

Title: Education and cognitive decline: An integrative analysis of global longitudinal studies of cognitive aging

Running Head: Cognitive reserve and cognitive pathology

Keywords: Cognitive reserve, Social determinants of health, Epidemiology,

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Contributions: SC defined the study scope, wrote the hypotheses, and created the method used herein. DS provided analytic clarity and helped to interpret results. YZ & SM helped to draft the first manuscript. WH supervised data analysis ensured that methods were appropriately described, and that statistical testing was correct. MR provided scientific oversight and helped with interpretation. BL provided scientific oversight and helped with theoretical development. All authors wrote parts of and later edited the manuscript prior to submission.

Title: Education and cognitive decline: An integrative analysis of global longitudinal studies of cognitive aging

Background: The objective of this study was to examine the association between education and incidence of accelerated cognitive decline.

Methods: Secondary analyses of data from the Health and Retirement Study (HRS), a nationally representative prospective cohort study of U.S. residents were conducted ($N=28,417$). Cox proportional hazards survival models were layered on longitudinal mixed-effects modeling to jointly examine healthy cognitive aging and incidence of accelerated cognitive decline consistent with patterns seen in preclinical Alzheimer's disease and related dementias (ADRD). Replication analyses were completed on a database including 62,485 additional respondents from HRS sister-studies. Life-expectancy ratios (LER) and 95% confidence intervals were reported.

Results: This study replicated research showing that education was positively associated with cognition at baseline. Model fit improved using the survival method compared to random-slopes models alone. Analyses of HRS data revealed that higher education was associated with delayed onset of accelerated cognitive decline (LER=1.031 95% C.I. = [1.013-1.015], $P<1E-06$). Replication analyses using data from 14 countries identified similar results.

Conclusions: These results are consistent with cognitive reserve theory, suggesting that education reduces risk of ADRD-pattern cognitive decline. Follow-up work should seek to differentiate specific dementia types involved and consider potential mechanisms.

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Alzheimer's disease and related dementias (ADRD) affect 5.4 million people in the United States and burden millions of caretakers (Alzheimer's Association, 2016). ADRD were recorded as the underlying cause of >110,000 deaths in 2017, making it the fifth most common cause of death (Alzheimer's Association, 2016). ADRD are age-related conditions detected by rapid declines in cognition resulting in impairments to multiple domains of fluid cognition including episodic memory (Richards & Deary, 2005). ADRD are costly and frightening, making them susceptible to substantial under-diagnosis at the population level (Connolly, Gaehl, Martin, Morris, & Purandare, 2011; Douzenis et al., 2010), with some estimates suggesting that 50-80% of all cases are never diagnosed (Prince, Bryce, & Ferri, 2011). Concurrently, due to the extended prodromal period of ADRD, which has been estimated to exceed 10 years (Hall, Lipton, Sliwinski, & Stewart, 2000) during which time there are influences on behaviors and emotions (Feldman et al., 2004), and because interventions in ADRD are increasingly being fielded at a time before wide-scale neurodegeneration has occurred (DeKosky & Marek, 2003), researchers have increasingly focused on preclinical forms of the disease when trying to understand risk factors for progression and development.

Preclinical ADRD can be differentiated from normal cognitive aging by the underlying force and pattern of decline. Cognitive aging is generally characterized by a slow but steady decay in fluid cognition (Salthouse, 2004) resulting from a seemingly unavoidable biological process (Richards & Deary, 2014). However, during the prodromal period, ADRD usually transition to more severe forms of cognitive impairment (Bruscoli & Lovestone, 2004; Jack et al., 2010), specifically showing an acceleration in the rate of decline (Figure 1) (Ichise et al., 2014; Insel et al., 2016). These

accelerated declines are often followed by ADRD-related diagnoses and death (Thorvaldsson et al., 2008; Wilson et al., 2012). It is, therefore, important that risk factors for accelerated decline are interrogated as one marker of ADRD-related disease.

[Figure 1]

Educational attainment has long been linked with increased cognitive function over the lifespan (Ceci, 1996) and with lowered risk of ADRD (Stern et al., 2018). One theory argues that education provides a form of lifelong benefit commonly termed “preserved differentiation” (Bielak, Cherbuin, Bunce, & Anstey, 2014). Specifically, education works to help improve childhood cognition (Deary, Strand, Smith, & Fernandes, 2007; Deary, Whiteman, Starr, Whalley, & Fox, 2004; Richards & Deary, 2014) and, through that, lifetime cognitive ability (De Graaf, De Graaf, & Kraaykamp, 2000; Deary & Johnson, 2010; Deary et al., 2007; Feinstein, 2003; Hatch, Feinstein, Link, Wadsworth, & Richards, 2007; Richards & Sacker, 2011; Tucker-Drob, Rhemtulla, Harden, Turkheimer, & Fask, 2011). Yet, while cognitive performance in childhood is a critical predictor of late-life cognitive health, somewhat paradoxically, education is not generally believed to be associated with the rate of normal cognitive aging (Foverskov et al., 2018; Glymour, Tzourio, & Dufouil, 2012; Gottesman et al., 2014; Muñoz-Terrera, Minett, Brayne, & Matthews, 2014; Piccinin et al., 2013; Zahodne, Stern, & Manly, 2015). Trying to make sense of the lack of finding, recent work suggests that a number of factors including education may play a role in delaying incidence of neuropathology and rates of decline among those with neuropathology (Stern et al., 2018). According to this hypothesis, education delays the onset of symptoms of neuropathology, allowing individuals to compensate with neurodegeneration, until the neuropathology progresses to

a level where cognitive decline can no longer be masked, and cognitive decline is, thereafter, more rapid than would be predicted by a normal aging trajectory. Thus, education does not affect normal aging, but instead changes the point at which accelerated declines due to ADRD occur. Crucial to our ability to test this hypothesis, recent analyses have noted that accelerated declines in cognitive function are fairly common and that they are predictive of incident reports of dementia diagnoses (Clouston, Glymour, & Terrera, 2015). Using the US *Health and Retirement Study* and a series of replication cohorts, this study extended developmental work by Clouston et al. (2015) with the objective being to examine whether education might be independently associated with onset of accelerated cognitive decline in a longitudinal layered survival model that examined, in a generalizable way, population predictors of the onset of ADRD-pattern accelerated declines.

Hypotheses

The study hypotheses were that higher education would be associated with 1) increased cognition at baseline, 2) delayed onset of accelerated cognitive declines, and 3) more rapid accelerated cognitive declines.

Methods

Sample

For this study, data from the Health and Retirement Study (HRS) were analyzed (Sonnegg et al., 2014). The HRS has been collecting cognitive information on a nationally representative sample of older U.S. community-dwelling respondents since 1992 (response rate in 1992 = 81.6%) (Ofstedal, Fisher, & Herzog, 2005). Because the outcome measure was modified for most respondents after the wave in 1994,

observations from the first two waves were excluded from further analyses. Additionally, participants were excluded if they had never completed cognitive assessments or were missing educational data. Since longitudinal evidence for cognitive aging has been observed in midlife, individuals younger than 50 years old at baseline were also excluded (Singh-Manoux et al., 2012). Since the original data collection efforts, the HRS has begun refreshing the sample regularly with new cohorts at regular intervals. Altogether, the dataset contained 207,814 observations made among 37,317 respondents. Applying inclusion/exclusion criteria resulted in reductions to the overall sample size due mostly to age and health exclusion criteria. The final sample included data from 28,417 individuals observed 152,523 times for an average of 5.37 times over 9.08 (SD=6.08) years for a total of 257,926.3 person-years of information.

Outcome

Episodic memory is a key measure of cognitive functioning that is sensitive to both cognitive aging and ADRD (Baddeley, 1992). Notably, prior work has consistently described accelerated rates of cognitive decline occurring approximately 10 years prior to diagnosis (Hall et al., 2000). To measure episodic memory, respondents were first provided with a list of ten words and asked to correctly recall as many as possible, with each correct word scoring one point. After intermediate distraction questions, lasting 10-15 minutes, respondents were again asked to correctly recall all ten words (un-cued delayed recall). The episodic memory index summed both immediate and delayed verbal recall (/20 points).

Proxy Information

The loss of cognitively impaired respondents in longitudinal studies is a common issue, though there is no clear level of cognitive impairment at which dropout is likely to occur (Weir, Faul, & Langa, 2011). When participants or their spouses were re-contacted for follow-up waves, but respondents were unable to complete the surveys because of a functional impairment, family members or caregivers were asked a series of proxy questions about the respondent's wellbeing and cognitive capacity (Jorm, 1994). Prior diagnostic work in the HRS has noted that 93.96% of respondents with proxy responses were cognitively impaired (Crimmins, Kim, Langa, & Weir, 2011). For exclusion purposes, therefore, those who had only proxy responses were excluded from analyses. Sensitivity analyses, completed to examine the influence of proxy responses on analyses, sought to incorporate these data by imputing unobserved data under the assumption that unobserved cognitive data would follow a monotonically decreasing trend.

Time Scale

Unfamiliarity with testing circumstances is believed to improve scores between an individual's first and second cognitive assessment (Goldberg, Harvey, Wesnes, Snyder, & Schneider, 2015), and thus a dichotomous flag was introduced for each individual's first cognitive test. While surveys were planned to occur ever 2-3 years, there can be substantial variability around the date of survey. Years since the first cognitive assessment was used in random slopes analyses to model change over time. Linear trends over time were assumed to occur in pre-accelerated declines. Consistent with research finding cohort-related improvements in cognitive function over time (Lee, Gorsuch, Saklofske, & Patterson, 2008), year of birth was incorporated as a covariate. Age in years, centered at age 50, was included to model the rate of aging. Statistical modeling

further incorporated an accelerated slope measure that enumerated the number of years since an inferentially determined node, as noted below in the statistical methods section.

Social and demographic variables

Educational attainment was measured at baseline assessment as years of formal schooling. Sex and year of birth were self-reported. Self-reported stroke, which Okura, Urban, Mahoney, Jacobsen, and Rodeheffer (2004) reported agreed with medical records 97.8% of the time, was included as a time-varying indicator of VaD.

Replication Data

The HRS has been globally replicated in “sister” studies catalogued by the *Integrative Analysis of Longitudinal Studies on Aging and Dementia* project (www.ialsa.org), and harmonized by the Gateway to Global Aging project (www.g2aging.org). For the purposes of this study, all HRS sister studies were examined for inclusion; studies were excluded if they did not have a third cognitive assessment (TILDA, SAGE, JSTAR, CHARLS, KLOSA, & LASI), or did not contain the ten-word episodic memory task (MHAS, CRELES). Thus, in addition to HRS data, data from ELSA (Steptoe, Breeze, Banks, & Nazroo, 2012), SHARE (Borsch-Supan et al., 2013) databases were analyzed. Harmonized data were accessed, but some differences between studies remained: education was measured categorically in ELSA, necessitating a transition whereby the length of schooling was attributed to individuals based on the average age that students earned educational qualifications. Applying inclusion/exclusion criteria to the replication databases resulted in a final replication study that included 62,485 respondents who were followed prospectively a total of 126,932 times with

measurements occurring between 2-3 years apart on average, in addition to the HRS sample.

Ethics

Secondary data analyses of publicly available deidentified data were deemed to be not human subjects research (CORIHS #498619).

Method

Longitudinal multilevel modeling (Rabe-Hesketh & Skrondal, 2008) was used to fit a layered change-point model (van den Hout, Muñiz-Terrera, & Matthews, 2011) here defined as a piece-wise linear pattern with each segment of the line bent at an individual-specific node (discussed below).

This study modeled latent incidence using a Cox proportional hazards model (Cox & Oakes, 1984) when estimating latent risk of “pathological” ADRD-related accelerated declines. Specifically, we proposed that a random continuous variable (τ) with probability density function could be written $f(t)$ with cumulative density function $F(t)$ and survival function $S(t)$, where $F(t) := \Pr(\tau < t)$. To accomplish this, a second regression was defined that overlapped the base longitudinal model. The second-layer regression relied upon a Cox proportional hazards model to define healthy life expectancy free of cognitive pathology ($\tau_i = e_x$) as a function of the incidence rate (r), specified as a function of participant’s age at entry into the study. The number of years after age 50 was used as the time scale so as to account for selective survival common in studies of older individuals (Lamarca, Alonso, Gomez, & Muñoz, 1998). The cumulative density function was then inferred using maximum likelihood estimation under the assumption that the

outcome, ADRD-pattern accelerated declines, was observed in the data. The layered random-slopes model was specified as noted in equation 1:

$$M_{it} = \beta_0 + \beta_1 C + \beta_2 A_t + \beta_3 V_t + \beta_4 U + \beta_5 E + \beta_6 F + \beta_7 E * A_t + \gamma_{0i} + \gamma_{1i} t + \max\left(t_{it} - \frac{e^{-rA_0}}{r} e^{\delta E}, 0\right) (\phi_0 + \phi_1 E) + \varepsilon_{it} \quad (1)$$

In this model, M refers to *episodic memory*, which differs between individuals (i) and changes over time (t). All models incorporated year of birth (C), age at assessment (A_t), incident stroke (V_t), unfamiliarity (U), education (E), and female sex (F) and random intercepts (γ_{0i}) to model individual differences in baseline capability. Nested models additionally added in random slopes ($\gamma_{1i} t$) (Model 2) to account for heteroskedasticity common in growth models (Rabe-Hesketh & Skrondal, 2008) and an unstructured covariance matrix (Model 3) was used to adjust for correlations between γ_{0i} and γ_{1i} . The layered models additionally incorporated an acceleration term (ϕ_1) (Model 4) defined using health life expectancy estimates determined using a function of the incidence rate (r) and age at study entry (A_0) that is defined when positive and zero otherwise and (Model 5) an interaction term linking education to the rate of decline after onset. Education (E) was, therefore, allowed to predict intercepts (β_5), incidence of accelerated decline (δ), and rate of accelerated decline (ϕ_1). Maximum likelihood estimation was used to fit the second-layer model; the incidence rate was reported. Since healthy life expectancy was the estimand in the second-layer models, results were interpreted as life expectancy ratios (LERs) with 95% confidence intervals and p-values. To examine impact of modeling decisions on fit statistics, each type of adjustment was entered into the model in a nested way. The cumulative incidence function was derived to show the number of respondents estimated to be experiencing onset of accelerated decline.

Replication data were interrogated within countries, and results were pooled across replication samples using the best fitting model (Model 5 above). Random-effects meta-analytic averages were reported, with both I^2 and τ^2 used to measure heterogeneity (IntHout, Ioannidis, & Borm, 2014). Analyses were completed in Stata 15/SE [StataCorp].

Results

Characteristics at baseline (Table 1), revealed a sample of majority-female respondents in their mid-sixties. Educational attainment was 12 years of education, equivalent to a high school degree.

[Table 1]

Nested models were examined (Table 2) beginning with the random intercepts model with covariates (Model 1). This model revealed significant associations, on average, between education and cognitive intercepts, and also identified associations between lower cognitive performance and age, incident major stroke, unfamiliarity on the first wave, and male sex. Models 2-3 showed improved fit statistics with the additional modeling components outlined above. Adjusting for survival parameters (Model 4) predicted that incidence of ADRD-pattern accelerated declines was relatively common (IR=51.03/1,000 person-years, 95% C.I. = [50.19-51.87]). Results further identified an association between education and delayed onset of accelerated decline. Finally, examining education as a predictor of post-onset rate of decline suggested that individuals with higher education had more rapid onset of accelerated decline (Model 5).

[Table 2]

Sensitivity analyses examining associations stratified by sex revealed similar associations among men and women. Furthermore, analyses using imputed scores when proxy responses were available provided substantively similar results.

The resulting cumulative incidence curve (Figure 2) was estimated comparing respondents with a high school degree to those with a university degree. The gap between curves is substantial, suggesting that the average respondent with 16 years of education (equivalent to a university degree) at age 60 could expect to have 2.30 years of extra life expectancy free of cognitive pathology compared to respondents with 12 years of education (equivalent to a high school credential).

[Figure 2]

Replication Data

Examining the relative impact of education on incidence across multiple countries (Figure 3; full results in Table S1) revealed a consistent positive association between increased education and healthy life expectancy across multiple countries. On average, education was significantly associated with delayed onset of ADRD-related accelerated declines, within all but one study and in meta-analyses combining results across studies. Indeed, meta-analytic results revealed a significant association but also revealed a high degree of between-study variability: for example, education appears to have a higher return on investment in the U.S., the Netherlands, Austria, or Sweden than in England.

[Figure 3]

Discussion

The present study posited that Alzheimer's disease or a related dementia (ADRD) might be usefully identified at a point earlier than typically diagnosed by the force and pattern of decline in cognition, and further posited that education may play a role in predicting delayed onset of accelerated cognitive declines. Layered survival modeling was used that relies on predicting the placement of a latent acceleration node determined by an unobserved survival process. The addition of layered change-point survival modeling resulted in improved fit statistics over other common models, including random slopes methods. Supporting a cognitive reserve theoretical framework (Stern, 2012), findings suggested that higher education was associated with both higher baseline functioning and with later onset of accelerated cognitive declines. Analyses identified a latent incidence rate of IR=51.03/1,000 person-years (95% C.I. = [50.19-51.88]) in the HRS that matched closely with replication analyses (IR = 58.16/1,000, 95% C.I. = [51.82-64.49] person-years). Additionally, we found that each year of increased education was attributable with a 3.2% increase in healthy life expectancy free of cognitive pathology. Finally, the rate of the accelerated decline was more rapid for more highly educated individuals, an expected result from an increased capacity to adapt to latent neuropathology. Effect size calculations suggest that an additional four-years of education, consistent with the time commonly spent earning a university degree, may be attributable with increases of 2.30 years in healthy life expectancy at age 60. This represents a first effort to carefully estimate the incidence of preclinical ADRD using accelerated cognitive declines, and therefore represents an important step in better understanding its association with other risk factors for disease.

Interpretation

Richards and Deary (2014) noted that there is, to date, no accepted definition of healthy cognitive aging. This study provided a novel examination of both ADRD-patterns of decline and healthy ones. First, this study uniquely defined healthy aging as occurring before onset of ADRD-related accelerated declines in cognition. Additionally, the current study was the first to implement an acceleration model defining possible ADRD as the observed clinical *acceleration* in the underlying force of cognitive decline occurring later in life. In creating these definitions of cognitive decline, this study provided a novel method with which to interrogate the risk of accelerated declines indicative of possible ADRD. Follow-up work should validate these data by determining whether individuals with different longitudinal patterns of cognitive decline are exhibiting signs of neuropathology.

Previous analyses have suggested that education provides individuals with improved cognitive reserve and access to more socioeconomic resources. While this study sought to establish these relationships, it remains unclear how brain reserve or another exogenous process might independently mediate relationships shown here. Indeed, while more efficient brain functioning allows individuals to function well despite significant pathology, a large body of work has linked diseases such as hypertension and diabetes to cognitive decline. Education may be influential either way, facilitating brain functioning as theorized in cognitive reserve research (Clouston et al., 2012) or improving brain-impacting behaviors such as physical inactivity and smoking (Richards & Deary, 2010). More work is warranted to identify the mechanisms through which education might relieve the risk of cognitive pathology.

This study tested three components of cognitive reserve theory (Stern et al., 2018). First, education was associated with improved cognitive functioning. Second, supporting the view that education might be a preventive factor for ADRD neuropathology despite playing a small role in healthy aging, education was also associated with delayed incidence of accelerated declines. Finally, the rate of the accelerated decline was more rapid for more highly educated individuals in U.S. data, an expected result from an increased capacity to adapt to latent neuropathology, but this result did not replicate in international data. Results therefore successfully and usefully merged three theories of the nature of cognitive aging and may have helped to explain why results diverge across literatures.

Results from this study replicated and extended a prior pilot analysis. Specifically, in their prior analyses (Clouston et al., 2015) used pattern-recognition protocols to lay the foundation for this work. Notably, they determined that acceleration of the sort being investigated here was a good “biomarker” for self-reported incident ADRD diagnoses among individuals with *at least five waves* of completed cognitive assessments. There were numerous limitations to the prior analysis, however. First, they could not reliably determine incidence rates since sample selection excluded more than three-quarters of the HRS sample. This study extends the prior study by proposing a novel theoretical framework and matching method that interprets these theories in a single, reliable, statistical model. As such, the current model represents an enormous gain over prior efforts to model acceleration – it provides an unbiased method with which to examine the onset of accelerated declines.

Limitations and Strengths

While intriguing, results should be interpreted in light of several key limitations. First, use of data from the refresher samples within the HRS may result in sample selection biases, though this has not been previously reported. Additionally, while data were meant to be harmonized, the structure, expectations, and measurement of educational systems differs substantially across countries analyzed. While we believe that years of education may be the most inclusive and comparable metric available, work seeking to instead compare clean categories such as those earning a University degree to those who have a secondary education may prove more comparable. Mild to severe cognitive impairment commonly causes respondents to leave longitudinal surveys such as those evaluated here. Yet, missing data are not always problematic: data that are missing at random (MAR) do not bias results when predictors are included in the model (Rubin, 1976). Base models used EM maximization algorithms, which concurrently model missing data under the MAR assumption (Graham, 2009). Attrition breaks the MAR assumption when linear “random slopes” do not accurately capture post-attrition rates of decline; however, since this study actively modeled acceleration we anticipate results will be more robust in cases where attrition is associated with accelerated rates of decline, explaining why estimates were robust to inclusion of imputed proxy information. However, while sensitivity analyses made a first step in understanding the implications of data that are missing due to accelerated declines in this study, further work is needed to determine the circumstances under which these models fail so that improved methods can be derived to help deal with these data. In this study, we were not able to differentiate subtypes of cognitive pathology. Prior work suggests that accelerated decline is common in patients with ADRD (Ichise et al., 2014; Insel et al., 2016), and has also shown that

accelerated declines are often followed by incident reports of AD RD diagnosis (Clouston et al., 2015). To account for cerebrovascular disease, self-reported incident stroke was used. Self-reported strokes are reliable indicators of diagnosed major-strokes (Okura et al., 2004). However, self-reports are ineffectual when detecting smaller strokes (e.g., transient ischemic attacks, small lacunar infarctions or ministrokes, and small vessel disease) or asymptomatic major strokes. These results suggest that more research is warranted to detect and differentiate unreported strokes. Finally, Cox proportional hazards analyses can be biased when people experience the outcome at the same time. We could not account for ties in the present analysis, and are not able yet to readily detect them, but note that because the outcome is identified inferentially with a high degree of specificity, ties are unlikely. While Cox models are biased by ties, other models including discrete-time survival analyses are not. One area of future research may be to determine strengths and weaknesses of alternative survival model specifications. To facilitate these improvements in layered survival regression, the Stata code utilized to generate these models is provided (Appendix A).

Most work in this field currently examines the extent of cognitive impairment and related functional limitations as key clinical outcomes. The current models were not used to distinguish levels of severity of cognitive impairments. While common in AD RD studies, these methods usually rely on cutoffs to determine cognitive impairment and additional measures to identify functional limitations. Cutoffs are sensitive to overall performance on cognitive exams and, thus, may be biased in cases where risk factors independently influence cognition. For example, poor memory may arise due to low intelligence, unobserved brain injury or cancers, or a number of other factors. If so, then

the results in this study may be more generalizable than those focusing on cutoff-related gradations in severity of underlying cognitive impairment.

Conclusions

Diagnosing dementia in a consistent and reliable way is expensive and difficult. The result is under-diagnosis at the population level (Connolly et al., 2011; Douzenis et al., 2010), with estimates of missed diagnoses exceeding 50-80% of cases (Prince et al., 2011). Noting that research is primarily interested in incidence of ADRD, this study sought to inferentially identify the incidence of ADRD-related pathology by utilizing the onset of accelerated cognitive declines. This analysis was, therefore, more closely aligned with the clinical phenotype of cognitive declines preceding ADRD diagnoses, and also provided results that are consistent with existing research. Together, these results suggest that more work is warranted utilizing this model to replicate known predictors of ADRD, and to expand these predictors to novel indicators. Given the potential importance of understanding timing of accelerated declines, future research is warranted to understand both healthy and pathological forms of cognitive aging.

Figure 1. Differentiating cognitive decline relating to Alzheimer’s disease and related dementia (ADRD) from healthy cognitive aging.

Legend: The solid line indicates clinically diagnostic levels of deficit deemed to be associated with cognitive impairment and dementia. The dotted line represents the expectations for individuals lacking ADRD pathology.

Figure 2. Cumulative incidence of ADRD-related accelerated cognitive declines estimated using posterior model predictions

Legend: Expected results were provided comparing those with 16 years of education (dashed lines - equivalent to a university degree) to those with 12 years of education (solid lines - equivalent to a high school diploma).

Figure 3. Meta-analysis examining association between education and onset of cognitive pathology in international studies of cognitive aging

Legend: Forest plot derived from random-effects meta-analysis showing a fairly consistent pattern in the associations between education and onset of accelerated declines. The diamond shows the estimated meta-analytic average.

Table 1. Sample characteristics, Health & Retirement Study 1992-2012

	Characteristics of analytic sample at first eligible observation		
	<u>Mean</u>	<u>SD</u>	<u>%</u>
Age in years	62.63	9.45	
Episodic Memory	10.06	3.58	
Year of birth	1937.72	13.27	
Education in years	12.24	3.36	
Female Sex			54.45
Any Incident Stroke			8.67

Note: Participants with a history of stroke were excluded from the study. Episodic memory scores range from 0-20. SD: Standard Deviation; %: Percent.

Table 2. Beta coefficients and standard errors jointly estimating cognitive capability, rate of cognitive decline, and onset of accelerated cognitive pathology, Health and Retirement Study 1992-2012

	Model 1		Model 2		Model 3		Model 4		Model 5	
Fixed effects	B	SE	B	SE	B	SE	B	SE	B	SE
Year of birth	-0.042	0.001	-0.049	0.001	-0.044	0.002	-0.031	0.002	-0.031	0.002
Age in years	-0.165	0.001	-0.172	0.002	-0.169	0.002	-0.143	0.002	-0.142	0.002
Incident stroke	-0.593	0.025	-0.582	0.025	-0.561	0.025	-0.478	0.026	-0.476	0.026
Unfamiliarity	-0.870	0.041	-0.855	0.044	-0.858	0.044	-0.791	0.043	-0.784	0.043
Education	0.352	0.004	0.353	0.004	0.352	0.004	0.349	0.004	0.357	0.004
Female sex	0.994	0.028	1.005	0.028	0.997	0.028	1.012	0.028	1.013	0.028
Accelerated Decline							-0.133	0.005	-0.147	0.006
Education x Accelerated Decline									-0.012	0.001
Intercept	9.285	0.024	9.297	0.024	9.297	0.024	9.268	0.024	9.268	0.024
Second Layer										
Education in Years							1.032	0.000	1.032	0.000
Incidence rate intercept							0.051	0.000	0.051	0.001
Random Effects										
Individual Capability (I)	2.003	0.012	1.956	0.012	2.185	0.015	2.177	0.015	2.176	0.015
Individual Slopes (S)			0.080	0.002	0.126	0.002	0.120	0.002	0.119	0.002
Correlation (I, S)					-0.416	0.012	-0.386	0.013	-0.388	0.013
Model Fit										
AIC	741987		741238		740269		739667		739545	
Δ AIC			-749.0		-968.9		-601.7		-121.7	
BIC	741996		741246		740275		739669		739569	
Δ BIC			-751.0		-970.9		-605.7		-99.7	

Note: Model 1 includes covariates and random intercepts; Model 2 added random slopes; while Model 3 accounted for correlation between the two. Model 4 incorporated the survival layer while Model 5 included an interaction variable linking education with accelerated declines. *All estimates were significant at the $P < 1E-06$ level.

Table S1. Replication of work by sample-country including meta-analytic average result and key meta-analytic characteristic

Fixed Effects	England		Austria		Germany		Sweden		Netherlands		Spain		Italy		France	
	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE
Year of birth	0.271	0.018	0.177	0.012	0.177	0.012	0.066	0.018	0.086	0.009	0.209	0.022	0.150	0.017	0.347	0.018
Age in years	0.128	0.018	0.054	0.013	0.055	0.013	-0.068	0.018	-0.032	0.010	0.091	0.023	0.033	0.017	0.229	0.018
Incident stroke	-0.986	0.122	-	-	-	-	-0.523	0.094	-	-	-0.441	0.378	-0.678	0.332	0.078	0.364
Unfamiliarity	0.081	0.060	-0.915	0.070	-0.896	0.068	-0.717	0.349	-0.486	0.059	-0.052	0.116	-0.406	0.095	0.120	0.088
Education in years	0.380	0.014	0.099	0.009	0.100	0.009	0.183	0.013	0.217	0.010	0.184	0.011	0.267	0.011	0.258	0.013
Female Sex	0.629	0.051	0.616	0.078	0.616	0.078	0.931	0.092	0.974	0.072	0.017	0.095	0.399	0.088	0.936	0.096
Accelerated Decline	-0.239	0.021	-0.170	0.020	-0.173	0.020	-0.221	0.048	-0.147	0.031	-0.181	0.048	-0.293	0.069	-0.407	0.045
Education x Accelerated Decline	0.006	0.003	0.006	0.003	0.006	0.003	-0.003	0.010	0.005	0.008	0.010	0.008	0.001	0.014	0.009	0.009
Intercept	11.739	0.161	9.273	0.220	9.239	0.221	9.439	0.107	9.262	0.063	7.460	0.124	7.872	0.083	9.025	0.096
Second Layer																
Education	1.011	0.000	1.046	0.007	1.016	0.003	1.029	0.002	1.033	0.006	1.016	0.003	1.013	0.001	1.016	0.002
Incidence Rate	0.034	0.000	0.110	0.013	0.059	0.006	0.064	0.003	0.061	0.004	0.059	0.005	0.054	0.003	0.059	0.003
Random Effects																
Random Intercepts	SD	SE	SD	SE	SD	SE	SD	SE	SD	SE	SD	SE	SD	SE	SD	SE
Random Slopes	1.465	0.165	2.627	0.480	2.627	0.480	1.920	0.496	2.138	0.449	1.763	0.009	1.814	0.488	2.153	0.509
Corr(I, S)	0.378	0.085	0.336	0.115	0.335	0.115	0.113	0.089	0.026	0.007	0.116	0.095	0.197	0.088	0.176	0.093
	0.018	0.077	-0.483	0.061	-0.483	0.061	-0.100	0.169	-0.321	0.092	-0.394	0.198	-0.279	0.096	-0.225	0.104
Fit																
Pseudo-R ²	0.101		0.054		-1.319		0.071		-0.948		0.074		0.082		0.087	

Table S1 Cont'd. Replication of work by sample-country including meta-analytic average result and key meta-analytic characteristic

Fixed Effects	Denmark		Greece		Switzerland		Belgium		Czech Republic		United States*		Random-Effects Meta-Regression				
	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE	P	I ²	τ ²
Year of birth	0.085	0.020	0.776	0.133	0.267	0.029	0.229	0.016	0.172	0.013	-0.031	0.002	0.191	0.041	0.000	99.4%	0.017
Age in years	-0.029	0.021	0.664	0.133	0.118	0.030	0.094	0.016	0.050	0.013	-0.142	0.002	0.066	0.041	0.127	99.3%	0.016
Incident stroke	-1.213	0.338	0.033	0.579	-0.684	0.662	-0.812	0.295	-		-0.476	0.026	-0.622	0.109	0.000	65.5%	0.052
Unfamiliarity	-0.533	0.116	1.943	0.347	0.291	0.166	-0.211	0.073	-0.228	0.059	-0.784	0.043	-0.229	0.181	0.228	96.5%	0.384
Education in years	0.262	0.019	0.182	0.013	0.065	0.018	0.235	0.013	0.309	0.010	0.357	0.004	0.221	0.025	0.000	99.1%	0.009
Female Sex	1.305	0.117	0.055	0.098	0.865	0.159	0.693	0.088	-0.031	0.021	1.013	0.028	0.641	0.109	0.000	98.9%	0.159
Accelerated Decline	-0.193	0.042	0.090	0.283	-0.272	0.070	-0.362	0.045	-0.426	0.065	-0.147	0.006	-0.236	0.026	0.000	86.2%	0.007
Education x Accelerated Decline	0.000	0.008	0.069	0.050	0.012	0.014	-0.019	0.010	0.675	0.059	-0.012	0.001	0.049	0.046	0.300	94.0%	0.026
Intercept	9.659	0.095	10.124	0.364	9.914	0.148	9.076	0.080	8.622	0.061	9.268	0.024	9.274	0.269	0.000	98.5%	0.988
Second Layer																	
Education	1.016	0.002	1.016	0.002	1.016	0.001	1.016	0.001	1.016	0.001	1.032	0.000	1.019	0.002	0.000	99.7%	0.000
Incidence Rate	0.059	0.004	0.060	0.003	0.059	0.002	0.059	0.001	0.059	0.002	0.051	0.001	0.058	0.003	0.000	98.9%	0.000
Random Effects																	
Random Intercepts	SD	SE	SD	SE	SD	SE	SD	SE	SD	SE	SD	SE	SD	SE	P	I ²	τ ²
Random Slopes	0.142	0.092	0.154	0.083	0.209	0.119	0.220	0.089	0.243	0.124	0.119	0.002	0.077	0.004	0.000	100.0%	0.000
Corr(I, S)	-0.206	0.138	-1.000	0.159	-0.306	0.152	-0.219	0.072	-0.184	0.108	-0.388	0.013	-0.326	0.064	0.000	100.0%	0.057
Fit																	
Pseudo-R ²	0.075		0.103		0.065		0.079		0.059		0.101						

Note: *Replicates results from HRS data shown above.

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