Title: Socioeconomic status and the onset of Alzheimer's-related accelerated cognitive declines

Authors:

Sean Clouston*, PhD, Program in Public Health and Department of Family, Population, and Preventive Medicine, Stony Brook University, Stony Brook, NY, USA

Yun Zhang, MMed, Program in Public Health, Stony Brook University, Stony Brook, NY, USA

***Correspondence to**: Program in Public Health, 101 Nichols Rd., Health Sciences Center, #3-071, Stony Brook University, Stony Brook, NY. Telephone: (631) 444-6593. Email: sean.clouston@stonybrookmedicine.edu. Facsimile: (631) 444-3480.

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Background: Alzheimer's disease and related dementia (ADRD) is a costly disease that is sensitive to avoidable risk factors. Fundamental cause theory (FCT) argues that individuals utilize resources in order to avoid disease. This study examined whether socioeconomic status (SES) was associated with incidence of ADRD-related cognitive declines.

Methods: The outcome was patterns of accelerated declines identified using repeated measures of episodic memory, a critical diagnostic outcome used in ADRD research. Occupational SES was determined using occupational codes from the U.S. census. Analyses used data from a nationally-representative prospective cohort study of U.S. older adults. Respondents were included if they had valid occupational codes, no history of stroke, and valid information on key variables of interest (N=28,417). Longitudinal layered Cox proportional hazards models were used to jointly model cognitive aging and incidence of ADRD-pattern declines in episodic memory. Life-expectancy ratios (LER) and 95% confidence intervals were reported.

Results: The dataset contained 152,523 observations made among 28,417 eligible respondents, 5.80 observations over an average of 8.56 years for a total of 243,240.96 person-years of information. The survival model indicated that that the incidence rate of ADRD-pattern declines was 7.3% per year in this sample. Analyses uniquely revealed that the life expectancy without ADRD-pattern declines was longer for individuals with higher SES (LER=1.043, 95% C.I. = [1.042-1.044]) than among those with lower SES.

Conclusions: This study uniquely examined the association between SES and onset of ADRD using a novel and objective indicator of the incidence of ADRD-related cognitive declines. This is the first study to separately examine SES in relation to healthy cognitive aging

and ADRD-pattern cognitive declines. Analyses supported FCT, but also suggested a key role for theories about preserved differentiation.

Alzheimer's disease and related dementias (ADRD) affect 5.4 million people in the United States and burdens millions of caretakers (Alzheimer's Association 2016). ADRD was recorded as the underlying cause of death in as many as 110,000 deaths in 2017, making it the fifth most common cause of death (Alzheimer's Association 2016). ADRD is a subtype of dementia that accounts for approximately 60-80% of all cases (Alzheimer's Association 2016), the remaining cases are made up of minor to major strokes and other cerebral ischemic attacks (Gorelick et al. 2011). These two disease processes are clinically differentiable by the speed with which declines occurred prior to diagnosis; in contrast to stroke, which results in a rapid and potentially drastic decline over a period of minutes or hours affecting only one or two domains of cognition (Levine et al. 2015), ADRD is usually presaged by years of "accelerated" cognitive declines in episodic memory, working memory, and processing speed that progress more rapidly than normal aging and transition through milder forms of cognitive impairment to clinical levels of dementia (Bruscoli and Lovestone 2004). ADRD-related accelerated cognitive declines are believed to directly relate to increasing presence of neural pathologies including, for example, increasing burden of β-amyloid and tauopathy (Jack et al. 2010). Common risk factors for ADRD include cardiovascular disease, depression, repeated head trauma, and low education though recently, research has begun to identify a number of other risk factors including air pollution, physical activity, and posttraumatic stress disorder among others.

Fundamental Cause theory (FCT), a critical sociomedical theory that is commonly used by social theorists to understand the role of social factors such as education, highlights this schism as a theoretical problem for ADRD research as a whole. FCT, which was developed to help clarify reasons and mechanisms linking social inequalities with disease outcomes (Phelan, Link and Tehranifar 2010), specifies that socioeconomic resources, including knowledge,

money, power, prestige, and beneficial social connections are actively employed by social actors to learn about, and gain timely access to, effective medical preventive and curative technologies (Link et al. 2008). Specifically, these resources are conceptualized as providing protection against the "risk of risks": in a context of unequal access to socioeconomic resources, some individuals are able to effectively avoid risk factors for disease while others are not (Phelan and Link 2005; Phelan et al. 2004).

To date, little is known about how FCT applies to diseases that lack a clear medical or behavioral prevention. Yet, as noted by FCT, resources are often implicated even in diseases without interventions because there are a broad range of mechanisms linking SES to outcomes such as ADRD. Indeed, research thus far has noted that domains of socioeconomic status (SES), including for example access to educational opportunities (Clouston et al. 2012; Mirowsky and Ross 2003), increased investment in cognitive reserve (Stern 2012), and cognitively-demanding occupations (Fisher et al. 2014), have long been considered central to understanding the processes involved in developing ADRD. Yet, the reasons that for associations between SES and ADRD remain unclear.

Suggesting a causal effect, some theorists have proposed that education changes the brain's functioning resulting in what is often termed "cognitive reserve" (Stern 2002), a form of functional resilience resulting in improved cognitive health (Glymour et al. 2008; Stern 2009). Critically, cognitive reserve theory posits that cognitively-demanding experiences and exposures impart different brain capabilities (Clouston et al. 2012; Glymour et al. 2008) and increased functional efficiency (Stern 2012). Together, this change in functioning is believed to improve the brain's ability to reduce brain pathology (Richards and Deary 2014) and maintain healthy functioning despite such pathology (Stern 2012).

In the context of ADRD, FCT additionally suggests that SES impacts the "risk of risks". Thus, SES should be a risk factor for ADRD irrespective of its effect on cognitive reserve because it has been shown to be a robust predictor of a broad range of health indicators (Mirowsky and Ross 2003) that are associated with risk of AD pathology and these inequalities have grown over time (Mackenbach et al. 2015). Mechanisms linking education to health are broad, but education is one of the largest predictors of access to higher status and lower-risk occupations throughout life (Becker 1980; Keeley 2007) which have lasting independent implications for health (Marmot 2004). Education helps to determine the neighborhoods in which individuals reside (Boone-Heinonen et al. 2011; Murray and Stafford 2014), and thus any environmental risk factors including to airborne pollutants (Block and Calderón-Garcidueñas 2009). Additionally, SES inequalities have been shown to be historically and geographically persistent: for example, cardiovascular disease, depression, and physical activity are all known to affect the rate of cognitive decline (Havranek et al. 2015; Huisman et al. 2013; Link and Phelan 1995; Mackenbach et al. 2004; Masters, Hummer and Powers 2012; Mirowsky and Ross 2003). Education also influences the ability to interpret and comply with health recommendations and to manage health outside of the clinic (Weaver et al. 2014) and, when active medical treatments are not available, education promotes healthier lifestyles in general (Christakis and Fowler 2007; Christakis and Fowler 2008; Willems et al. 2005).

Problem Statement

While FCT is critical within the ADRD field, research has been hampered by a disconnect about its impact on cognitive aging more generally. Indeed, a number of studies of cognitive aging have noted that longitudinal associations between education and the rate of cognitive aging are inconsistent or often null (Clouston 2014; Glymour, Tzourio and Dufouil

2012; Gottesman et al. 2014; Muñiz-Terrera et al. 2014; Zahodne, Stern and Manly 2015). Thus, while cognitive aging and ADRD research overlap, the impact of SES appears to differ quite markedly between them. This may be due, in part, to the fact that cognitive aging research emerges from a separate paradigm.

Impact of Cognitive Aging

Cognitive aging is conceptualized as indicating the everyday loss of functioning that is believed to occur at a relatively steady rate over the life span (Salthouse 2009) and affect most domains of "fluid cognition" including episodic and working memory as well as spatio-visual and executive functioning. Such declines are believed to occur relatively consistently with time, at a rate of -3% of a standard deviation per year of life starting as early as age 20 (Salthouse 2004), and are believed to be unavoidable. In this line of research, the impact of SES is often ascribed to a selection effect that may emerge early in life and during educational exposures (Ceci 1996; Manly et al. 2002), or due to genetic effects (Deary 2012; Deary, Johnson and Houlihan 2009). Irrespective of the outcome, aging researchers argue that the impact of early life SES on cognitive aging is mediated by "preserved differentiation" (Bielak et al. 2014). Specifically, cognitive function is defined early in life, in part due to a process of differentiation and contextual exposure to cognitively enhancing factors (De Graaf, De Graaf and Kraaykamp 2000; 2010; Deary et al. 2007; Feinstein 2003; Hatch et al. 2007; 2011; Tucker-Drob et al. 2011). This definition then results in an aging-related degradation that is mirrored later in life (Deary et al. 2007; Deary et al. 2004; Richards and Deary 2014).

Fundamental cause theory, therefore, highlights a core tension in this literature. On the one hand, domains of SES should not be associated with unavoidable and interminable aging processes, outside of an important influence on cognitive development. On the other hand, SES

should be highly active in older age as individuals seek to avoid known risk factors for the disease.

Objective

We propose that in order to understand the difference in role of SES on both cognitive aging and the risk of ADRD, we need to differentiate aging from ADRD-pattern declines. In this study, we propose to utilize layered acceleration modeling in order to examine whether SES is differently associated with onset of ADRD-pattern cognitive declines (Bruscoli and Lovestone 2004).

Hypotheses

Differentiating healthy cognitive aging from ADRD-pattern declines provide us with hypotheses (graphical representations in Figure 1) about the influence of education:

1) Higher SES will be associated with improved cognitive performance.
2) Higher SES will be associated with a later onset of AD pathology.

[Figure 1]

Data

For this study, we utilized data from the Health and Retirement Study (Sonnega et al. 2014), which has been prospectively collecting cognitive information on a nationally representative sample of older U.S. non-institutionalized residents since inception in 1992 (response rate = 81.6%). (Ofstedal, Fisher and Herzog 2005). Participants were excluded if they had never completed cognitive assessments, did not report a main occupation, or were missing education and household income information. Because the first two waves used a different version of the cognitive tests with different score ranges, and because this choice affected the estimated means, data from waves 1 and 2 were excluded. Additionally, since longitudinal

evidence for cognitive aging has been observed only as early as midlife, we excluded individuals younger than 50 years old (Singh-Manoux et al. 2012). In the most recent wave, data were collected on more than 35,000 individuals aged from 50-110. Descriptive analyses were weighted to the U.S. population to maintain representativeness.

Outcome

Episodic memory (/20 points) is a key measure of cognitive functioning that is both sensitive to cognitive aging and AD (Baddeley 1992). To measure episodic memory, respondents were first provided with a list of ten words and asked to correctly recall as many as possible to the interviewer with each correct word scoring one point. After intermediate distraction questions, lasting 10-15 minutes, respondents were again asked to correctly repeat all ten words back to the interviewer with each correct answer being scored as one. Because the first two waves utilized a 20-item word list, total scores for the two waves were divided by two to match later assessment procedures.

Modeling Time

Learning between an individual's first and second cognitive assessment have been reliably detailed (Goldberg et al. 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. Therefore, years since the first cognitive assessment was used in random slopes analyses to model change over time. Consistent with aging research (Salthouse), linear trends over time were assumed to occur in pre-accelerated declines. Consistent with demographic research and on research promoting the role of cohort in improving cognitive function over time (Lee et al. 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

Socioeconomic status (SES) was measured using a class occupational SES ranking tool . Specifically, our measure of SES sought to rank occupations based on the level of education required, and income associated with, that occupation. In this calculation, individuals' education, income, and occupation were necessary. Occupation was gathered and census categories from 1980, the most encompassing and comparable year available for the HRS, was used. Educational attainment was measured at baseline assessment as years of formal schooling. Household income was measured using the income from all potential sources and the natural log-transformed version was used to account for skewed income data. Occupational SES was then scored as the standardized average of both education and income within each occupation and was standardized so that a one-unit increase in SES referred to an increase of one standard deviation (SD).

Respondent sex and date of birth were recorded. Since respondents with cognitive issues sometimes misreport current age, age in years was calculated using date of interview and date of birth. Self-reported stroke was recorded to be used as a confounder. Reported strokes agree with medical records strokes most (AUC=0.99) of the time (Okura et al. 2004).

Method

Base "Random Slopes" Model

Prior methods remark upon the linear acceleration of rates of cognitive decline occurring 5-10 years prior to clinical diagnosis. Longitudinal multilevel modeling (Rabe-Hesketh and Skrondal 2008) was used to first fit a standard random slopes model following equation 1:

$$Y_{it} = \beta_0 + \beta_1 C + \beta_2 L_t + \beta_3 A_t + \beta_4 R + \delta_2 S_t + \gamma_{0i} + \gamma_{1i} t_{it} + \varepsilon_{it} \quad (1)$$

where Y is the outcome, which in this case is objectively-measured indicators of episodic memory. Y varies between individuals (*i*) over time (*t*). Age (A) updates each observation and thus changes over time (t). Models further adjust for year of birth (*C*), race/ethnicity (R), and for learning (*L*). Individuals with a history of stroke were excluded; therefore, in analyses examining stroke, ($\delta_2 S_t$) was added to model incident stroke. Models incorporated random intercepts (γ_{0i}) to model individual capability and random slopes (γ_{1i}) to account for heteroskedasticity common in growth models (Rabe-Hesketh and Skrondal 2008). An unstructured covariance matrix was used to adjust for correlations between γ_{0i} and γ_{1i} that, when negative, might indicate regression to the mean (Liu et al. 2009).

Second Layer Model

As noted above, diagnoses of neurodegenerative diseases including Alzheimer's disease tend to be unobserved. This study therefore utilized a proportional hazards modeling specifications to identify a latent survival curve under the assumption that we were only interested in ADRD-pattern cognitive declines (Cox and Oakes 1984). Specifically, a random continuous variable (*T*), with a cumulative density function *F(t)*, where $F(t) \coloneqq \Pr(T < t)$, was defined as indicating a moment where life expectancy (e_x) could be calculated. The survival curve was then inferentially derived from the latent cognitive trend and incidence rates were estimated following equation 2:

$$Y_{it} = \beta_0 + \beta_1 C + \beta_2 L + \delta_2 S_t + \gamma_{0i} + \vartheta A_t + \gamma_{1i} t_{it} + \rho * max\left(t_{it} - \frac{e^{-rt} e^{\boldsymbol{XB}}}{r}, 0\right) + \varepsilon_{it} \quad (2)$$

Maximum likelihood estimation was used to fit the second-layer model. Variance estimates were derived from Fisher's information matrix (Pawitan 2001). Incidence rates and exponentiated beta-coefficients entitled life expectancy ratios (LER) were reported. Analyses were completed in Stata 15/SE [StataCorp].

Results

The dataset contained 152,523 observations made among 28,417 eligible respondents, 5.80 observations over an average of 8.56 years. The analytic dataset included a total of 243,240.96 person-years of information.

At baseline when weighted to the U.S. population (Table 1), the sample was in their late-fifties when first examined and the population was gender-balanced. A majority of respondents were white, with sizable minorities being Black or Hispanic.

[Table 1]

Multivariable modeling examining cognitive decline were able to identify negative age-related changes in cognition (Model 1). In these models, higher socioeconomic status was associated with better cognitive performance at baseline ($A_{SES} \neq 0$). Analyses also found that incident strokes were attributable with relatively large changes to cognitive functioning. Women outperformed men in these analyses, but individuals from minority backgrounds had lower episodic memory at baseline.

Incorporating analyses of within-person rates of change (Model 2) improved model fit, as evidenced by large negative changes to both AIC and BIC statistics indicating that individual-level random intercepts and slopes were important additions to the model. The random-effects correlation was negative, indicating a potential for regression to the mean over time in these data.

However, the addition of random effects did not change substantive interpretations found in Model 1.

Incorporating the survival layer (Model 3) also improved model fit. Additionally, analyses found that incorporating the survival layer provided a highly significant variable showing an average rate of decline of -0.142 words/year after the onset of expected declines. Accounting for ADRD-pattern declines reduced the effect of age by, on average, 43.85% in this population. The impact of SES actually increased after the integration of the survival model. Finally, the impact of birth cohort inverted suggesting that later-born cohorts have improved episodic memory.

The survival model (Model 3, survival layer) indicated that that the incidence rate of ADRD-pattern declines was 7.3% per year in this sample. These analyses uniquely revealed that the life expectancy without ADRD-pattern declines was longer for individuals with higher SES (LER=1.043, 95% C.I. = [1.042-1.044]) than among those with lower SES.

Discussion

This study sought to examine whether SES was associated with later onset of ADRD-pattern cognitive declines. Layered survival regression was used to determine life expectancy prior to onset of ADRD-pattern declines. These models improved model fit over other methods including random slopes methods. Findings suggested that higher SES was associated with both higher baseline functioning, indicative of preserved differentiation, and later onset of ADRD-pattern cognitive declines indicative of possible latent ADRD neuropathology. On average, these analyses revealed that each SD increase in SES was attributable with a 4.3% increase in healthy life expectancy free of cognitive pathology.

Results from this study showed that models that consider "healthy" aging as occurring separately from ADRD-related pathological aging, which effectively fits both the clinical and psychological theories, as well as the HRS data, better. If healthy aging occurs more slowly for most of life but then accelerates nearer to ADRD onset, then efforts to stem the onset of acceleration would result in substantial improvements to quality of life. In these results, we found that education had a significant influence on delaying onset of ADRD-related accelerated declines and estimated that the effect was 4.3% *per SD of SES*. Nevertheless, these results point to the possibility that increased SES might return as much as two years in improved life expectancy without pathological declines in memory. Future work is needed that seeks to improve our understanding of this effect and its generalizability in other datasets as well as internationally in countries such as the United Kingdom or the Netherlands that have fundamentally different educational systems from the U.S.

In this paper, we have closed the theoretical gap identified by Richards and Deary (2014) by providing a method for usefully differentiating and predicting ADRD-pattern cognitive declines. As noted above, we proposed a shift in our definition of cognitive aging in order to define pathological cognitive as a change in the underlying force of aging. Future theoretical work should seek to determine the extent to which other types of declines might be usefully identified and differentiated from those proposed here.

The proposed definition of ADRD-related pathological declines is not, however, particularly useful without a methodological option with which to validate the utility of such a theory. As such, this paper also provided a novel manner through which to interrogate this question. The method proposed is a first step in what we hope is a fruitful line of research. Follow-up steps include methodological validations of the parameters, novel measures for

determining analytic power. A particularly important follow-up analysis includes the determination of the best functional forms on which to base survival analyses; these analyses relied on well-known parameter-free Cox proportional hazards regression as a first step. However, future work is needed that identifies whether parametric or non-parametric models reflect substantial improvements over the models presented here.

Limitations and Strengths

While exciting, results should be interpreted in light of a number of key limitations. The first is the potential for bias due to missing data. Data that are missing at random (MAR) do not bias results when predictors are included in the model (Rubin 1976) and EM maximization algorithms model missing data under the MAR assumption (Graham 2009). Adjustments potentially accounting for such missingness included random intercepts are incorporated as an individual-specific covariate that models time-invariant individual-level baseline capability, while random slopes model individual rates of change over time. Under the MAR assumption, attrition is problematic only when linear "random slopes" do not accurately capture post-attrition rates of decline (a situation called missing not at random (MNAR)). This study additionally modeled acceleration in individual rates of decline, suggesting that when properly specified, layered survival models account for a larger range of missing data than previously examined.

Results do not rely on diagnoses of ADRD. As a result, it is unclear whether 1) respondents have neuropathology needed for to meet diagnostic criteria in research situations (Knopman et al. 2018), or 2) whether they experience significant limitations needed to meet clinical diagnostic criteria for dementia (McKhann et al. 2011). However, while this is a significant limitation, it may also be a critical strength since more than 50% of all dementias remain undiagnosed upon death. It is likely that those dementias that go undiagnosed are

different in a key way than those that are diagnosed. Furthermore, despite the fact that evidence of decline is a core indicator for diagnosis of mild cognitive impairment and dementia, diagnoses rely on static cutoffs rather than dynamic vectors of change thereby increasing the chance for bias. Since accelerated declines predict incident dementia diagnoses (Clouston, Glymour and Terrera 2015), we are optimistic that the characterization highlighted in this model is an objective, but as of yet unobserved, marker of Alzheimer's disease and related dementias.

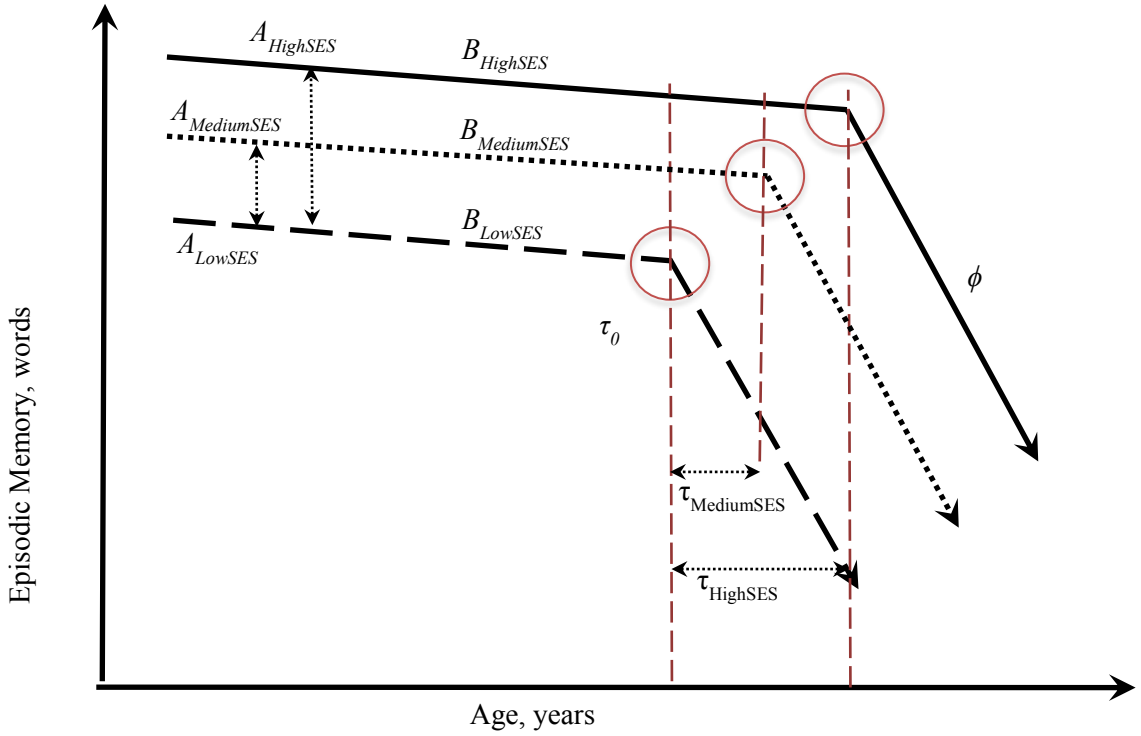
In this study we did not seek to differentiate subtypes of ADRD, in part because relevant criteria for longitudinal models do not exist for doing so. Also, these models are targeted at improving detection of early declines rather than identification of ADRD-related impairments *per se*.

The current models were not used to distinguish levels of severity of cognitive impairment. Yet, research in Alzheimer's disease is increasingly utilizing common cut-offs on screening exams (such as the Mini Mental State Examination or the Montreal Cognitive Assessment) in multistate modeling framework (Jackson et al. 2003). These methods rely on cutoffs to determine cognitive impairment, potentially conflating cognitive capability with cognitive decline and impairment. As such, inequalities under that rubric may be attributable to differences in capability rather than mechanisms relating to social inequality, limiting their applicability and biasing interpretation. Research into the distribution of B-amyloid have found that upon the intrusion of the molecule into the brain, perfusion throughout the brain occurs at a consistent pace – mirroring the results found in this study. If so, then the results in this study may provide more generalizable results than those focusing instead on cutoff-related gradations in severity.

Conclusions

Diagnosing dementia in a consistent and reliable way is expensive and difficult. The result is underdiagnosis at the population level (Connolly et al. 2011; Douzenis et al. 2010), with estimates of missed diagnoses exceeding 50-80% of cases (Prince, Bryce and Ferri 2011). Noting that research is primarily interested in incidence of ADRD, this study sought to determine whether SES was associated with incidence of ADRD-pattern cognitive declines. This analysis was, therefore, more closely aligned with longitudinal and clinical theories about the shape of cognitive decline, and also provided results that are consistent with work examining cognitive reserve in the clinic. More work is warranted utilizing this model to replicate known predictors of Alzheimer's disease including, for example, apolipoprotein allele possession. 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. Graphical hypotheses linking higher socioeconomic status with later onset of accelerated declines in episodic memory indicative of latent Alzheimer's disease or related dementia



Note: Graphs show expected trajectories for low, middle, and high SES subgroups. Individuals with higher socioeconomic status should experience delayed onset of ADRD-related declines, as indicated by a later estimated accelerated decline.

Table 1. Sample characteristics weighted to the U.S. population, Health & Retirement Study 1996-2014

Characteristic	Mean	Standard Deviation
Episodic memory, words	10.39	3.47
Year of birth	1941.21	13.22
Age, years	57.06	9.26
Socioeconomic status, standard deviations	0.25	1.05
	%	
Female	50.57	
White	77.01	
Black	11.15	
Hispanic	8.57	
Other	3.27	

Note: Socioeconomic status indicates the average education and household income of people in the same jobs. Episodic memory ranges from 0-20. All measures are estimated at baseline.

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 1996-2014

	Model 1			Model 2			Model 3		
Characteristics	B	SE	P	B	SE	P	B	SE	P
Year of birth	-0.008	0.002	<1E-06	-0.010	0.002	<1E-06	0.013	0.002	<1E-06
Age in years	-0.157	0.001	<1E-06	-0.160	0.002	<1E-06	-0.106	0.002	<1E-06
Incident stroke	-0.896	0.042	<1E-06	-0.876	0.044	<1E-06	-0.766	0.044	<1E-06
Unfamiliarity	-0.562	0.026	<1E-06	-0.535	0.025	<1E-06	-0.370	0.026	<1E-06
Socioeconomic status	0.169	0.010	<1E-06	0.195	0.011	<1E-06	0.230	0.011	<1E-06
Female sex	1.000	0.029	<1E-06	1.009	0.030	<1E-06	1.026	0.030	<1E-06
White	Reference			Reference			Reference		
Black	-1.862	0.040	<1E-06	-1.855	0.040	<1E-06	-1.850	0.040	<1E-06
Hispanic	-1.177	0.093	<1E-06	-1.178	0.094	<1E-06	-1.197	0.094	<1E-06
Other	-1.860	0.048	<1E-06	-1.856	0.049	<1E-06	-1.823	0.049	<1E-06
Accelerated Decline							-0.142	0.004	<1E-06
Intercept	9.541	0.026		9.544	0.026		9.567	0.026	
Random Effects				ES	SE		ES	SE	
Individual Slopes				0.119	0.002	<1E-06	0.109	0.002	<1E-06
Individual Capability				2.383	0.017	<1E-06	2.359	0.017	<1E-06
Correlation (I, S)				-0.471			-0.452		
Incidence Layer							ES	SE	P
Socioeconomic status							0.043	0.000	<1E-06
Incidence rate							0.073	0.002	<1E-06
Model Fit									
AIC	744813			743274			742077		
ΔAIC				-1539			-1197		
BIC	744879			743350			742164		
ΔBIC				-1529			-1186		

Note: All estimates were significant at the P<1E-06 level, so significance was not marked.

Model 1 includes fixed effects predictors and random intercepts; Model 2 incorporated random

intercepts, slopes, and correlations between intercepts and slopes; Model 3 added the layered survival model.

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