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J. Neurol. Neurosurg. Psychiatry 2006;77;308-316
doi:10.1136/jnnp.2005.072306

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Education and rates of cognitive decline in incident Alzheimer’s disease

N Scarmeas, S M Albert, J J Manly, Y Stern


The identification of predictors of disease progression in Alzheimer’s disease (AD) is important for planning and decision making both for patients’ families and for public health policies. A relationship between education and progression of AD is predicted by the cognitive reserve hypothesis. Only a few previous studies have addressed the predictive ability of education for disease course in AD. Some epidemiological observations have reported faster cognitive decline and higher mortality in more educated AD patients. There are also studies that reported slower decline and higher mortality in more educated AD patients. We wanted to address the association between education and rates of decline in AD.

Methods: During the course of a community based multiethnic prospective cohort study of individuals aged ≥65 years living in New York, 312 patients were diagnosed with incident AD and were followed overall for 5.6 (up to 13.3) years. The subjects received an average of 3.7 (up to 9) neuropsychological assessments consisting of 12 individual tests. With the aid of a normative sample, a standardised composite cognitive score as well as individual cognitive domain scores were calculated. Generalised estimating equation models were used to examine the association between education and rates of cognitive decline.

Results: Composite cognitive performance declined by 9% of a standard deviation per year. Rates of decline before and after AD incidence were similar. For each additional year of education there was 0.3% standard deviation lower composite cognitive performance for each year of follow up. The association between higher education and faster decline was noted primarily in the executive speed (0.6%) and memory (0.5%) cognitive domains and was present over and above age, gender, ethnicity, differential baseline cognitive performance, depression, and vascular comorbidity.

Conclusions: We conclude that higher education AD patients experience faster cognitive decline.

METHODS

Sample and procedure
AD patients for the present analyses were identified and followed through the following three cohorts, which have been described in more detail elsewhere. Briefly, the first cohort consisted of a community registry of subjects enrolled between 1989 and 1992 from regional medical facilities (inpatient and outpatient services and private practitioners in New York City). The second cohort consisted of a community registry of subjects enrolled between January 1994 and December 1996 from regional medical facilities in the same area. The third cohort consisted of a community registry of subjects enrolled between January 1998 and December 2000 from regional medical facilities in the same area.

Abbreviations: AD, Alzheimer’s disease; CR, cognitive reserve; GEE, generalised estimating equation; HCFA, Health Care Financing Administration; MMSE, Mini-Mental State Examination; WAT, Word Accentuation Test; WHICAP, Washington Heights and Inwood Aging Project; WRAT-3, Wide Range Achievement Test–Version 3
the community), nursing homes serving local residents, a state agency list of home care recipients, senior centres and housing, volunteers or self referred, and some spouses of individuals identified as patients. Because of the enrolment procedure of this cohort, it may not be completely representative of the community; however, only 11% of the incident AD patients (n = 33) used in the present analyses were from this cohort. Most (89%, n = 279) incident AD patients were identified via the other two cohorts (the Washington Heights and Inwood Aging Project (WHICAP) 1992 cohort (enrolling since 1992) and the WHICAP 1999 cohort (enrolling since 1999)) which included subjects identified from a probability sample of Medicare beneficiaries residing in an area of three contiguous tracts in the northern Manhattan communities of Washington Heights and Inwood in New York City. Access to the names of individuals was provided by the Health Care Financing Administration (HCFA). The original HCFA list of names was then divided into six strata based on ethnic group and age (65–74 years and 75 years and older). We used HCFA data, supplemented by 1990 United States Census files that included a Hispanic surname list to categorise ethnic group. These strata were further subdivided into representative subsamples so that the distributions by ethnic group and age within each subsample would be similar. This provided the means to ensure equal representation of the community during the initial assessment of participants. Excluding those who died, the proportion of individuals in each age stratum who did not wish to participate for any reason, including refusal, did not differ by ethnic group. Based on the distributions within the subsamples, the proportion of individuals within each ethnic group and age stratum who participated in the study did not differ significantly from the source population.

A physician elicited each subject’s medical and neurological history and conducted a standardised physical and neurological examination. All ancillary information (medical charts, CTs, or MRIs) was considered in the evaluation, if available. Medical diagnoses were assigned when applicable. This examination was repeated at each follow up.

The neuropsychological battery was administered either in English or Spanish, took approximately 1 h to complete, and contained tests of memory (short and long term verbal and non-verbal), orientation, abstract reasoning (verbal and non-verbal), language (naming, verbal fluency, comprehension, and repetition), and construction (copying and matching). Test scores were evaluated using a fixed paradigm: criterion scores (education uncorrected) were applied to each test score, and subjects performing below these scores on two of the three aspects of memory testing as well as two other areas (orientation, language, abstract reasoning, or construction) were considered to have sufficient cognitive deficit to meet criteria for dementia. In addition to the above, the short version of the Blessed Memory Information and Concentration Test as well as the Blessed Dementia Rating Scale (part I, sections A and B) and the Schwab and England Activities of Daily Living Scale were administered to a subset of patients during the first evaluation only.

The initial clinical diagnosis of the presence, aetiology, and severity of dementia was made by a neurologist who examined the subjects. A subsequent consensus diagnosis of dementia was made at a diagnostic conference of physicians and neuropsychologists where information from all the above evaluations was presented. Evidence of cognitive deficit (based on the neuropsychological scores as described above), evidence of impairment in social or occupational function (as assessed by the Blessed Dementia Rating Scale, the Schwab and England Activities of Daily Living Scale, and the physician’s assessment), and evidence of cognitive and social-occupational function decline as compared to the past were the criteria used for the diagnosis of dementia as required by the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R). The type of dementia was subsequently determined. For the diagnosis of probable or possible AD, the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association were used.

Subjects included in the current analyses met our operational criteria for incident dementia: they did not have dementia at their initial diagnostic evaluation and were diagnosed with probable or possible AD at a subsequent evaluation.

Measures

Outcomes

The primary outcome in our analyses was rate of decline in cognition as assessed at each study visit. Selected neuropsychological tests were grouped into the following cognitive domains. The memory domain included the total recall and delayed recall of the Selective Reminding Test and the recognition component of the multiple choice version of the Benton Visual Retention Test. The abstract reasoning domain included the age scaled score of the WAIS-R similarities subtest and the identities and oddities subtest of the Dementia Rating Scale. The visual-spatial domain included the five selected items from the Rosen drawing test and the matching component of the multiple choice version of the Benton Visual Retention Test. The language domain included the total naming score for 15 selected items from the Boston Naming Test and the first six items from the repetition and comprehension subtests of the Boston Diagnostic Aphasia Examination. The executive speed domain included the phonemic fluency (controlled oral word association test) and category fluency (animals, food, clothing) mean scores. A composite cognitive measure was also developed to summarise these cognitive domains.

To derive the cognitive domain and composite measure, each of the 12 individual cognitive tests was first transformed into z scores. Means and standard deviations (SD) for each test were calculated from baseline scores of 548 subjects who were deemed cognitively healthy both at baseline and at follow-up evaluations and were age, gender, and education matched to the 312 incident AD patients identified in this cohort. More specifically, there were no differences between the 548 subjects and the 312 incident AD patients regarding gender (χ² = 0.19; p = 0.67), age tertiles (χ² = 4.16 = 0.13), or education tertiles (χ² = 1.53; p = 0.47). There were some ethnicity differences with the group of 548 control subjects which, compared to the incident AD group, consisted of similar numbers of Hispanic subjects (53% v 55%) but somewhat more white subjects (20% v 11%) and fewer black subjects (26% v 32%) (χ² = 13; p = 0.005). Selecting another sample of controls matched to the incident AD patients not only for age, gender, and education but also for ethnicity did not change the results. Based on z scores for each individual test, mean z scores for each cognitive domain and for the composite measure were calculated. If individual test scores were missing, the domain measure or the composite measure was considered as missing unless at least half of the individual scores had valid scores, in which case the domain score or the composite score was based on the valid test scores.

The z score of the composite cognitive measure at each evaluation was the primary outcome. In supplementary analyses we investigated the association between education and rates of change in individual cognitive domain scores.
Predictors

Years of education was the primary predictor tested. The following variables were also included in the model: age at intake (in years), gender, ethnicity, and composite cognitive measure z scores at baseline.

Regarding ethnicity, at the baseline interview, ethnic group was confirmed by self report using the format of the 1990 United States Census. Each individual was first asked to indicate their racial group, then asked whether or not they were of Hispanic origin. Subjects were then separated into three groups: black subjects (African-American, non-Hispanic), white subjects (non-Hispanic), or Hispanic subjects and ethnicity was used as a dummy variable with white subjects as the reference category.

The composite cognitive measure (in its z score form as described above) from baseline assessment was used as a continuous variable in the model. In the supplementary analyses with individual cognitive domain scores as the outcome, the baseline z scores of the specific cognitive domains were used.

Because of previous reports indicating associations between literacy and rates of decline, we also examined the possible confounding effect of literacy measures. For English speaking subjects we used the Wide Range Achievement Test–Version 3 (WRAT-3) and for Spanish speaking subjects the Word Accentuation Test (WAT). Using the means and SD for these two scores from the first visit for all subjects in the cohort who did not have dementia at baseline and did not develop dementia during follow up (WRAT-3 available for n = 1725 and WAT available for n = 691 subjects), we calculated literacy z scores for our incident AD subjects. Considering only subjects who had literacy evaluations before dementia onset, literacy z scores were available for 139 incident AD subjects (65 English speaking and 74 Spanish speaking).

Vascular risk factors were considered in additional analyses. We used the following data recorded during the first evaluation: LDL cholesterol (as a continuous variable), history of (either treated or untreated, in dichotomous forms) stroke, heart disease, hypertension, diabetes, and current smoking status (dichotomously).

Because previous reports have indicated associations between depression, education, and risk for AD and cognitive decline, depression qualifies as a potential confounder. During each evaluation of this cohort, the examining physician recorded whether, according to his clinical impression, there was evidence of depression or not. Because depression may fluctuate over time, we considered these dichotomous depression ratings both from the first evaluation and from any evaluation.

Statistical analyses

We computed descriptive statistics for the variables intended to be included in the model. The data were examined to ensure that the variables included in the models met the model assumptions (that is, normality). Variables at baseline were compared using linear regression, t test, or χ² analyses.

We used generalised estimating equations (GEE) to test whether education was associated with differential rates of cognitive change. GEE takes into account the multiple visits per subject and the fact that the characteristics of the same individual over time are likely to be correlated. The repeated measures for each subject are treated as a cluster. The initial GEE model included the summary cognitive measure as the dependent variable and, as predictors, education, time (in years from baseline assessment), and an education×time interaction. A significant education effect would indicate a difference in cognitive performance for each year of education at the initial visit. A significant time effect would indicate a change in test scores over time (for all educational levels combined). A significant interaction term would indicate differential rates of change in cognitive function as a function of education. The main adjusted GEE model included terms for the following possible confounders: gender, age, and ethnicity. We created models with and without adjustment for baseline composite cognitive score.

Supplementary models

In order to test whether rates of cognitive decline differ before and after incidence, we created a GEE model with composite cognitive score as the outcome and the following terms as predictors: (i) a dichotomous term indicating whether the evaluation was performed pre or post-incidence, (ii) a term for time (years from first evaluation for the pre-incidence visits and years from incidence for the post-incidence visits), and (iii) their interaction. A significant pre-post incidence term effect would indicate differences in composite cognitive scores between first evaluation and incidence. A significant interaction effect would indicate that rates of composite cognitive score decline differ before and after incidence.

In order to examine non-linear rates of decline, we included a term for time squared. The quadratic term for time examines whether the rate of cognitive decline significantly decreases or increases with the passage of time. We calculated the above supplementary models separately for pre-incidence and post-incidence data and in high and low education groups.

In order to examine whether the relationship between education and cognitive decline varied by ethnicity, we created the following GEE model. We included a dichotomous term for ethnicity (Hispanic v black subjects, because black and Hispanic subjects comprised 87% of our population), education, time, time×education interaction, time×ethnicity interaction, and time×education×ethnicity interaction (as well as baseline cognitive score, gender, and age). A significant time×ethnicity interaction term would indicate differential rates of cognitive decline for Hispanic subjects as compared to black subjects. The three way interaction (time×education×ethnicity) would indicate whether the relationship between education and cognitive decline varies by ethnicity.

In order to examine whether the relationship between education and cognitive decline varied by literacy, we created the following GEE model. We included terms for education, literacy, time, time×education interaction, time×literacy interaction, and time×education×literacy interaction (as well as baseline cognitive score, gender, age, and ethnicity). A significant time×literacy interaction term would indicate differential rates of cognitive decline for different baseline literacy levels. The three way interaction (time×education×literacy) would indicate whether the relationship between education and cognitive decline varies by literacy level.

In order to examine possible contributions of vascular comorbidity in rates of decline, we simultaneously included LDL cholesterol, history of stroke, heart disease, hypertension, diabetes, and smoking in a single GEE model (along with age, gender, ethnicity, baseline cognitive score, time, education, and time×education interaction).

In order to examine possible confounding by depression, we included the depression ratings (either from the first or from any evaluation) in a GEE model (along with age, gender, ethnicity, baseline cognitive score, time, education, and time×education interaction).

RESULTS

Demographic and clinical follow up information is presented in table 1. Overall, the 312 included AD subjects had 1159 separate cognitive assessments. All participants had by
impairment at the baseline evaluation, with subjects who
As depicted in table 2, there was evidence of cognitive
Decline of cognition over time
the form of a recoded four level categorical variable.
In supplementary analyses that used language domain as the outcome in
chological measures. The results were similar in supplemen-
tary scores were even lower at the AD incidence
visit, with cognitive performance 0.89 SD below that of the
controls.
Over all evaluations, there was significant decline of cognitive performance over time for all domain scores. For
the composite score, \( \beta = -0.09 \) (p<0.001), indicating a 9% decline in the score per year of follow up. For the individual
domains, results were as follows: memory \( \beta = -0.12 \) (p<0.001), abstract reasoning \( \beta = -0.05 \) (p<0.001), visual-
spatial \( \beta = -0.07 \) (p<0.001), language \( \beta = -0.07 \) (p<0.001), and executive speed \( \beta = -0.10 \) (p<0.001).
Rates of cognitive decline before and after the AD incidence visit were similar (time \times pre-post incidence inter-
action term \( \beta = 0.007; p = 0.57 \)). For example, for the composite score rates of decline were \(-0.09\) SD/year (p<0.001) before and \(-0.08\) SD/year (p<0.001) after the incident visit.

We detected no evidence of gradual acceleration or deceleration of rates of decline. This was the case both pre-
incidence (time \( ^2 \beta = 0.001; p = 0.66 \)) and post-incidence (time \( ^2 \beta = 0.001; p = 0.75 \)). This was also the case both in
high education (pre-incidence time \( ^2 \beta = 0.001, p = 0.75 \); post-incidence time \( ^2 \beta = 0.000, p = 0.94 \)) and low education
(pre-incidence time \( ^2 \beta = 0.000, p = 0.89 \); post-incidence time \( ^2 \beta = 0.001, p = 0.69 \)) patients.

Education, baseline cognitive performance, and
demographic characteristics
There was no association between age and education
(\( r = 0.09, p = 0.14 \)) or between age and baseline composite score (\( r = 0.10, p = 0.08 \)). There was no association between
education and gender (mean years of education 7.2 for males and 7.1 for females; p = 0.86). Men performed slightly better
than women: mean baseline composite score was –0.35 for men and –0.50 for women (p = 0.03). There were significant
difference between Hispanic subjects (mean 10.2 years of education) and black subjects (mean 8.9 years
of education). Similarly, there were significant cognitive performance differences among ethnicities (omnibus ANOVA
\( F = 29.1, p < 0.001 \)). In post-hoc Scheffe’s tests, Hispanic
subjects (mean 5.2 years of education) had significantly lower education as compared to both white subjects (mean 10.2 years of education) and black subjects (mean 8.9 years
of education). There were also significant cognitive performance differences among ethnicities (omnibus ANOVA
\( F = 5.47, p = 0.001 \)). In post-hoc Scheffe’s tests, Hispanic
subjects (mean baseline composite z score –0.57) had significantly lower baseline cognitive performance as
compared to black subjects (mean baseline composite z score –0.32) but had similar baseline cognitive performance as

### Table 1 Demographic and follow-up information of incident AD patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at study entry (years)</td>
<td>81.6 (6.8)</td>
<td>67–103</td>
</tr>
<tr>
<td>Education (years)</td>
<td>7.1 (1.4)</td>
<td>0–20</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>83</td>
<td>27</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White subjects</td>
<td>38</td>
<td>12</td>
</tr>
<tr>
<td>Black subjects</td>
<td>102</td>
<td>33</td>
</tr>
<tr>
<td>Hispanic subjects</td>
<td>168</td>
<td>54</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Follow up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before incidence (n=312)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years from first evaluation</td>
<td>3.8 (2.70)</td>
<td>0.8–13.1</td>
</tr>
<tr>
<td>to incidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of evaluations</td>
<td>1.9 (1.21)</td>
<td>1–7</td>
</tr>
<tr>
<td>before incidence*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After incidence (n=131)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years from incidence to last</td>
<td>3.9 (2.39)</td>
<td>0.9–11.1</td>
</tr>
<tr>
<td>evaluation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of evaluations</td>
<td>1.8 (1.07)</td>
<td>1–5</td>
</tr>
<tr>
<td>after incidence*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (n=312)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years from first to last</td>
<td>5.6 (3.27)</td>
<td>0.8–13.3</td>
</tr>
<tr>
<td>evaluation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of all evaluations</td>
<td>3.7 (1.65)</td>
<td>2–9</td>
</tr>
</tbody>
</table>

*Not including the incidence evaluation.

### Table 2 Cognitive performance at first and AD incidence evaluation

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Mean z score</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>First evaluation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite</td>
<td>–0.37</td>
<td>0.51</td>
</tr>
<tr>
<td>Memory</td>
<td>–0.41</td>
<td>0.66</td>
</tr>
<tr>
<td>Abstract reasoning</td>
<td>–0.19</td>
<td>0.71</td>
</tr>
<tr>
<td>Visual-spatial</td>
<td>–0.35</td>
<td>0.89</td>
</tr>
<tr>
<td>Language</td>
<td>–0.19</td>
<td>0.68</td>
</tr>
<tr>
<td>Executive speed</td>
<td>–0.68</td>
<td>0.76</td>
</tr>
<tr>
<td>AD incidence evaluation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite</td>
<td>–0.89</td>
<td>0.48</td>
</tr>
<tr>
<td>Memory</td>
<td>–1.30</td>
<td>0.51</td>
</tr>
<tr>
<td>Abstract reasoning</td>
<td>–0.52</td>
<td>0.70</td>
</tr>
<tr>
<td>Visual-spatial</td>
<td>–0.82</td>
<td>0.94</td>
</tr>
<tr>
<td>Language</td>
<td>–0.60</td>
<td>0.82</td>
</tr>
<tr>
<td>Executive speed</td>
<td>–1.20</td>
<td>0.65</td>
</tr>
</tbody>
</table>
compared to white subjects (mean baseline composite z score = -0.38). As expected, AD patients with more education had better baseline composite cognitive performance ($r = 0.14$, $p < 0.001$).

**Education and rates of cognitive decline**

In models unadjusted for baseline cognitive score, there was borderline faster decline for higher education subjects (composite z score $\beta = -0.002; p = 0.060$), driven mostly by faster decline in memory ($\beta = -0.003; p = 0.019$) and executive speed ($\beta = -0.006; p = 0.002$). There was no association between education and rates of abstract reasoning ($\beta = -0.002; p = 0.191$), visual-spatial ($\beta = -0.001; p = 0.987$), or language ($\beta = 0.002; p = 0.168$). Decline.

In models adjusted for baseline cognitive performance, each additional year of education was associated with an additional decline of 0.003 z score units of the composite cognitive score per year of follow up (table 3; fig 1). In analyses of separate cognitive domains, there was an association between education and z score decline for executive speed, memory, and abstract reasoning domains, while there was no association between education and rates of visual-spatial and language decline (table 3; fig 1).

As expected, baseline cognitive performance scores were significant and there was significant decline of all cognitive domain z scores over time (table 3). Higher education was associated with significantly higher baseline performance in all cognitive domains except language ($p = 0.08$). Female gender and younger age were associated with lower baseline abstract reasoning z scores. Black subjects had lower baseline visual-spatial z scores.

There was no evidence of different rates of decline among ethnicities: time*ethnicity: $\beta = -0.009; p = 0.65$. Additionally, there was no evidence that the relationship between education and cognitive decline varied by ethnicity: time*education*ethnicity: $\beta = 0.03; p = 0.23$.

There was no evidence of differential rates of decline for different literacy levels: $\beta = 0.01; p = 0.43$. Additionally, there was no evidence that the relationship between education and cognitive decline varied by literacy: $\beta = -0.001; p = 0.60$.

Vascular risk factors of the incident AD patients were as follows: LDL levels mean 118.7 mg/dl (SD 36.16); history of stroke 21%; hypertension 69%; heart disease 25%; diabetes 27%; and current smoking 11%. As expected, AD patients with higher education had less hypertension ($t = 2.30; p = 0.022$) and diabetes ($t = 2.36; p = 0.019$). There was no significant association between education and LDL, history of heart disease, stroke, or current smoking. When we simultaneously considered all the above variables in a single GEE model, the results were unchanged: higher education patients had faster cognitive decline: $\beta = -0.003; p = 0.017$. None of the vascular variables was significant in this model.

Examining individual cognitive domains with the vascular variables in the model did not change the results: there was significant time*education interaction for memory ($\beta = -0.005; p = 0.002$), abstract reasoning ($\beta = -0.003; p = 0.026$), and executive speed ($\beta = -0.007; p < 0.001$), but not for the visual-spatial ($\beta = -0.001; p = 0.73$) and language ($\beta = 0.001; p = 0.46$) domains.

Depression at first evaluation was present for 8% of the subjects and was not related to educational level ($t = 1.57; p = 0.12$). When controlled for in the GEE model, higher education patients had again faster cognitive decline; $\beta = -0.003; p = 0.015$. Depression at any point during the follow up was present for 32% of the subjects and was not related to educational level ($t = 1.25; p = 0.21$). When considered in the GEE model, the association between education and rates of cognitive decline was again unchanged: time*education: $\beta = -0.003; p = 0.012$. When we considered depression together with vascular risk factors, the results did not change either: time*education: $\beta = -0.003; p = 0.017$.

**Figure 1** Regression lines (GEE predicted z scores) (y axis) over the course of follow up (pre- and post-incidence evaluations—incidence visit: 0) in years (y axis) separately for the high (solid) and low (dashed) education groups (defined by the median cut off of 8 years of education), for each cognitive domain and the overall composite score.
Post-incidence visits only

These analyses included only 131 subjects for whom there was at least one post-incidence follow-up evaluation (181 subjects had only pre-incidence and incidence, but no post-incidence evaluations available). In a model with gender, age, ethnicity, time, education, and cognitive scores (at incidence), we detected faster decline for higher education patients in the executive speed domain ($\beta = -0.007; p = 0.025$). The memory domain was borderline non-significant ($\beta = -0.004; p = 0.067$). There were no differential rates of decline for the other cognitive domains: abstract reasoning ($\beta = -0.003; p = 0.31$), visual-spatial ($\beta = 0.002; p = 0.47$), and language ($\beta = -0.002; p = 0.49$).

Pre-incidence visits only

A similar model, adjusted for all covariates, was calculated for all patients’ evaluations preceding (and not including) the incidence visit. There was faster decline for higher education AD patients in the memory ($\beta = -0.004; p = 0.037$) and executive speed domains ($\beta = -0.008; p = 0.006$). There were no differential rates of decline for abstract reasoning ($\beta = -0.002; p = 0.33$), visual-spatial ($\beta = -0.001; p = 0.81$), and language ($\beta = -0.001; p = 0.78$).

DISCUSSION

We found a faster rate of cognitive decline in incident AD patients with higher educational attainment compared to those with lower education. This association was particularly noted in the specific domains of executive speed and memory. Only incident AD patients were used in these analyses. Subjects were assessed at points surrounding the time at which incident AD was noted. The association between education and cognitive decline was still noted after controlling for differential cognitive performance at the initial visit and was not accounted for by literacy, vascular comorbidity, or depression.

Some previous studies have noted a similar association between education and rates of cognitive decline in AD. One study \(^7\) followed 143 patients with probable AD for an average of 3 (up to 5) years with the Folstein Mini-Mental State Examination (MMSE) \(^8\) and the Mattis Dementia Rating Scale \(^9\) and found faster rates of decline for higher education subjects. The patients were clinic based, and those with very mild or very severe dementia were excluded. The study controlled for average dementia severity throughout the course of the disease but not baseline cognitive performance. Another study followed 132 probable AD patients semi-annually for an average of 2.5 years (up to 7.5). A random effects model demonstrated faster rates of cognitive decline in patients with higher education. \(^7\) The patients in that study were self referred to a university based AD research centre and the MMSE was used as the cognitive outcome. Another study examined the effect of education in word list learning and animal fluency scores of 22 patients with dementia identified in a community based study. \(^7\) Higher education subjects with dementia (but not controls) had greater cognitive decline from their estimated premorbid cognitive ability levels. Other investigators followed 494 participants with AD semi-annually for up to 4 years. \(^7\) Rates of decline for a composite measure of global cognition accelerated more rapidly for higher education subjects. These participants were recruited from an AD research centre and health care facilities in the Chicago area. In a previous report \(^7\) from the present cohort, 177 patients with AD were followed for 2.4 years and a memory score (the total recall of the Selective Reminding Test \(^7\)) was used as the cognitive outcome. In order to control for baseline cognitive performance, subjects were stratified into two groups based on their baseline memory performance. Using GEE, faster rates of memory decline were demonstrated for higher education subjects (but only for the subgroup with lower baseline memory performance). Most of the subjects in that report were prevalent cases and the effect of education in other cognitive domains was not examined. A recently published study examined rates of change performance in four cognitive tests over a 9 year period before AD incidence, for 215 future community based (south-western France) AD patients. \(^7\) Higher education subjects experienced faster decline in the few years preceding dementia onset for all neuropsychological tests (including visual-spatial memory, verbal fluency, abstract reasoning, and global cognition).

Using MMSE as the cognitive measure, a previous study reported slower rates of decline in higher education AD patients (mixture of mild and moderate levels of severity) seen in an AD research centre. \(^7\) Two previous reports have detected no significant association between education and rates of cognitive decline in AD, but the validity of their results is limited by their very low power: 28 AD patients in one \(^7\) and 16 in the other. \(^7\) The relationship was equivocal in some other reports. A study followed 410 AD patients (self referred to an AD research centre) with 17 cognitive function tests (from which a composite cognitive score was derived) annually for an average of 3.8 assessments. \(^7\) Using a random effects model the authors demonstrated faster cognitive decline in patients with higher education. However, after controlling for demographics and premorbid reading

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**Table 3 Six separate GEE analyses with different cognitive domains as outcomes**

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Outcomes (cognitive z scores), $\beta$ and $p$ values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Memory</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>0.007</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.004</td>
</tr>
<tr>
<td>Ethnicity (black)</td>
<td>-0.068</td>
</tr>
<tr>
<td>Ethnicity (Hispanic)</td>
<td>0.012</td>
</tr>
<tr>
<td>Baseline cognitive score</td>
<td>0.603</td>
</tr>
<tr>
<td>Time (years)</td>
<td>-0.089</td>
</tr>
<tr>
<td>Education (years)</td>
<td>0.016</td>
</tr>
<tr>
<td>Time x education</td>
<td>-0.005</td>
</tr>
</tbody>
</table>

All predictors are simultaneously included in each GEE model.

*Significant ($p < 0.05$) coefficients for interaction terms ($p$ values included only for significant associations).
activities, the association with education did not remain significant. In another report, 11 16 1 AD patients were followed for 2.2 (maximum 6) years with the Blessed Memory Information and Concentration Test. 31 Using a random effects model the authors reported borderline none-significant (p = 0.06) faster rates of decline for higher education subjects; the AD patients were recruited from a mixture of different sources (physicians’ private practices, AD research centre, community and nursing homes).

Confidence in the present findings is strengthened by several factors. This is one of the largest studies examining this hypothesis and provided sufficient power for detection and more precise calculation of effects of interest as well as the control for potential confounders. The large range and variety of education in our multiethnic population offers the advantage of higher power and generalisability. Clinical diagnosis was based on uniform application of widely accepted criteria via a consensus diagnostic conference procedure. Evaluations were performed approximately every 1.5 years for an average of 5.6 (and up to 13.3) years, which provides multiple assessments of cognitive performance and therefore permits more accurate slope calculations. We used a comprehensive battery of cognitive assessment, permitting evaluation of a full range of cognitive domains. Previous reports studied more impaired AD patients (either prevalent cases or patients seeking medical attention) capturing the part of disease course corresponding to more advanced stages, while the design of the present study enables testing of the hypothesis during earlier stages of disease. In contrast to most previous studies which included AD patients who were self referred to clinics or university based AD research centres, the current investigation was performed in a representative sample of a multiethnic community, which provides increased generalisability of the findings.

The cognitive reserve (CR) hypothesis has been proposed as one possible explanation for the association between higher education and faster cognitive decline. The CR hypothesis suggests that there are individual differences in the ability to cope with AD pathology. 1 2 4 4 The neural substrate of CR may take the form of a higher number of healthy synapses or neurons resulting in an increased number of remaining available synapses or neurons when a certain percentage has been affected by a pathological process. Alternatively, even if the number of neurons or synapses is the same, more efficient circuits of synaptic connectivity or more efficient use of alternative brain networks might exist in subjects with higher CR. Lower linguistic ability (as expressed by idea density and grammatical complexity) in early life has been suggested to affect the development of AD pathology. Therefore, it is also conceivable that CR related factors may even affect the development of AD pathology.

Epidemiological data supporting the CR hypothesis include observations that lower educational attainment is associated with increased risk for incident dementia. 11 20 45–51 The above observations are consistent with the prediction that people with more CR can cope with advancing AD pathology longer before it is expressed clinically. However, this would mean that when AD is clinically manifested in patients with higher education, brain pathology is already quite advanced. Actually this has been demonstrated in some imaging studies. 32–55 The CR hypothesis predicts that among AD patients with similar cognitive status, those with more CR would have (or be able to tolerate) more severe degrees of brain pathology. In an MRI study of AD patients, controlling for cognitive performance, higher levels of education were associated with more severe parietal atrophy (an indirect measure of brain AD pathology). 56 In a Xenon study, AD patients with higher education 57 manifested more prominent cerebral blood flow deficits (and hence more AD pathology) when controlling for clinical severity. Thus subjects with higher education can manifest clinical deficits comparable to those in subjects with lower education despite higher burdens of pathological involvement. Important for the current observation, this would predict that subjects with higher education would have a heavier brain pathological burden than those with lower education when AD is first clinically manifested. Results from the Religious Order Study, including clinical and neuropathological data from 130 older Catholic clergy, contested this. 57 The association between cognitive function and AD pathology was modified by education: there was less effect of AD pathology on cognitive function for patients with higher education. This may be because AD pathology progresses independently of educational attainment (or CR), when pathological burden becomes more severe and widespread, sufficient neural substrate is no longer available and a faster decline may ensue.

Alternative explanations for the education effect have been suggested. One possibility is that individuals with higher education have a younger age of onset of AD 13 57 so that they are already at more advanced stages when compared with lower education subjects. Our results do not support this since we know that the onset of clinical AD occurred during the evaluation period for these subjects and we included age as a covariate in the analyses. It is also possible that patients with higher education perform better on cognitive tests at time of diagnosis and therefore have more room for decline. However, we included baseline scores as covariates in the analyses and the results were unchanged.

We included pre-incidence evaluations in the analyses. We know that AD pathological changes already exist in the brain for years before the disease is clinically manifested. Several studies have shown that subtle cognitive changes antedate the clinical diagnosis of AD by many years. 9 17 46 Our incident AD patients’ cognitive performance 3.9 years before incident was already 0.37 SD lower than that of age, gender, and education matched controls. In addition, rates of cognitive decline were almost identical before and after incidence. We therefore feel that data collected for a few years prior to AD clinical incidence reflect the effects of AD associated pathological changes. In supplementary analyses which included only the post-incidence evaluations, both the direction and the magnitude of the coefficients were very similar despite in the smaller number of patients included in these analyses.

Many prospective studies have suggested that higher education is associated with reduced risk of incident AD. 11 20 45–51 Assuming that the progression of AD pathology does not differ as a function of education, this delay in clinical onset may result from differences in rate of cognitive decline, differences in the time when cognitive decline begins (“inflection point”), or a combination of both. One could therefore imagine at least four hypothetical scenarios for differential cognitive decline prior to incident AD as a function of education (fig 2). The results of the present analyses are suggestive of model B-a in fig 2: the lower incidence of AD reported in previous studies may be the result of a later inflection point and not of a slower pre-incidence rate of decline for higher education AD patients. Graphical representations of cognitive decline over a 9 year period before dementia incidence (deriving from actual data from a previous population based study) 7 are also supportive of the above model.

This study has limitations. First, our diagnosis of AD is a clinical one. It is conceivable that some of these subjects either do not have dementia or suffer from some other type of dementia. The used standard diagnostic criteria have a
types of non-linear decline may be present. Fourth, it is possible that other 
and non-linear (quadratic) terms, it is possible that other 
although we examined rates of decline using both linear 
testable with neuropsychological assessments). Third, 
to the earlier disease stages (during which subjects are still 
disease. However, the hypothesis tested here is most relevant 
incidence follow up was relatively limited (1.8 years), it is 
biomarker there is always the possibility of assessment bias. 
we used pre-incidence data and the post-
work up, in the absence of a 
authors' affiliations
Y Stern, Cognitive Neuroscience Division of the Taub Institute for Research in Alzheimer’s Disease and the Aging Brain, Columbia University Medical Center, New York, NY, USA
S M Albert, J J Manly, The Gertrude H Sergievsky Center, Columbia University Medical Center, New York, NY, USA

sensitivity of ~81% with a specificity of ~70%. Therefore, 
despite the use of standard criteria, the diagnostic expertise 
of our centre, and the thorough work up, in the absence of a 
biomarker there is always the possibility of assessment bias. 
Second, because we used pre-incidence data and the post-
incidence follow up was relatively limited (1.8 years), it is 
possible that we have not fully captured the later stages of the 
disease. However, the hypothesis tested here is most relevant to 
the earlier disease stages (during which subjects are still 
estable with neuropsychological assessments). Third, 
although we examined rates of decline using both linear 
and non-linear (quadratic) terms, it is possible that other 
types of non-linear decline may be present. Fourth, it is 
always possible that education is just a surrogate for some 
other factor that is not included in the models and is truly 
associated with faster rates of cognitive decline. Fifth, years 
of schooling cannot completely capture all aspects of 
educational experience (that is, different quality of education 
in different educational systems, etc).

Authors' affiliations
Y Stern, Cognitive Neuroscience Division of the Taub Institute for Research in Alzheimer’s Disease and the Aging Brain, Columbia University Medical Center, New York, NY, USA
S M Albert, J J Manly, The Gertrude H Sergievsky Center, Columbia University Medical Center, New York, NY, USA

REFERENCES

Figure 2 Four theoretical scenarios of association between education and rates of cognitive decline. (A) The inflection point (the time when cognitive decline begins) is the same for both high and low education subjects, but high education subjects decline more slowly after that point resulting in a later incidence date. (B-a, B-b, B-c) The inflection point occurs later for individuals with high education resulting again in a later incidence date. After this point, as compared to low education patients, high education patients may decline faster (B-a), slower (B-b), or with equal rates (B-c).


