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Financial and health literacy predict incident AD dementia and AD pathology

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Abstract

Background—Domain specific literacy is a multidimensional construct that requires multiple resources including cognitive and non-cognitive factors.

Objective—We test the hypothesis that domain specific literacy is associated with AD dementia and AD pathology after controlling for cognition.

Methods—Participants were community based older persons who completed a baseline literacy assessment, underwent annual clinical evaluations for up to 8 years and agreed to organ donation after death. Financial and health literacy was measured using 32 questions and cognition was measured using 19 tests. Annual diagnosis of AD dementia followed standard criteria. AD pathology was examined post-mortem by quantifying plaques and tangles. Cox models examined the association of literacy with incident AD dementia. Performance of model prediction for incident AD dementia was assessed using indices for integrated discrimination improvement and continuous net reclassification improvement. Linear regression models examined the independent association of literacy with AD pathology in autopsied participants.

Results—All 805 participants were free of dementia at baseline and 102 (12.7%) developed AD dementia during the follow-up. Lower literacy was associated with higher risk for incident AD dementia ($p < 0.001$), and the association persisted after controlling for cognition (Hazard Ratio=1.50, $p = 0.004$). The model including the literacy measure had better predictive performance than the one with demographics and cognition only. Lower literacy also was associated with higher burden of AD pathology after controlling for cognition ($\beta = 0.07$, $p = 0.035$).

Conclusion—Literacy predicts incident AD dementia and AD pathology in community-dwelling older persons, and the association is independent of traditional measures of cognition.

Keywords

Domain Specific Literacy; Cognition; AD dementia; AD pathology

INTRODUCTION

Domain specific literacy, particularly the ability to access, understand, and utilize financial and health information, has recently been reported to be associated with risk of dementia in old age[1, 2]. On the one hand, domain specific literacy requires cognitive ability; therefore, it is possible that its association with dementia is simply reflective of literacy acting as a surrogate measure for cognition. On the other hand, however, domain specific literacy also requires non-cognitive resources that enable one to seek, access and comprehend health and financial materials, integrate different sources of information, weigh competing alternatives, make inferences, communicate effectively in institutional settings, and engage in lifelong learning as needed to utilize domain specific information and concepts (e.g. financial concepts such as inflation and compound interest) [3–6]. Our prior work demonstrated that domain specific literacy involves a complex interplay among multiple inter-related resources including early life factors (e.g., education, word knowledge/reading), personality-related factors (e.g. decision making style), and cognition[7]. Thus, domain specific literacy is a multidimensional construct that extends well beyond cognition and involves active learning and information seeking to acquire relevant domain specific knowledge, in addition to a flexibility of thought that allows for continual refinement of the knowledge and skills needed to function effectively in modern society. Given the multidimensional nature of domain specific literacy, we hypothesized that the association of literacy with dementia is likely due in part to facets other than cognition; we are not aware of studies that have examined this directly.

Findings from studies examining the impact of literacy on late life health outcomes and its relationship with cognition are mixed. For example, a cross-sectional study reported that the Mini Mental State Examination (MMSE) has high sensitivity and specificity in classifying persons with inadequate literacy[8]. Data from the same cohort showed that literacy was associated with functional health; however, this association was no longer significant after taking cognition into account[9]. In contrast, some studies have reported independent associations of literacy with health outcomes including mortality and performance on everyday health tasks[4, 5, 10]. The extent to which lower literacy is associated with adverse health outcomes above and beyond cognition remains unclear. Disentangling the relationship between literacy, cognition, and Alzheimer's (AD) dementia is even more challenging because the clinical hallmark of AD dementia is cognitive impairment. However, we recently showed that the presence of apolipoprotein E (*APOE*) ϵ 4, the most potent genetic risk factor for late onset AD, has a negative impact on literacy among older persons without dementia and this association is relatively independent of cognition[11]. This new evidence suggests that literacy reflects a domain of behavior that is susceptible to the early deleterious effects of accumulating ϵ 4-related AD pathology (e.g. beta amyloid) that is not fully captured by cognition.

In this study we investigated the independent association of literacy with incident Alzheimer's disease (AD) among community based older persons. We first tested the hypothesis that literacy is associated with incident AD dementia, controlling for demographics and cognitive function. Next, since statistical significance does not necessarily imply improvement in disease risk prediction[12], we evaluated the models with and without the literacy measure to assess the additive utility of literacy in predicting AD dementia. Finally, for subjects who had died and undergone autopsies, we examined the association of literacy with burden of AD pathology to address the neurobiologic basis underlying the relationship between literacy and AD dementia.

MATERIALS AND METHODS

Participants

Data came from an ongoing longitudinal clinical pathologic cohort study of aging and dementia, the Rush Memory and Aging Project (MAP)[13]. The study was approved by the Institutional Review Board of Rush University Medical Center. Participants were enrolled without known dementia, underwent annual clinical evaluations, and agreed to organ donation after death. A written informed consent and an anatomical gift act were obtained from each participant.

MAP started in 1997 and assessment of literacy was introduced in 2010. At the time of this study, 1,903 participants had enrolled and 1,847 had complete baseline evaluation for the parent study. 618 participants had died and 78 had withdrawn before the literacy assessment. We excluded 72 participants who had severe difficulties with language, hearing, vision, understanding, or no longer living in the geographical area. Of the remaining 1,079 eligible participants, 979 (90.7%) participants had completed at least 1 literacy assessment. Primary analysis on incident AD dementia was conducted in 805 participants who were free of dementia at baseline literacy assessment, and had at least 1 follow-up clinical evaluation. The age at analytic baseline on average was 81.5 years (standard deviation [SD]: 7.7, range: 58.8–100.2). 76.7% were females and the mean years of education was 15.3 (SD: 3.0, range: 5–28).

Literacy and Cognitive Assessment

Literacy was measured annually using a battery of 32 questions[14]. The battery was designed to assess domain specific knowledge of financial and health information relevant to older population. The financial literacy component consists of 23 questions, many of which were adapted from the Health and Retirement Survey. These questions assess knowledge on financial concepts as well as ability to perform simple monetary calculation. The health literacy component consists of 9 questions, which assess knowledge on Medicare, leading causes of death in old age, and the ability to follow prescription instructions and understand drug risk. Each of the 32 questions was scored correct or incorrect, and the percent of total correct was calculated separately for financial and health literacy components. A composite score for total literacy was obtained by averaging the two percentages. We focused on the total literacy measure throughout the analyses because the composite score covers both skills and is statistically more appealing distribution-wise. Further, we observed a strong positive

correlation between financial and health literacy components (Pearson's r : 0.44, $p < 0.001$). Total literacy has also been related to various health behaviors and outcomes in older persons[15–21].

Annual cognitive assessment was performed using a battery of 19 tests. The assessment covers a broad range of cognitive processes that are commonly affected by aging, including episodic memory (7 tests), semantic memory (3 tests), working memory (3 tests), perceptual speed (4 tests), and visuospatial ability (2 tests). Raw scores from each test were standardized using baseline mean and standard deviation of the entire cohort, and then averaged to obtain a composite measure of global cognition. Higher scores indicate better cognitive performance. Psychometric properties of these cognitive tests and application of the summary score have been extensively validated in this and other cohorts[22–25]. For the purpose of this study, baseline literacy and cognitive measures were used as predictors in relation to incident AD dementia and subsequently neuropathologic indices of AD.

Clinical Diagnosis of AD Dementia

Annual diagnosis of AD dementia follows standard criteria, and the decision rules implemented in this cohort have been described previously[26]. Briefly, cognitive assessment results were reviewed by neuropsychologists for signs of cognitive impairment, and clinical diagnoses were made by clinicians after reviewing all available data and examination of the participants. The AD diagnosis requires a history of cognitive decline and evidence of impairment in memory and at least one other cognitive domain. Participants who were not cognitively normal but didn't meet clinical criteria for dementia were classified as mild cognitive impairment (MCI)[27].

Neuropathologic indices of AD

All participants in the MAP cohort agreed to organ donation after death. Brain autopsy was performed following a standard procedure[28]. Each brain was cut coronally into 1cm slabs, and slabs designated for diagnosis purpose were fixed in 4% paraformaldehyde. Using modified Bielschowsky silver stain, counts of neuritic plaques, diffuse plaques and neurofibrillary tangles were quantified using tissues from five predetermined brain regions (midfrontal, midtemporal, inferior parietal, entorhinal cortices and hippocampus)[29]. For each of the 3 markers, raw counts from each region were first scaled using region specific standard deviation and then averaged across all the five regions. A composite measure for global AD pathology was obtained by averaging scores for plaques and tangles. Since the measure was right skewed, square root transformation was applied prior to the analysis. For descriptive purpose, a pathologic AD diagnosis was defined by intermediate or high likelihood according to the modified National Institute on Aging (NIA)-Reagan criteria[30].

Statistical Analysis

Pearson correlations and student t-tests described bivariate relationship between demographic, cognitive, and literacy measures at baseline. Cox proportional hazards models examined the associations with incident AD dementia. In these models, the outcome variable was time in years to incident AD dementia (event time). Time was right-censored at death or

last clinical evaluation for participants with no event. We first fit a model including terms for age, sex, education and total literacy, and we repeated by adding a term for cognition.

The model performance in predicting incident AD dementia was assessed using the indices for integrated discrimination improvement (IDI)[12] and continuous net reclassification improvement (NRI)[31]. Briefly, let $p(Z_{(old)};t_0)$ and $p(Z_{(new)};t_0)$ be the risks of AD dementia at time t_0 where $Z_{(old)}$ and $Z_{(new)}$ represent covariate vectors under two working survival models, and let T be the event time. If $Z_{(new)}$ predicts better than $Z_{(old)}$, we expect that $p(Z_{(new)};t_0) > p(Z_{(old)};t_0)$ for event (i.e. $T < t_0$), and $p(Z_{(new)};t_0) < p(Z_{(old)};t_0)$ for nonevent (i.e. $T > t_0$). The continuous NRI statistic can be defined by,

$$P \left\{ p(Z_{(new)};t_0) > p(Z_{(old)};t_0) \mid T < t_0 \right\} - P \left\{ p(Z_{(new)};t_0) > p(Z_{(old)};t_0) \mid T > t_0 \right\}.$$

Similarly, the IDI statistic can be defined as the difference in mean risks for population with and without events

$$E \left\{ p(Z_{(new)};t_0) - p(Z_{(old)};t_0) \mid T < t_0 \right\} - E \left\{ p(Z_{(new)};t_0) - p(Z_{(old)};t_0) \mid T > t_0 \right\}.$$

We elected these 2 statistics over traditional c-statistic because recent literatures suggest that the c-statistic is not sensitive enough to evaluate clinically useful markers[32, 33].

Finally, for participants who had died and undergone brain autopsies (N=173), multivariable linear regression was performed to examine the independent association of total literacy with AD pathology. In these models, square root transformed global AD pathology was the continuous outcome. The covariates of sex and education were not associated with AD pathology in the initial screening; we therefore only controlled for age at death and cognition for model parsimony.

Statistical inference for IDI and NRI was performed using a R package (survIDINRI)[34], and the rest of analyses were programmed using SAS/STAT® software, Version 9.3 of the SAS System for Linux (SAS Institute, Cary, NC).

RESULTS

Baseline characteristics of the study participants are summarized in Table 1. We observed a strong positive correlation between literacy and the cognitive measures (e-Figure 1) where the Pearson correlation for total literacy and global cognition was 0.62 ($p < 0.001$). In addition, older age (Pearson's r : -0.31, $p < 0.001$) and fewer years of education (Pearson's r : 0.37, $p < 0.001$) was correlated with lower literacy. On average, male participants (Mean: 72.3%, SD: 13.5%) had higher total literacy scores compared to female participants (Mean: 66.7%, SD: 14.4%, $p < 0.001$). Approximately 80% (N=642) of the participants had no cognitive impairment (NCI) at the baseline literacy assessment, and the remaining 20% (N=163) had MCI. Consistent with our previous report[16], participants with MCI had lower

total literacy (Mean: 59.7%, SD: 14.8%) than those with NCI (Mean: 70.1%, SD: 13.5%, $p<0.001$).

Association of Literacy with Incident AD Dementia

Participants were followed for an average of 3.7 years (SD: 1.7, range: 1–7 years), during which 102 (12.7%) were diagnosed with AD dementia. As shown in Table 2, in a model adjusted for age, sex and education, lower literacy was associated with higher risk for incident AD dementia (Hazard Ratio [HR]: 2.68, 95% Confidence Interval [CI]: 2.10–3.41, $p<0.001$). After further controlling for global cognition, this association, while attenuated, remained significant (HR: 1.50, 95% CI: 1.14–1.99, $p=0.004$). Figure 1 illustrates cumulative hazards of incident AD dementia for representative participants with different levels of literacy. We repeated the analysis by controlling for five specific cognitive domains, each separately. The domain analyses revealed even stronger associations for total literacy (Table 3).

To further assess the robustness of the finding on literacy and incident AD dementia, we conducted a series of secondary analyses. First, we examined the associations of financial and health literacy components with AD dementia separately. After controlling for demographics and global cognition, lower health literacy was associated with higher risk for AD dementia (HR: 1.43, 95% CI: 1.12–1.82, $p=0.004$). Financial literacy showed a similar trend, but the association did not reach the traditional threshold for statistical significance (HR: 1.21, 95% CI: 0.92–1.59, $p=0.164$).

Next, considering that the association of literacy with incident AD dementia may differ between participants starting with NCI and those with MCI, we repeated our primary Cox proportional hazards model using MCI status as strata and examined whether the literacy association was dependent on MCI status (i.e. strata interaction). The likelihood ratio test showed that the model with terms for strata interactions did not significantly improve the fit ($\chi^2=3.17$, degrees of freedom=5, $p=0.674$); this suggests that the association of literacy with incident AD dementia did not vary by MCI status. Further, in the stratified model without terms for strata interactions, the result for literacy association with incident AD dementia remained essentially the same as in the primary model (HR: 1.53, 95% CI: 1.16–2.03, $p=0.002$), suggesting that the association of literacy with AD was robust against diagnostic status.

Improvement of AD Prediction due to Literacy

To examine whether the literacy measure improved the prediction of AD above and beyond global cognition, we next evaluated the predictive performance of the model with demographics, cognition and literacy in comparison with the model with only demographics and cognition. Figure 2 illustrates the participant specific risk scores estimated from the two models. Notably, for participants diagnosed with AD dementia (left panel), 64% had higher risk scores under the model with literacy measure than the model without, indicating improved sensitivity. For participants without AD dementia (right panel), 55% had lower risk scores under the model with literacy measure, indicating improved specificity. The graphical comparisons of the estimated risk scores suggest an improvement in predictive

performance when the literacy measure was added to the model. Indeed, test statistics showed that the model with total literacy resulted in significant improvement in risk prediction. Specifically, for a 5-year AD risk, the estimated increase in IDI was 0.023 (95% CI: 0.003–0.058, $p=0.018$) and the estimated increase in continuous NRI was 0.245 (95% CI: 0.040–0.364, $p=0.030$).

Consistent with the findings from the association analysis, the models replacing global cognition with individual domains showed stronger results for improvement of risk prediction due to literacy. The estimated increase in IDI ranged from 0.055 to 0.124 and the estimated increase in continuous NRI ranged from 0.298 to 0.434 (all $p<0.01$).

Association of Literacy with AD Pathology

To further confirm the independent relationship between literacy and AD, we leveraged neuropathology data in 173 autopsied participants and examined the association of total literacy with AD pathology. Of this group, 46.5% were NCI, 33.5% had MCI and 20.0% had AD dementia at death. A majority (63.8%) met criteria for a pathologic diagnosis of AD. Baseline total literacy was lower in participants with pathologic AD (Mean: 57.5%, SD: 14.1%) than those without (Mean: 65.0%, SD: 13.2%, $p=0.001$). In a multivariable regression model adjusted for age at death and global cognition, lower total literacy was associated with higher burden of global AD pathology (β : 0.07, Standard error [SE]: 0.03, $p=0.035$). Notably, in this small sample, baseline global cognition explained approximately 7% of the total variance in global AD pathology, and baseline total literacy explained an additional 2% above and beyond cognition.

DISCUSSION

In this study of more than 800 community-based older persons without dementia, we found that domain specific literacy, particularly financial and health literacy, is associated with the risk of incident AD dementia and that this association is independent of cognition. In addition, the literacy measure improved performance in predicting incident AD dementia. Further, we provided evidence that lower literacy is related to a more severe burden of AD pathology even after controlling for cognition. Findings from this study have several important implications for research investigating aging and dementia.

To our knowledge, this is the first study that attempts to disentangle literacy and cognition in relation to AD dementia. Literacy requires cognitive ability, and the two measures have been highly correlated in this and other cohorts[15, 35–37]. An early study proposed that the MMSE test has “considerable face validity” as a surrogate marker for health literacy[8]. This raises a fundamental question as to whether the literacy association with AD dementia is simply reflective of impairment in cognition. Many but not all prior studies suggest that the impact of health literacy on health outcomes is mediated by cognitive abilities[4, 9]. Surprisingly, our data showed that lower literacy predicts incident AD dementia above and beyond cognition. There are at least 2 possible explanations for this finding. First, the literacy measure may represent yet another dimension of cognition that is not captured by traditional cognitive measures. Second, literacy is a complex multidimensional construct that involves not only cognition but also personality related factors and domain specific

knowledge[7]. Attainment of domain-specific knowledge in particular involves interaction with the world, proactive information seeking, and goal-focused behavior. Therefore, it is very possible that the association of literacy with AD is reflective of dysfunction in non-cognitive abilities that are vulnerable to AD. While we suspect the latter may be driving the association of literacy with AD, the distinction may not be critical in practice. In essence, findings from this study indicate that for older persons with comparable cognition (traditionally measured), those who have lower literacy are more likely to develop AD dementia. Thus, literacy measures may help to identify and possibly predict the earliest manifestation of AD. Indeed, our data suggest that literacy improves the risk prediction of AD dementia with higher sensitivity and specificity. Thus, additional attention on constructs that involve more complex abilities such as literacy may facilitate detection of persons at higher risk for dementia or cognitive impairment.

Another innovation of this study is that we are able to directly interrogate the relationship between literacy and AD pathology in postmortem human brain; thus, our results offer new insight into the neurobiologic basis underlying the association of literacy with AD dementia. A popular theory is that literacy may contribute to cognitive reserve which preserves cognitive health against brain insults due to AD and other age-related neuropathology[38]. This reserve theory implies two separate processes. On the one hand, neuropathology accumulates slowly in the aging brain which leads to cognitive impairment and eventually dementia; on the other hand, independent from the disease process, attainment of literacy skills may promote structural resilience or enhance functional connectivity and therefore help to maintain cognition in the face of accumulating disease pathology in the brain. In this study, we found that both literacy and cognition are independently associated with AD pathology. The direct association of literacy with AD pathology works against the reserve theory, but is consistent with our previous report that *APOE*, the best known AD susceptibility gene that is implicated in abnormal beta amyloid deposition and clearance, affects literacy independent of traditional cognitive measures. Taken together, these findings support the hypothesis that AD pathology may impair a broader spectrum of behavior than currently recognized, including domain specific literacy skills in older persons, and low literacy and low cognitive ability likely share common pathologic underpinnings.

This study has many strengths. Data came from a large group of well characterized community based older persons. Participants were followed prospectively with uniform clinical evaluation administered each year. The instrument for cognitive assessment was based on a battery of well-established and psychometrically validated tests which covers a wide range of cognitive processes. Further, the availability of brain autopsy data provides a unique opportunity to better understand the involvement of neuropathology in the complex relationship between literacy, cognition and AD dementia. Limitations are also noted. MAP is a voluntary cohort; therefore the generalizability of our findings awaits replications from other cohorts. Another potential limitation is the relative brevity of our literacy measure. Nonetheless, the measure has been adopted in a number of prior studies and is associated with numerous important health outcomes in old age. Finally, while our findings show that domain specific literacy, on average, predicts AD dementia above and beyond traditional measures of cognition, it is premature to recommend using the current literacy measure as an assessment tool in clinical settings. Future studies are warranted to further validate the utility

of this or another literacy measure as a tool for early identification of AD and to design metrics that are tailored for disease detection at an individual level.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Literacy is associated with incident AD dementia illustrates cumulative hazards of incident AD dementia for representative participants (i.e. females with mean age, education, and global cognition) with different levels of literacy. The red curve represents cumulative hazards for participant with low (10th percentile) total literacy, the black curve for participant with median (50th percentile) total literacy, and the blue curve for participant with high (90th percentile) total literacy.

Figure 2. Literacy improves prediction of incident AD dementia

shows the pair plots of person-specific risk scores (presented as linear predictors) estimated from the model with demographics and global cognition (x-axis) and the model with demographics, global cognition and total literacy. The left panel is for participants with diagnosis of incident AD dementia (events), and the red area of the pie chart represents the proportion of events who had higher risk scores under the model with literacy measure. The right panel is for participants without diagnosis of incident AD dementia (nonevents), and the blue area of the pie chart represents the proportion of nonevents who had lower risk scores under the model with literacy measure.

Table 1

Characteristics of the study participants

Age in Years	81.5, 7.7
Females (N, %)	617, 76.7%
Education in Years	15.3, 3.0
Baseline MCI (N, %)	163, 20.3%
Baseline global cognition	0.2, 0.5
Baseline MMSE (Median, IQR)	29, 27–30
Baseline total literacy	68.0, 14.4
Baseline financial literacy	73.4, 15.8
Baseline health literacy	62.6, 18.2
Length of follow-ups in years	3.7, 1.7

Unless otherwise noted, means and standard deviations (SD) are presented.

IQR: Interquartile range.

Table 2

Associations of literacy with incident AD dementia, controlling for global cognition

	HR (95% CI, <i>p</i>)	HR (95% CI, <i>p</i>)
Age	1.08 (1.04–1.12, <0.001)	1.08 (1.04–1.12, <0.001)
Male sex	1.14 (0.67–1.96, 0.625)	0.79 (0.45–1.37, 0.396)
Education	1.04 (0.97–1.12, 0.254)	1.11 (1.03–1.19, 0.007)
Global cognition	–	11.76 (6.68–20.72, <0.001)
Total literacy	2.68 (2.10–3.41, <0.001)	1.50 (1.14–1.99, 0.004)

HR: Hazard ratio; CI: Confidence interval

Table 3
Associations of total literacy with incident AD dementia, controlling for cognitive domains

	HR (95% CI, <i>p</i>)	HR (95% CI, <i>p</i>)	HR (95% CI, <i>p</i>)	HR (95% CI, <i>p</i>)	HR (95% CI, <i>p</i>)
Age	1.08 (1.04–1.12, <0.001)	1.07 (1.04–1.11, <0.001)	1.08 (1.05–1.12, <0.001)	1.06 (1.03–1.10, <0.001)	1.08 (1.04–1.11, <0.001)
Male sex	0.76 (0.43–1.35, 0.353)	0.79 (0.45–1.39, 0.416)	1.04 (0.61–1.78, 0.890)	0.98 (0.56–1.70, 0.942)	1.17 (0.67–2.04, 0.573)
Education	1.08 (1.00–1.17, 0.050)	1.11 (1.03–1.21, 0.007)	1.07 (0.99–1.15, 0.088)	1.04 (0.97–1.13, 0.254)	1.06 (0.98–1.14, 0.160)
Episodic memory	4.51 (3.23–6.31, <0.001)	–	–	–	–
Semantic memory	–	3.60 (2.42–5.36, <0.001)	–	–	–
Working memory	–	–	1.86 (1.32–2.62, <0.001)	–	–
Perceptual speed	–	–	–	1.59 (1.20–2.32, 0.001)	–
Visuospatial ability	–	–	–	–	1.30 (0.97–1.74, 0.074)
Total literacy	1.99 (1.52–2.61, <0.001)	1.96 (1.50–2.58, <0.001)	2.33 (1.81–3.01, <0.001)	2.32 (1.79–3.02, <0.001)	2.55 (1.98–3.30, <0.001)

HR: Hazard ratio; CI: Confidence interval