Association of Lifetime Intellectual Enrichment With Cognitive Decline in the Older Population

Prashanthi Vemuri, PhD; Timothy G. Lesnick, MS; Scott A. Przybelski, BS; Mary Machulda, PhD, LP; David S. Knopman, MD; Michelle M. Mielke, PhD; Rosebud O. Roberts, MB, ChB; Yonas E. Geda, MD; Walter A. Rocca, MD, MPH; Ronald C. Petersen, PhD, MD; Clifford R. Jack Jr, MD

IMPORTANCE  Intellectual lifestyle enrichment throughout life is increasingly viewed as a protective strategy against commonly observed cognitive decline in the older population.

OBJECTIVES  To investigate the association of lifetime intellectual enrichment with baseline cognitive performance and rate of cognitive decline in an older population without dementia and to estimate the years of protection provided against cognitive impairment by these factors.

DESIGN, SETTING, AND PARTICIPANTS  Prospective analysis of individuals enrolled from October 1, 2004, and in 2008 and 2009 in the Mayo Clinic Study of Aging, a longitudinal, population-based study of cognitive aging in Olmsted County, Minnesota. We studied 1995 individuals without dementia (1718 cognitively normal individuals and 277 individuals with mild cognitive impairment) who completed intellectual lifestyle enrichment measures at baseline and underwent at least 1 follow-up visit.

MAIN OUTCOMES AND MEASURES  We studied the effect of lifetime intellectual enrichment by separating the variables into 2 nonoverlapping principal components: education/occupation score and mid/late-life cognitive activity based on self-report questionnaires. A global cognitive z score served as the summary cognition measure. Linear mixed-effects models were used to investigate the associations of demographic and intellectual enrichment measures with global cognitive z score trajectories.

RESULTS  Baseline cognitive performance was lower in older individuals; individuals with lower education/occupation score, lower mid/late-life cognitive activity, and APOE genotype; and men (P < .001). The interaction between the 2 intellectual enrichment measures was significant (P < .03) such that the beneficial effect of mid/late-life cognitive activity on baseline cognitive performance was reduced with increasing education/occupation score. Only baseline age, mid/late-life cognitive activity, and APOE4 genotype were significantly associated with longitudinal change in cognitive performance from baseline (P < .05). For APOE4 carriers with high lifetime intellectual enrichment (75th percentile of education/occupation score and midlife to late-life cognitive activity), the onset of cognitive impairment was approximately 8.7 years later compared with low lifetime intellectual enrichment (25th percentile of education/occupation score and mid/late-life cognitive activity).

CONCLUSIONS AND RELEVANCE  Higher education/occupation scores were associated with higher levels of cognition. Higher levels of mid/late-life cognitive activity were also associated with higher levels of cognition, but the slope of this association slightly increased over time. Lifetime intellectual enrichment might delay the onset of cognitive impairment and be used as a successful preventive intervention to reduce the impending dementia epidemic.

Published online June 23, 2014.

Copyright 2014 American Medical Association. All rights reserved.
The older population in the United States is expected to more than double from 35 million in 2000 to 72 million in 2030. Commonly observed cognitive decline in the older population due to the pathologic aging of the brain will have a significant effect on public health. Intellectual lifestyle enrichment throughout life is increasingly viewed as a protective strategy against cognitive decline in the older population. Numerous studies have found that all components of intellectual enrichment, including higher lifetime nonleisure learning components, such as education and primary occupation, and cognitively stimulating activities, are protective against cognitive decline and Alzheimer disease (AD)-related dementia. Intellectual enrichment may succeed as a preventive intervention if we understand the relative influence of intellectual enrichment factors on baseline cognitive performance and rate of decline and estimate the years of protection provided against cognitive impairment by these factors.

Lifetime intellectual enrichment can be grouped into 2 major components: early life and midlife noncognitive activities, such as educational attainment and major occupation, and mid/late-life cognitive activity. In this study, we separate these 2 components and closely examine their effects on baseline cognition and the subsequent rate of cognitive decline in a population-based sample of older individuals without dementia. The number of years of protection provided by each component was estimated for subsequent onset of cognitive impairment.

**Methods**

**Selection of Participants**

This study was approved by the Mayo Clinic Institutional Review Board, and written informed consent was obtained from all participants or their surrogates. Study participants were individuals from the Mayo Clinic Study of Aging (MCSA), an epidemiologic study of the prevalence, incidence, and risk factors of mild cognitive impairment (MCI) and dementia among Olmsted County, Minnesota, residents 70 to 89 years of age. The study participants consisted of the original sampled cohort from October 1, 2004, and replenishment sampling cohorts that occurred in 2008 and 2009. We included all 1995 participants without dementia at baseline (1718 cognitively normal participants and 277 participants with MCI) with the APOE genotype, intellectual enrichment variables (described below), complete neuropsychological assessments, and at least 1 additional clinical follow-up with complete neuropsychological assessments. The MCSA uses the Rochester Epidemiology Project records linkage system infrastructure, and complete details of the MCSA design have been published elsewhere.

**Intellectual Enrichment Variables**

The primary intellectual enrichment variables, assessed at baseline, included education/occupation score and mid/late-life cognitive activity. The intellectual enrichment data were recorded for all study participants at the MCSA enrollment visit. Educational attainment is self-reported and based on the number of years of school completion. The job level score is based on the participants’ primary occupation during most of their adult life. All the occupations were then assigned to 1 of 6 groupings based on similar attributes and complexity of the jobs. Details about the cognitive activity questionnaires used for recording are available in the eAppendix in the Supplement. The same form was used to record their cognitive activities during the past 12 months (late life) and cognitive activities at 50 to 65 years of age (midlife). Each component score is weighted based on the amount of activity participation. The 10 cognitive activities are added to determine the cognitive activity score. Television, which is the 11th component that is captured, is not included in the final cognitive activity score.

Using principal components applied to these 4 measures (ie, educational attainment, occupational score, midlife cognitive activity, and late-life cognitive activity), we separated the uncorrelated components of early-life nonleisure activity and mid/late-life cognitive activity. The first 2 principal components explained 84% of the variance, and after a varimax rotation, the data were consolidated into 2 distinct composite measures of intellectual enrichment: education/occupation score (ie, lifelong nonleisure intellectual learning) assessed from years of education/occupation score (weighted contribution was 0.688 for years of education and 0.725 for occupational score) and mid/late-life cognitive activity from a self-report of cognitive activities in the previous 12 months and at 50 to 60 years of age (weighted contribution was 0.708 for midlife and 0.700 for cognitive activity in the previous 12 months).

**Global Cognition Measure**

The neuropsychological battery of tests was constructed as previously described. Four cognitive domains were assessed from 9 tests: executive (Trail Making Test Part B and Wechsler Adult Intelligence Scale–Revised Digit Symbol), language (Boston Naming Test and category fluency), memory (Wechsler Memory Scale–Revised Logical Memory II [delayed recall], Wechsler Memory Scale–Revised Visual Reproduction II [delayed recall], and Auditory Learning Verbal Test delayed recall), and visuospatial performance (Wechsler Adult Intelligence Scale–Revised Picture Completion and Block Design). Individual test scores were first converted to z scores using means (SDs) from the MCSA 2004 enrollment cohort that consisted of individuals without dementia (n = 1969). A global cognitive summary score was estimated from the z transformation of the mean of the 4 domain z scores and was used to assess cognitive impairment in our study participants. The baseline global z score and rate of decline were the primary outcomes of interest. Of the 1995 study participants, 1675 had not undergone testing at the time of enrollment into this study, and 320 had previously completed the neuropsychological battery of tests as part of an earlier study. We controlled for the number of times the participant underwent the battery of tests before enrollment into the MCSA using a variable named baseline visit number because practice effects influence the measured outcome variable (global cognition over time). A total of 1675 patients had a baseline visit number of 1 (ie, the first.
time they took the test was at baseline of the study), 34 patients had a baseline visit number of 2 (ie, tested once before baseline), 39 patients had a baseline visit number of 3 (ie, tested twice before baseline), and 247 patients had a baseline visit number of 4 or more.

**Statistical Analysis**

We examined the intellectual enrichment measures and demographic variables as predictors of longitudinal global cognitive \( z \) scores using linear mixed-effects models fit by maximum likelihood. In these models, the coefficients that are not associated with time from baseline or any interactions that include time from baseline estimate shifts in global \( z \) scores, which are consistent over time from baseline. The coefficients associated with time from baseline and any interactions that include time from baseline estimate deviations in the rates of global \( z \) score change. A significant interaction indicates that shifts in global \( z \) scores vary with time rather than remaining constant. The initial model included baseline age (in years), sex, \( APOE4 \) carrier status, time from baseline (in years), baseline visit number, education/occupation score, and mid/late-life cognitive activity. The model also included 6 two-way interactions: baseline age with time from baseline, mid/late-life cognitive score with time from baseline, \( APOE4 \) carrier status with time from baseline, baseline visit number with time from baseline, baseline visit number with education/occupation score, and an interaction of the 2 intellectual enrichment variables. The random intercepts (\( P < .001 \)) and random slopes (\( P < .001 \)) were deemed necessary.

**Results**

The demographic, clinical, and intellectual enrichment variables of the participants without dementia included in this analysis are given in Table 1. The results of the linear mixed-effects models are presented in Table 2. Baseline global \( z \) scores were lower in men, older participants, \( APOE4 \) carriers, those
with lower education/occupation scores, and those with lower mid/late-life cognitive activity. Participants who had previous exposure to the neuropsychological battery of tests performed better, and this effect diminished as time progressed.

Better education/occupation score and mid/late-life cognitive activity were associated with better cognitive performance. Mid/late-life cognitive activity also had a significant interaction with time from baseline ($P = .045$), where the slope of this association increased over time. Qualitatively, the change in slope of this association was small relative to the magnitudes of the shifts in cognition associated with intellectual activity. In addition, a significant interaction was found between the 2 intellectual enrichment variables ($P = .03$). Within the observed follow-up period, higher mid/late-life cognitive activity was associated with higher baseline global $z$ scores, but the association was slightly attenuated as the education/occupation score increased (Figure 1). We separated the plots by sex and APOE4 carrier status because the baseline cognitive performance differed between these groups. Low to high mid/late-life cognitive activity was related to better cognitive performance if the education/occupation score was low, thus shifting the low education/occupation score curve higher. This shift in the cognitive performance was smaller if the education/occupation score was high.

### Table 2. Lifetime Intellectual Enrichment, Baseline Cognition, and Cognitive Decline*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient (SE)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>6.05 (0.29)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Baseline age</td>
<td>−0.07 (0.004)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>−0.18 (0.04)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Time</td>
<td>0.70 (0.06)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Education/occupation score</td>
<td>0.33 (0.03)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mid/late-life cognitive activity</td>
<td>0.17 (0.02)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>APOE4 genotype</td>
<td>−0.20 (0.04)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Baseline visit number</td>
<td>0.05 (0.01)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Baseline age × time</td>
<td>−0.01 (0.001)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mid/late-life cognitive activity × time</td>
<td>0.01 (0.003)</td>
<td>.04</td>
</tr>
<tr>
<td>APOE4 genotype × time</td>
<td>−0.04 (0.01)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Baseline visit number × time</td>
<td>−0.01 (0.002)</td>
<td>.02</td>
</tr>
<tr>
<td>Baseline visit number × education/occupation score</td>
<td>−0.02 (0.01)</td>
<td>.04</td>
</tr>
<tr>
<td>Education/occupation score × mid/late-life cognitive activity</td>
<td>−0.04 (0.02)</td>
<td>.03</td>
</tr>
</tbody>
</table>

* Time refers to time from baseline. The terms without interaction with time indicate the variables that were significantly associated with baseline global cognition, and the terms with interaction with time refer to variables that were significantly associated with annual change in cognition over time.

### Figure 1. Predicted Cognitive Global $z$ Scores as a Function of Time From Baseline for Different Levels of Intellectual Enrichment Measures

The graphs illustrate the interaction between education/occupation score and mid/late-life cognitive activity. Low and high intellectual enrichment were defined by 25th and 75th percentiles.
To estimate the number of additional years remaining cognitively normal that was associated with high intellectual activity, we used the fitted model to predict when these curves cross a threshold of -0.74, which is the 10th percentile of z scores in cognitively normal individuals. We chose this cut point because it was previously used for the operationalization of the National Institute on Aging and the Alzheimer’s Association preclinical criteria for AD to indicate cognitive impairment in cognitively normal individuals.20 This cut point is also close to the mean global z score of -0.8 seen in incident MCIs in the MCSA. Because the predicted times to reach the threshold sometimes exceeded the follow-up in our study, requiring extrapolation, we limited our example of prediction to 80-year-old APOE4 carriers. We had 142 participants with follow-up that extended more than 6 years and 602 participants with follow-up that extended more than 5 years. Predicted times within a few years of these values are likely fairly accurate, whereas times farther away could be subject to increasing inaccuracies from nonlinearity and other unmeasurable factors. Predicted times for 80-year-old APOE4 noncarriers exceeded 10 years and are therefore not given.

Figure 2 illustrates the differences in the predicted times for an 80-year-old APOE4 carrier who never received the neuropsychological battery of tests before baseline to reach a cognitive threshold associated with subtle cognitive impairment depending on sex, education/occupation score, and mid/late-life cognitive activity. We stratified low, medium, and high intellectual enrichment scores by the 25th, 50th, and 75th percentiles. A sample interpretation of the data are as follows: in participants with medium education/occupation scores, engaging in high mid/late-life activity will have an associated later onset of cognitive impairment of 3.3 years for male APOE4 carriers and 3.6 years for female APOE4 carriers. Overall, going from low lifetime intellectual enrichment (low education/occupation score and low mid/late-life cognitive activity) to high lifetime intellectual enrichment (high education/occupation score and high mid/late-life cognitive activity) could delay the onset of cognitive impairment by approximately 8.7 years for male APOE4 carriers and 8.8 years for female APOE4 carriers.

Among all the intellectual enrichment and demographic variables tested, only older age at baseline visit, baseline visit number, mid/late-life cognitive activity, and APOE4 genotype had significant interactions with time from baseline. An interaction was also found between baseline visit number and education/occupation score, indicating that the learning effect that was provided as participants had more exposures to the battery of tests was attenuated in those with higher education/occupation scores. The cognitive z-score trajectories for different baseline ages separated by sex and APOE4 carrier status are illustrated in Figure 3. Older participants had lower global z scores and declined more rapidly after baseline. The steeper decrease in cognitive z scores at older ages would affect the number of years to a cognitive threshold associated with intellectual activity. For example, the constant vertical shift over time in z scores associated with education/occupation score would have a larger horizontal shift (time to threshold) for shallow declines (young ages) than for steep declines (old ages).

Discussion

The major conclusions of the study are that the protective effect of intellectual enrichment is primarily manifested as a relative consistency higher cognitive performance over time. Mid/late-life cognitive activity had an increasing effect over time, but qualitatively the magnitude of this effect relative to the overall shift in cognitive performance was minor. High lifetime intellectual enrichment (75th percentile) may delay the onset of cognitive impairment by approximately 8.7 years in male APOE4 carriers and 8.8 years in female APOE4 carriers compared with a low lifetime intellectual enrichment (25th percentile). The protective effect of mid/late-life cognitive activity on baseline cognitive performance decreases with increasing education/occupation score.

Higher levels of educational, occupational, and cognitive activity are independently associated with a lower risk of dementia consistent with earlier studies.2-10 The contribution of education/occupation score (model coefficient = 0.33) was larger than the contribution of mid/late-life cognitive activity (model coefficient = 0.17). This result is logical and consistent with a previous finding.17 Intellectual development due to educational attainment and occupation exerts an effect during the entire adult lifespan, whereas mid/late-life cognitive activities refer to a more limited portion of an individual’s life.

The negative interaction between mid/late-life cognitive activity and education/occupation score was intriguing. We found that an individual with a low education/occupation score benefited more by engaging in high mid/late-life cognitive activity than an individual with a high educational education/
occupation score. These findings suggest that the effect of late-life cognitive training programs to delay the onset of AD may be reduced in those with high education/occupation scores, which implies the need to account for this interaction when designing preventive trials based on cognitive training. However, a significant protection can be gained from engagement in high mid/late-life cognitive activity irrespective of the individual’s lifelong nonleisure activity through educational attainment and occupation.

The education/occupation score was not associated with the rate of cognitive decline, but mid/late-life cognitive activity was slightly associated with the rate of cognitive decline. However, the effect of mid/late-life cognitive activity on the rate of cognitive decline (model coefficient = 0.01; \( P = .04 \)) was minimal compared with its effect on baseline cognitive performance (model coefficient = 0.17; \( P < .001 \)). The lack of association between education/occupation score and rate of cognitive decline is consistent with an earlier longitudinal study\(^{21}\) that followed up more than 9000 people semiannually for 15 years. The association between mid/late-life cognitive activity and rate of cognitive decline in older individuals without dementia is consistent with earlier studies.\(^{22,23}\) How­ever, the weaker association of mid/late-life cognitive activity with rate of decline compared with its larger effect on baseline cognitive performance is important to consider.\(^{24}\) These results support that the protection provided by lifetime intellectual enrichment is largely driven by its effect on baseline cognitive performance and marginally due to its effect on the rate of cognitive decline.

Among the demographic variables (other than intellectual enrichment variables), older age, male sex, and APOE4 genotype were predictors of lower baseline global z scores; older age and APOE4 genotype were significantly associated with future cognitive decline. The fact that men had lower cognitive performance at baseline is consistent with the literature reporting that men are at higher risk of MCI, particularly at younger ages, because of elevated cardiovascular risk factors.\(^{15}\) Age\(^{25}\) and APOE4 genotype\(^{26,27}\) are the strongest risk factors for sporadic AD. Because the proportion of individuals without dementia who develop dementia increases in older individuals and those with the APOE4 genotype and because the rate of cognitive decline increases as a person moves closer to a dementia diagnosis, it is logical that higher baseline age and APOE genotype may be associated with faster cognitive decline\(^{28}\) and worse performance in a population without dementia. Multivariate analysis enabled us to isolate the significant associations after accounting for all other demographic and intellectual enrichment variables, which strengthen our findings of the association of APOE4 genotype and age with rate of cognitive decline. Although practice effects were not a focus of this study, the finding that greater past exposure to the test resulted in better performance and a reduced effect of educational attainment is consistent with the literature.\(^{18,19}\)

A report\(^{29}\) by the Alzheimer’s Association projected that a treatment breakthrough that can delay the onset of AD by 5 years means reducing the expected number of patients with AD by approximately 43% in the United States by the year 2050. The estimation of the years of protection against cognitive im-

---

**Figure 3. Predicted Cognitive Global z-Score Trajectories for Different Baseline Ages Separated by APOE Carrier Status and Sex**

---

The mean trajectories are shown for participants 75, 85, and 95 years old.
pairment provided by educational attainment and occupation and mid/late-life cognitive activity in a population-based sample in this study (Figure 2) provides guidelines that can be used to understand the public health effect of using intellectual enrichment as a preventive intervention.

For the education/occupation score, we found that the number of years of protection provided by higher educational attainment (keeping cognitive activity constant) is at least 5 years irrespective of sex and APOE4 carrier status. The decrease in the risk of dementia with increasing educational attainment in the past century supports these findings and highlights the importance of intervening early for larger public health effect. Specifically, future reduction in the epidemic of dementia will come from public investments to increase access to education and better jobs for the young adults in our population.

For mid/late-life cognitive activity, although the effect of the education/occupation score was larger than mid/late-life cognitive activity, the years of protection provided by high mid/late-life cognitive activity vs low mid/late-life cognitive activity was at least 3.2 years for APOE4 carriers (7.3 years for non-carriers [data not shown]). Although the optimal intervention time may be intellectual enrichment in early life, there are substantial benefits of using a public health campaign by providing intellectual enrichment to midlife to late-life individuals. In this study, high mid/late-life engagement in cognitively stimulating activities (75% percentile) corresponded to engaging in several cognitively stimulating activities at least 3 times a week during midlife to late life. Examples of these activities include reading books and magazines, playing games and music, participating in artistic activities, participating in crafts, participating in group activities, participating in social activities, and participating in computer activities.

The study has some limitations. First, the results do not preclude the possibility that active lifestyle intervention might prospectively alter the rate of cognitive decline in an active interventional study. However, we did not find evidence of this in our observational, population-based sample in which participants self-reported information about their mid/late-life cognitive activities. Second, when estimating delay in disease onset due to higher levels of enrichment, we assumed that cognitive decline is linear over time, which, although probably true for short intervals (ie, several years), is likely not true for longer periods of observation. However, by limiting estimation of time to only APOE4 carriers, we are not extrapolating much more than the follow-up time. Increasing pathological burden with age may cause an acceleration of the decline. Third, the study results are pertinent to individuals without dementia in the population and may be different in individuals with dementia. Fourth, we did not have measurements for early-life cognitive activities and assumed that educational attainment and occupation are the major components of the intellectual enrichment in early life.

The study also has major strengths. First, the population-based nature of the sample makes the results of the study generalizable and enhances their external validity. Second, the use of principal components aided us in separating 2 major intellectual enrichments in life, educational attainment and occupation and mid/late-life cognitive activities, into 2 uncorrelated variables. Third, the multivariate analysis enabled us to isolate the independent significant associations of the multiple components.

Conclusions

Higher education/occupation scores were associated with higher levels of cognition. Higher levels of mid/late-life cognitive activity were also associated with higher levels of cognition, but the slope of this association slightly increased over time. Lifetime intellectual enrichment might delay the onset of cognitive impairment and be used as a successful preventive intervention to reduce the impending dementia epidemic.


