cognitive reserve may better predict cognitive functioning in response to pathology.

References

Alexander, G.E., Furey, M.L., Grady, C.L., Pietrini, P., Brady, D.R., Mentis, M.J., Schapiro, M.B., 1997. Association of premorbid intellectual function with cerebral metabolism in Alzheimer's disease: Implications for the cognitive reserve hypothesis. Am. J. Psychiatry 154, 165–172. https://doi.org/10.1176/ajp.154.2.165

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. J. Int. Neuropsychol. Soc. 12, 147–152. https://doi.org/10.1017/S1355617706060206

Bakkour, A., Morris, J.C., Dickerson, B.C., 2009. The cortical signature of prodromal AD; Regional thinning predicts mild AD dementia. Neurology 72, 1048–1055.

Bennett, D.A., Schneider, J.A., Wilson, R.S., Bienias, J.L., Arnold, S.E., 2005. Education modifies the association of amyloid but not tangles wiht cognitive function. Neurology 65, 953–955. https://doi.org/10.1016/0006-3207(73)90069-4

Bennett, D.A., Wilson, R.S., Schneider, J.A., Evans, D.A., Mendes de Leon, C.F., Arnold, S.E., Barnes, L.L., Bienias, J.L., 2003. Education modifies the relation of AD pathology to level of cognitive function in older persons. Neurology 60, 1909–1915. https://doi.org/10.1212/01.WNL.0000069923.64550.9F

Blennow, K., Dubois, B., Fagan, A.M., Lewczuk, P., de Leon, M.J., Hampel, H., 2015. Clinical utility of cerebrospinal fluid biomarkers in the diagnosis of early Alzheimer's disease. Alzheimer's Dement. 11, 58–69. https://doi.org/10.1016/j.jalz.2014.02.004.Clinical

Brewster, P., Melrose, R., Marquine, M., Johnson, J., Napoles, A., MacKay-Brandt, A., Farias, S., Reed, B., Mungas, D., 2014. Life Experience and Demographic Influences on Cognitive Function in Older Adults. Neuropsychology 28, 846–858. https://doi.org/10.1037/neu0000098.Life

Christensen, H., Hofer, S., Mackinnon, A., Korten, A., Jorm, A., Henderson, A., 2001. Age is no kinder to the better educated : absence of an association investigated using latent growth techniques in a community sample. Psychol. Med. 31, 15–28.

Crane, P.K., Carle, A., Gibbons, L.E., Insel, P., Mackin, R.S., Gross, A., Jones, R.N., Mukherjee, S., Curtis, S.M.K., Harvey, D., Weiner, M., Mungas, D., 2012. Development and assessment of a composite score for memory in the Alzheimer's Disease Neuroimaging Initiative (ADNI). Brain Imaging Behav. 6, 502–516. https://doi.org/10.1007/s11682-012-9186-z

Crane, P.K., Narasimhalu, K., Gibbons, L.E., Pedraza, O., Mehta, K.M., Tang, Y., Manly, J.J., Reed, B.R., Mungas, D.M., 2008. Composite scores for executive function items: demographic heterogeneity and relationships with quantitative MRI. J. Int. Neuropsychol. Soc. 14, 746–759. https://doi.org/10.1017/S1355617708081162.Composite

Devanand, D.P., Bansal, R., Liu, J., Hao, X., Pradhaban, G., Peterson, B.S., 2012. MRI hippocampal and entorhinal cortex mapping in predicting conversion to Alzheimer's disease. Neuroimage 60, 1622–1629. https://doi.org/10.1016/j.neuroimage.2012.01.075

Fagan, A.M., Roe, C.M., Xiong, C., Mintun, M.A., Morris, J.C., Holtzman, D.M., 2007. Cerebrospinal Fluid tau/B-Amyloid 42 Ratio as a Prediction of Cognitive Decline in Nondemented Older Adults. Arch. Neurol. 64, 343–349.

Fischl, B., Van Der Kouwe, A., Destrieux, C., Halgren, E., Ségonne, F., Salat, D.H., Busa, E., Seidman, L.J., Goldstein, J., Kennedy, D., Caviness, V., Makris, N., Rosen, B., Dale, A.M., 2004. Automatically Parcellating the Human Cerebral Cortex. Cereb. Cortex 14, 11–22. https://doi.org/10.1093/cercor/bhg087

Garibotto, V., Borroni, B., Kalbe, E., Herholz, K., Salmon, E., Holtoff, V., Sorbi, S., Cappa, S.F., Padovani, A., Fazio, F., Perani, D., 2008. Education and occupation as proxies for reserve in aMCI converters and AD. Neurology 71, 1342–1349.

Gibbons, L.E., Carle, A.C., Mackin, R.S., Harvey, D., Mukherjee, S., Insel, P., Curtis, S.M.K., Mungas, D., Crane, P.K., 2012. A composite score for executive functioning, validated in Alzheimer's Disease Neuroimaging Initiative (ADNI) participants with baseline mild cognitive impairment. Brain Imaging Behav. 6, 517–527. https://doi.org/10.1007/s11682-012-9176-1

Glass, T.A., Mendes De Leon, C.F., Bassuk, S.S., Berkman, L.F., 2006. Social engagement and depressive symptoms in late life: Longitudinal findings. J. Aging Health 18, 604–628. https://doi.org/10.1177/0898264306291017

519 Ho, A.J., Raji, C.A., Becker, J.T., Lopez, O.L., Kuller, L.H., Hua, X., Dinov, I.D., Stein, J.L., Rosano, C., Toga,
520 A.W., Paul, M., 2011. The Effects of Physical Activity, Education, and Body Mass Index on the Aging
521 Brain. Hum. Brain Mapp. 32, 1371–1382. https://doi.org/10.1002/hbm.21113.The

522 Jack, C.R., Bernstein, M.A., Fox, N.C., Thompson, P., Alexander, G., Harvey, D., Borowski, B., Britson, P.J.,
523 Whitwell, J.L., Ward, C., Dale, A.M., Felmlee, J.P., Gunter, J.L., Hill, D.L.G., Killiany, R., Schuff, N.,
524 Fox-Bosetti, S., Lin, C., Studholme, C., DeCarli, C.S., Krueger, G., Ward, H.A., Metzger, G.J., Scott,
525 K.T., Mallozzi, R., Blezek, D., Levy, J., Debbins, J.P., Fleisher, A.S., Albert, M., Green, R., Bartzokis, G.,
526 Glover, G., Mugler, J., Weiner, M.W., 2008. The Alzheimer's Disease Neuroimaging Initiative (ADNI):
527 MRI methods. J. Magn. Reson. Imaging 27, 685–691. https://doi.org/10.1002/jmri.21049

528 Jefferson, A.L., Gibbons, L.E., Rentz, D.M., Carvalho, J.O., Manly, J., Bennett, D.A., Jones, R.N., 2011. A
529 Life Course Model of Cognitive Activities, Socioeconomic Status, Education, Reading Ability, and
530 Cognition. J. Am. Geriatr. Soc. 59, 1403–1411. https://doi.org/10.1111/j.1532-5415.2011.03499.x.A

531 Kemppainen, N.M., Aalto, S., Karrasch, M., Någren, K., Savisto, N., Oikonen, V., Viitanen, M., Parkkola, R.,
532 Rinne, J.O., 2008. Cognitive reserve hypothesis: Pittsburgh compound B and fluorodeoxyglucose
533 positron emission tomography in relation to education in mild Alzheimer's disease. Ann. Neurol. 63,
534 112–118. https://doi.org/10.1002/ana.21212

535 Koepsell, T.D., Kurland, B.F., Harel, O., Johnson, E.A., Zhou, X.H., Kukull, W.A., 2008. Education, cognitive
536 function, and severity of neuropathology in Alzheimer disease. Neurology 70, 1732–1739.

537 Krueger, K.R., Wilson, R.S., Kamenetsky, J.M., Barnes, L.L., Bienias, J.L., Bennett, D.A., 2009. SOCIAL
538 ENGAGEMENT AND COGNITIVE FUNCTION IN OLD AGE. Exp. Aging Res. 35, 45–60.
539 https://doi.org/10.1016/j.cortex.2009.08.003.Predictive

540 Le Carret, N., Victor, U., Bordeaux, S., Lafont, S., Claude, U., Lyon, B., Letenneur, L., Dartigues, J., Victor,
541 U., Bordeaux, S., Fabrigoule, C., 2003. The Effect of Education on Cognitive Performances and Its
542 Implication for the Constitution of the Cognitive Reserve. Dev. Neuropsychol. 23, 317–337.

543 Letenneur, L., Commenges, D., Dartigues, J., Barberger-Gateau, P., 1994. Incidence of dementia and
544 Alzheimer's disease in elderly community residents of south-western France. Int. J. Epidemiol. 23,
545 1256–1261.

546 Martin, S.B., Smith, C.D., Collins, H.R., Schmitt, F.A., Gold, B.T., 2010. Evidence that volume of anterior
547 medial temporal lobe is reduced in seniors destined for mild cogntive impairment. Neurobiol.
548 Aging 31, 1099–1106. https://doi.org/10.1016/j.neurobiolaging.2008.08.010.Evidence

549 Mortimer, J.A., 1997. Brain reserve and the clinical expression of Alzheimer's disease. Geriatrics 52, S50–
550 S53.

551 Mouton, P.R., Martin, L.J., Calhoun, M.E., Dal Forno, G., Price, D.L., 1998. Cognitive decline strongly
552 correlates with cortical atrophy in Alzheimer's dementia. Neurobiol. Aging 19, 371–377.

553 Olsson, A., Vanderstichele, H., Andreasen, N., De Meyer, G., Wallin, A., Holmberg, B., Rosengren, L.,
554 Vanmechelen, E., Blennow, K., 2005. Simultaneous measurement of β-amyloid(1-42), total Tau,
555 and phosphorylated Tau (Thr181) in cerebrospinal fluid by the xMAP technology. Clin. Chem. 51,
556 336–345. https://doi.org/10.1373/clinchem.2004.039347

557 Petersen, R.C., 2008. Alzheimer's Disease Neuroimaging Initiative, ADNI 2: Defining Alzheimer's Disease.

Petersen, R.C., Aisen, P.S., Beckett, L.A., Donohue, M.C., Gamst, A.C., Harvey, D.J., Jack, C.R., Jagust, W.J., Shaw, L.M., Toga, A.W., Trojanowski, J.Q., Weiner, M.W., 2010. Alzheimer's Disease Neuroimaging Initiative (ADNI): Clinical characterization. Neurology 74, 201–209. https://doi.org/10.1212/WNL.0b013e3181cb3e25

Prencipe, M., Casini, A.R., Ferretti, C., Lattanzio, M.T., Fiorelli, M., Culasso, F., 1996. Prevalence of dementia in an elderly rural population: effects of age, sex, and education. J. Neurol. Neurosurg. Psychiatry 60, 628–633.

Reuter, M., Schmansky, N.J., Rosas, H.D., Fischl, B., 2012. Within-subject template estimation for unbiased longitudinal image analysis. Neuroimage 61, 1402–1418. https://doi.org/10.1016/j.neuroimage.2012.02.084

Roe, C.M., Xiong, C., Miller, J.P., Morris, J.C., 2007. Education and Alzheimer disease without dementia; Support for the cognitive reserve hypothesis. Neurology 68, 223–228.

Salthouse, T.A., 1991a. Cognitive facets of aging well. Gener. J. Am. Soc. Aging 35, 35–38.

Salthouse, T.A., 1991b. Mediation of Adult Age Differences in Cognition by Reductions in Working Memory and Speed of Processing. Psychol. Sci. 2, 179–183.

Scarmeas, N., Zarahn, E., Anderson, K.E., Habeck, C.G., Hilton, J., Flynn, J., Marder, K.S., Bell, K.L., Sackeim, H.A., Heertum, R.L. Van, Moeller, J.R., Stern, Y., 2003. Association of Life Activities With Cerebral Blood Flow in Alzheimer Disease. Arch. Neurol. 60, 359–365.

Schnohr, C., Hojbjerre, L., Riegels, M., Ledet, L., Larsen, T., Schultz-Larsen, K., Petersen, L., Prescott, E., Gronbaek, M., 2004. Does educational level influence the effects of smoking, alcohol, physical activity, and obesity on mortality? A prospective population study. Scand. J. Public Health 32, 250–256. https://doi.org/10.1080/14034940310019489

Shaw, B.A., Spokane, L.S., 2008. Examining the association between education level and physical activity changes during early old age. J. Aging Health 20, 767–787. https://doi.org/10.1177/0898264308321081

Shaw, L.M., Vanderstichele, H., Knapik-Czajka, M., Clark, C.M., Aisen, P.S., Petersen, R.C., Blennow, K., Soares, H., Simon, A., Lewczuk, P., Dean, R., Siemers, E., Potter, W., Lee, V.M.Y., Trojanowski, J.Q., 2009. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. Ann. Neurol. 65, 403–413. https://doi.org/10.1002/ana.21610

Singh-Manoux, A., Marmot, M., Glymor, M., Sabia, S., Kivimaki, M., Dugravot, A., 2011. Does cognitive reserve shape cognitive decline? Ann. Neurol. 70, 296–304. https://doi.org/10.1038/jid.2014.371

Stern, Y., 2009. Cognitive Reserve. Neuropsychologia 47, 2015–2028. https://doi.org/10.1016/j.neuropsychologia.2009.03.004.Cognitive

Stern, Y., 2002. What is cognitive reserve? Theory and research application of the reserve concept. J. Int. Neuropsychol. Soc. 8, 448–460.

Stern, Y., Albert, S., Tang, M., Tsai, W., 1999. Rate of memory decline in AD is related to education and occupation. Neurology 53, 1942–1947.

595 Stern, Y., Alexander, G.E., Prohovnik, I., Mayeux, R., 1992. Inverse relationship between education and
596 parietotemporal perfusion deficit in Alzheimer's disease. Ann. Neurol. 32, 371–375.
597 https://doi.org/10.1002/ana.410320311

598 Stern, Y., Arenaza-Urquijo, E.M., Bartrés-Faz, D., Belleville, S., Cantilon, M., Chetelat, G., Ewers, M.,
599 Franzmeier, N., Kempermann, G., Kremen, W.S., Okonkwo, O., Scarmeas, N., Soldan, A., Udeh-
600 Momoh, C., Valenzuela, M., Vemuri, P., Vuoksimaa, E., Arenaza Urquiljo, E.M., Bartrés-Faz, D.,
601 Belleville, S., Cantillon, M., Chetelat, G., Clouston, S.A.P., Estanga, A., Ewers, M., Franzmeier, N.,
602 Gold, B., Habeck, C., Jones, R., Kempermann, G., Kochhann, R., Kremen, W., Lim, Y.Y., Martínez-
603 Lage, P., Morbelli, S., Okonkwo, O., Ossenkoppele, R., Pettigrew, C., Rosen, A.C., Scarmeas, N.,
604 Soldan, A., Song, X., Udeh-Momoh, C., Stern, Y., Valenzuela, M., Van Loenhoud, A.C., Vemuri, P.,
605 Vuoksimaa, E., 2018. Whitepaper: Defining and investigating cognitive reserve, brain reserve, and
606 brain maintenance. Alzheimer's Dement. 1–7.

607 Stern, Y., Gurland, B., Tatemichi, T.K., Tang, M.X., Wilder, D., Mayeux, R., 1994. Influence of Education
608 and Occupation on the Incidence of Alzheimer's Disease. JAMA J. Am. Med. Assoc. 271, 1004–1010.
609 https://doi.org/10.1001/jama.1994.03510370056032

610 Stern, Y., Tang, H.M.X., Denaro, J., Mayeux, R., 1995. Increased Risk of Mortality in Alzheimer's Disease
611 Patients with More Advanced Educational and Occupational Attainment. Ann. Neurol. 37, 590–595.

612 Teri, L., McCurry, S.M., Edland, S.D., Kukull, W.A., Larson, E.B., 1995. Cognitive Decline in Alzheimer's
613 Disease: A Longitudinal Investigation of Risk Factors for Accelerated Decline. Journals Gerontol. Ser.
614 A 50, 49–55.

615 Tucker-Drob, E.M., Johnson, K.E., Jones, R.N., 2009. The Cognitive Reserve Hypothesis: A Longitudinal
616 Examination of Age-Assocaited Declines in Reasoning and Processing Speed. Dev. Psychol. 45, 431–
617 446. https://doi.org/10.1037/a0014012.The

618 Valenzuela, M., Brayne, C., Sachdev, P., Wilcock, G., Matthews, F., 2011. Cognitive lifestyle and long-
619 term risk of dementia and survival after diagnosis in a multicenter population-based cohort. Am. J.
620 Epidemiol. 173, 1004–1012. https://doi.org/10.1093/aje/kwq476

621 Valenzuela, M., Sachdev, P., 2006. Brain reserve and dementia: a systematic review. Psychol. Med. 36,
622 441–454. https://doi.org/10.1017/S0033291705006264

623 Vemuri, P., Weigand, S., Przybelski, S., Knopman, D., Smith, G., Trojanowski, J., Shaw, L., Decarli, C.,
624 Carmichael, O., Bernstein, M., Aisen, P., Weiner, M., Peterson, R., Jack Jr, C., 2011. Cognitive
625 reserve and Alzheimer's disease biomarkers are independent determinants of cognition. Brain 134,
626 1479–1492.

627 Vos, S.J.B., Xiong, C., Visser, P.J., Mateusz, S., Hassenstab, J., Grant, E.A., Cairns, N.J., Morris, J.C.,
628 Holtzman, D.M., Fagan, A.M., 2013. Preclinical Alzheimer's disease and its outcome: a longitudinal
629 cohort study. Lancet Neurol. 12, 957–965. https://doi.org/10.1016/S1474-4422(13)70194-
630 7.Preclinical

631 Zahodne, L., Glymour, M., Sparks, C., Bontempo, D., Dixon, R., MacDonald, S., Manly, J., 2011. Education
632 does not slow cognitive decline with aging: 12-year evidence from the Victoria longitudinal study. J.
633 Int. Neuropsychol. Soc. 17, 1039–1046. https://doi.org/10.1017/S1355617711001044.Education

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Table 1
Participant Demographics at Baseline

Characteristic	Total (N=441)	MCI (N=313)	AD (N=128)	*p*-value
Age (Years)	72.5 (7.7)	71.7 (7.3)	74.4 (8.4)	0.001
Female (n, %)	191 (43.3)	140 (44.7)	51 (39.8)	0.347
Education (Years)	16.2 (2.6)	16.4 (2.6)	15.8 (2.6)	0.021
Tau/$A\beta_{42}$ ratio*	0.73 (0.55)	0.60 (0.47)	1.05 (0.60)	<0.001
MEM Cognitive Composite	-0.073 (0.82)	0.25 (0.70)	-0.88 (0.49)	<0.001
EF Cognitive Composite	-0.028 (1.07)	0.32 (0.92)	-0.87 (0.96)	<0.001
MEM Pathology Composite	0 (0.34)	-0.12(0.30)	0.27(0.27)	<0.001
EF Pathology Composite	0 (0.45)	-0.14(0.40)	0.34(0.36)	<0.001

Demographic, pathology, and performance information is displayed for all participants. Reported values are mean with standard deviation, beside gender. Those with AD were significantly older, had greater AD pathology burden, were less educated, and performed worse on neurocognitive testing than those with MCI. *A total of 15 participants were missing data on this component of the pathology composite.

Table 2: AD

	Memory			EF		
Category	Beta	F-value	*p*-value	Beta	F-value	*p*-value
Age	-0.001	0.019	0.889	0.003	0.116	0.734
Gender	-0.155	3.465	0.065	-0.159	1.180	0.280
Education	0.063	5.006	0.027	0.154	6.586	0.012
Pathology Composite	-0.837	39.523	<0.001	-1.216	41.90	<0.001
Time	-0.446	34.772	<0.001	-0.780	19.87	<0.001
Path Composite × Time	-0.034	5.257	0.003	0.191	2.135	0.103
Education × Path	-0.140	1.712	0.193	-0.198	0.490	0.486
Education × Time	0.141	2.374	0.078	0.174	1.419	0.245
Education x Path x Time	-0.313	1.118	0.348	-0.003	0.916	0.438

Unstandardized beta, F and *p* values are reported for linear mixed models for both MEM and EF in those with AD. There were no education x pathology interactions either at baseline or longitudinally through 2 years.

Table 3: MCI

		Memory			EF	
Category	Beta	F-value	*p*-value	Beta	F-value	*p*-value
Age	-0.008	3.222	0.074	-0.027	15.372	<0.001
Gender	-0.215	12.227	0.001	-0.104	1.341	0.248
Education	0.076	4.805	0.029	0.132	4.757	0.030
Pathology Composite	-1.244	156.122	<0.001	-0.789	58.864	<0.001
Time	-0.107	18.210	<0.001	-0.072	1.918	0.127
Path Composite × Time	-0.538	13.794	<0.001	-0.357	5.692	0.001
Education × Path	0.053	0.070	0.792	-0.151	3.753	0.054
Education × Time	0.006	0.158	0.924	-0.076	1.376	0.250
Education x Path x Time	-0.122	1.236	0.297	-0.176	0.960	0.412

Unstandardized beta, F and *p* values are reported for linear mixed models for both MEM and EF in those with MCI. There were no education x pathology x time interactions through 2 years, although there was a trend for an education x pathology interaction at baseline for EF. However, in this interaction EF scores were not as negatively affected by pathology in lower education than those with higher education, which the opposite direction expected using cognitive reserve theory.

Table S1
Predictors for Cognitive Performance

Memory	Executive Function
Corpus Callosum Total	Corpus Callosum Posterior
Entorhinal	Fusiform
Medial Orbitofrontal	Supramarginal
Middle Temporal	Inferior Temporal
Pallidum	Cerebellum Cortex
Superior Frontal	Hippocampus
Cerebellum Cortex	Precuneus
Hippocampus	Temporal Pole
Precuneus	Tau/$A\beta_{42}$ ratio
Temporal Pole	
Tau/$A\beta_{42}$ ratio	

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655 Statistically significant bilateral predictor variables using backwards linear regression at
656 $p < 0.05$ for both MEM and EF cognitive composites. ICV-corrected and z-scored
657 predictor variables were not required to be unique to a cognitive domain.

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Table S2: AD

Memory		<75			>=75	
Category	Estimate	F-value	*p*-value	Estimate	F-value	*p*-value
Age	0.000	0.000	>0.999	0.021	3.660	0.061
Gender	-0.226	2.903	0.094	-0.270	6.975	0.011
Education	0.084	3.204	0.080	0.088	3.422	0.070
Pathology Composite	-1.132	27.851	<0.001	-0.603	10.046	0.003
Time	-0.447	18.374	<0.001	-0.497	17.826	<0.001
Path Composite × Time	-0.019	2.237	0.114	-0.089	2.789	0.055
Education × Path	0.150	0.001	0.972	-0.417	1.044	0.311
Education × Time	0.171	2.095	0.134	0.088	0.645	0.592
Education x Path x Time	-0.602	1.529	0.240	0.452	0.262	0.852
EF		<75			>=75	
Category	Estimate	F-value	*p*-value	Estimate	F-value	*p*-value
Age	0.051	8.815	0.005	-0.015	0.539	0.467
Gender	-0.338	2.734	0.106	0.028	0.022	0.883
Education	0.131	1.387	0.244	0.138	2.526	0.117
Pathology Composite	-1.187	23.259	<0.001	-1.384	22.222	<0.001
Time	-0.924	66.288	<0.001	-0.883	11.267	<0.001
Path Composite × Time	0.450	33.580	<0.001	-0.710	0.829	0.487
Education × Path	-0.148	0.049	0.826	-0.184	0.502	0.482
Education × Time	0.015	0.863	0.486	0.154	0.219	0.883
Education x Path x Time	0.033	4.232	0.030	-0.349	0.229	0.876

Unstandardized beta, F and *p* values are reported for linear mixed models for both MEM and EF in those with AD when divided into younger (<75 years of age) and older (>=75 years of age) groups using a median split. There were no education x pathology interactions at baseline, and although there were largely no education x pathology x time interactions through 2 years it was significant for EF in the younger group. This supports cognitive reserve in a limited context.

Table S3: MCI

Memory		<72			>=72	
Category	Estimate	F-value	*p*-value	Estimate	F-value	*p*-value
Age	-0.005	0.183	0.669	-0.001	0.010	0.919
Gender	-0.229	6.138	0.014	-0.146	3.190	0.076
Education	0.058	0.697	0.405	0.049	1.547	0.215
Pathology Composite	-1.272	66.189	<0.001	-1.146	77.067	<0.001
Time	-0.098	6.019	0.001	-0.123	11.547	<0.001
Path Composite × Time	-0.551	5.981	0.001	-0.500	6.380	<0.001
Education × Path	-0.140	0.782	0.378	0.263	2.725	0.101
Education × Time	0.013	0.271	0.846	-0.005	0.874	0.457
Education x Path x Time	-0.150	0.483	0.695	-0.075	0.839	0.475
EF		<72			>=72	
Category	Estimate	F-value	*p*-value	Estimate	F-value	*p*-value
Age	-0.006	0.129	0.720	-0.012	0.763	0.384
Gender	-0.191	1.992	0.160	0.014	0.013	0.908
Education	0.112	0.439	0.509	0.126	2.614	0.108
Pathology Composite	-0.723	21.525	<0.001	-0.811	32.702	<0.001
Time	-0.134	4.041	0.009	-0.051	0.353	0.787
Path Composite × Time	-0.504	7.615	<0.001	-0.226	0.801	0.495
Education × Path	-0.179	3.292	0.072	-0.146	0.776	0.380
Education × Time	-0.078	1.639	0.183	-0.074	0.664	0.576
Education x Path x Time	-0.228	1.923	0.128	-0.076	0.269	0.848

Unstandardized beta, F and *p* values are reported for linear mixed models for both MEM and EF in those with MCI when divided into younger (<72 years of age) and older (>=72 years of age) groups using a median split. There were no education x pathology interactions either at baseline or longitudinally through 2 years.

Table S4
Sample Size at Timepoints

Sample	Baseline	6 Month	12 Month	24 Month	Mean Duration in Years (S.D.)
MCI					
MEM	313	294	292	252	1.74 (0.56)
EF	313	294	292	249	1.73 (0.56)
AD					
MEM	128	116	97	30	1.07 (0.60)
EF	128	115	94	28	1.04 (0.60)

Total sample size of AD and MCI groups at each timepoint by availability of cognitive composite (MEM and EF).

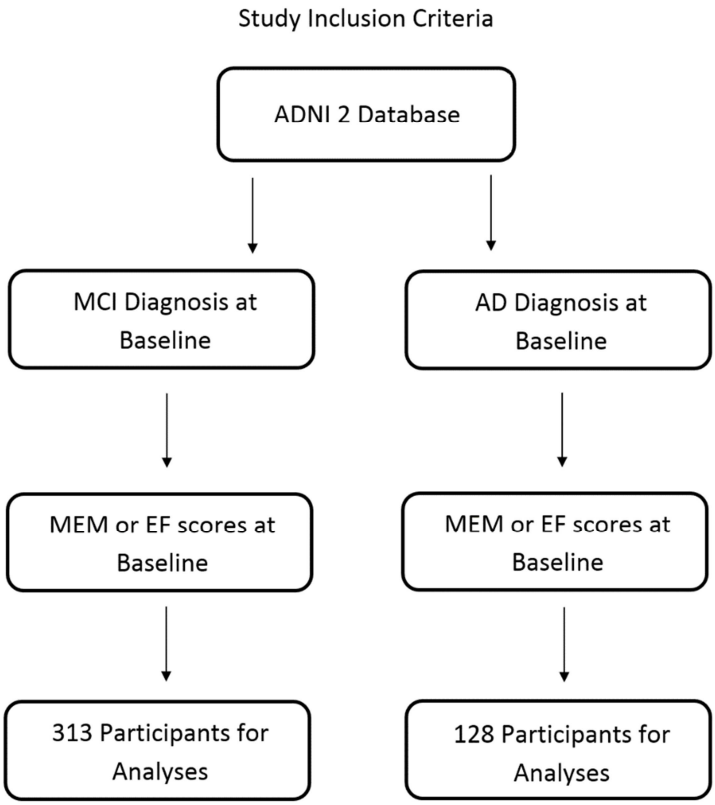

Figure S1. Flowchart of study inclusion criteria. Participants were included in this study if they had a diagnosis of MCI or AD at baseline, and if they further had available memory or executive function composite data. A total of 441 participants met these criteria.

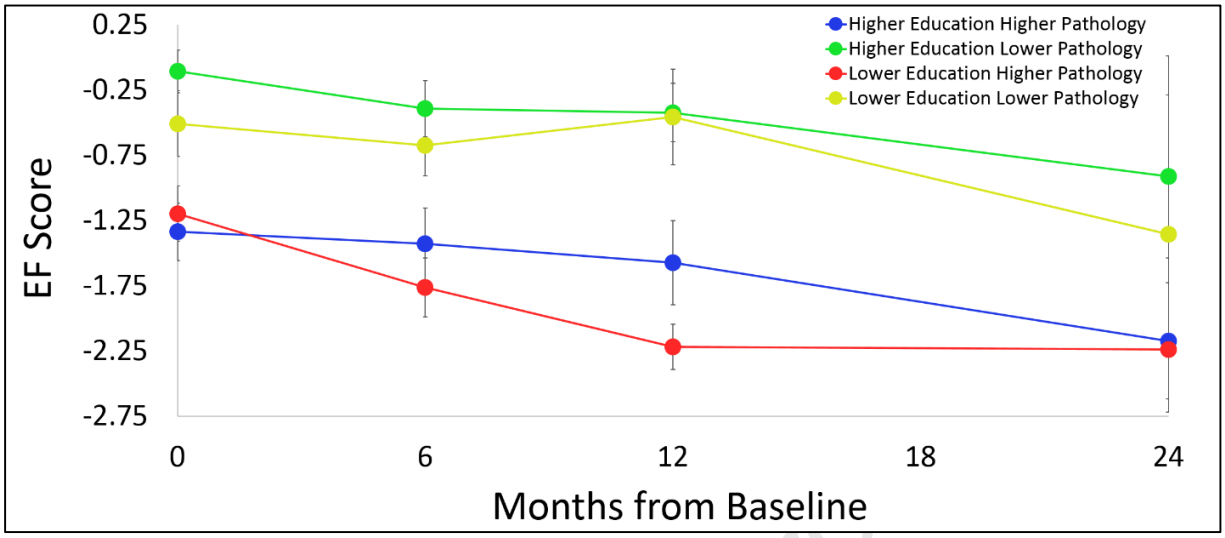

Figure S2. Time from baseline is plotted on the x-axis with mean composite EF score plotted on the y-axis. Subgroups of younger AD participants with higher education/higher pathology (blue), higher education/lower pathology (green), lower education/higher pathology (red) and lower education/lower pathology (yellow) were formed using a median split for optimal visual display (the statistical model was run with education and pathology as continuous variables). Younger AD participants with low pathology tend to show roughly similar EF decline over time regardless of education level. In contrast, younger AD participants with higher pathology but higher education tend to show less steep EF decline over year 1 than those with similar levels of pathology but lower education. Error bars represent standard error of the mean.

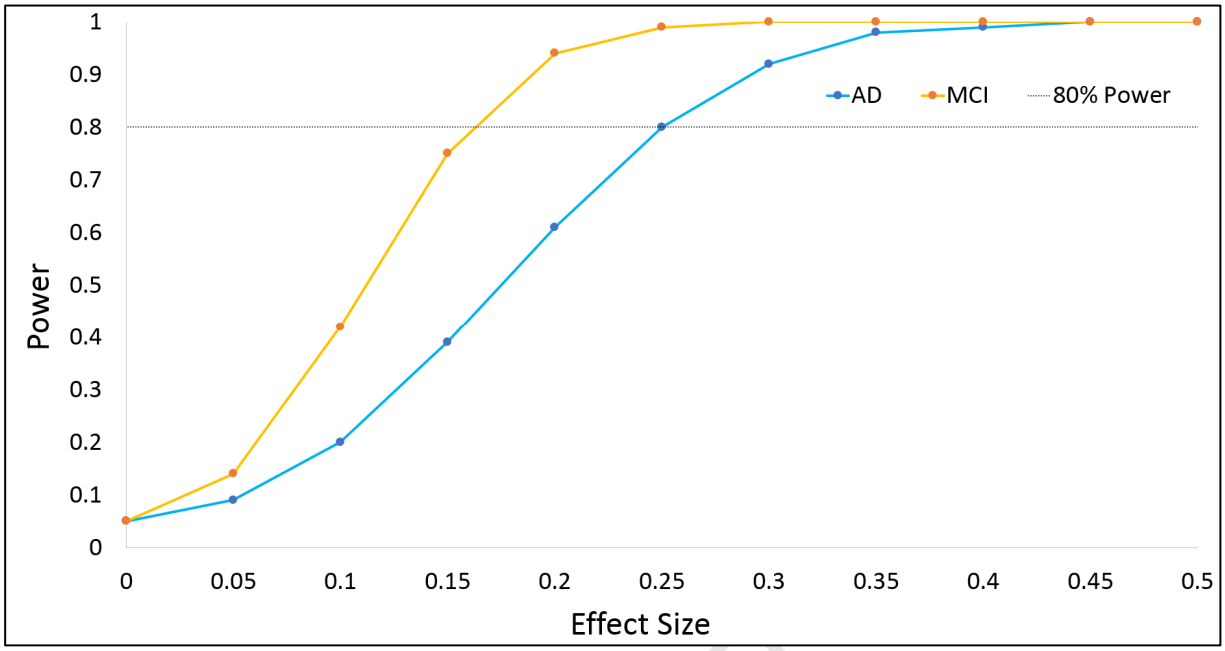

Figure S3. Effect size, on the x-axis, increases with estimated power on the y-axis in both AD and MCI groups. A moderate effect size of 0.4 (horizontal line) was expected based on the published literature. Sufficient power was obtained at even lower effect sizes in both groups. The current study was sufficiently powered to detect any education x pathology interactions, had they existed in our data.