Life-course predictors of later-life cognitive impairment: disentangling educational attainment, labor force participation, and social engagement

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Abstract

In 2018, an estimated 5.7 million Americans have Alzheimer's disease—the incurable disease that is the most common cause of dementia and the sixth leading cause of death in the U.S. Like many conditions, dementia risk is influenced by a combination of social, behavioral, and biological factors. There is strong evidence that there are independent and interactive effects of life-course disadvantage (race/ethnicity, childhood SES, education, occupation) on later-life fluid cognition, net of time-varying confounders like smoking and comorbidities (Hale unpublished). The next step, and focus, of this project is to examine labor force participation and social engagement as intervention scenarios. To what extent can the association between disadvantage (especially race/ethnicity and lower education) and later-life cognitive function be mitigated by the time-varying measures of labor force participation and social engagement? Are either or both effective and feasible later-life intervention points? We will employ recent methodological innovations in counterfactual causal inference to disentangle social risk factors for later-life cognitive impairment. We will use data from the U.S. Health and Retirement Survey (1998-2014) to model the association between fluid cognitive function and life-course predictors. Using the parametric g-formula, we can interpret causal effects, adjust for intermediate confounders, and separate conditional and population-averaged effects. Through this more flexible modeling strategy, we expect to offer insights into mechanisms that create the pathway to dementia, knowledge that is critical to prevention and intervention efforts.

Keywords: cognitive impairment, dementia, life course, health disparities, g-formula

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Introduction

In 2018, an estimated 5.7 million Americans have Alzheimer's disease (AD)—the incurable disease that is the most common cause of dementia and the sixth leading cause of death in the U.S. AD is the underlying cause of death for more than one-third of those over age 75, and deaths attributable to AD rose by two-thirds between 2000 and 2013 (James et al. 2014; McGinnis 2015). Dementia is also one of the most expensive diseases, as it requires high levels of care, often for years (Hurd et al. 2015). A person aged 70-80 with AD averages four years of life severely impaired; for those who survive to age 80 with AD, 75% have nursing home placements, compared with only 4% of those without AD (Arrighi et al. 2010). As a result of these care needs, Medicare and Medicaid payments for those with dementia are, respectively, three and 23 times higher per beneficiary than for those without dementia (Alzheimer's Association 2018). In 2018, health care, long-term care, and hospice for elders over age 65 years with dementia is estimated to cost Americans $277 billion (Alzheimer's Association 2018). Furthermore, because of population aging and lengthening life expectancies, U.S. prevalence of dementia is anticipated to more than double and health care costs to reach $1 trillion annually by 2050 (Hebert et al. 2013). These costs and forecasts, combined with the incurability of AD, have driven research to identify modifiable risk factors.

Evidence suggests that multiple disadvantages accumulate and interact over the life course to affect cognitive health (Glymour and Manly 2008; Hale 2017), but quantifying the contributions of social, behavioral, and health risk factors has proved elusive. Traditional regression analysis has been unable to identify the salience of life-course risk factors because of a set of interrelated methodological barriers, variously expressed as longitudinal interdependence, intermediate confounding, time-varying mediators, as well as the challenges of analyzing non-linear mediators or outcomes (Bijlsma, Tarkiainen, et al. 2017; Bijlsma and Wilson 2017; Daniel et al. 2013; De Stavola et al. 2015; Robins 1986). To overcome these barriers, we will employ recent methodological innovations in counterfactual causal inference. The parametric g-formula will enable us to examine the interdependent influences of life course processes – such as race/ethnicity, early-life SES, education, labor force participation, and social engagement – on

multiple measures of cognitive impairment. We will use multiple sensitivity analyses, such as detecting bias due to unobserved heterogeneity (VanderWeele 2010, 2013). This will be the first analysis of cognitive impairment that analyzes life course processes using advanced counterfactual modeling. These methods significantly decrease bias caused by applying standard regression models in cases where there is longitudinal interdependence. This is a significant contribution because these models will allow us to disentangle mechanisms across the life course and examine feasible policy interventions (Bijlsma, Daniel, et al. 2017; Daniel et al. 2013).

Our research question is: What are the direct and indirect effects of educational attainment, labor force participation, and social engagement on later-life cognitive function? Accurately assessing life course risk factors is fundamental to making appropriate prevention and intervention recommendations for this incurable disease.

Background

A lack of theorizing about how life-course factors are dynamically interconnected means dementia research often focuses exclusively on single characteristics, such as education or race/ethnicity, not accounting for the ways multiple disadvantages interact to affect cognitive function (Cho et al. 2013; Collins 2015; Diez Roux 2012; Weber and Parra-Medina 2003). Based on the sociological theories of cumulative disadvantage and intersectionality, we will study how social factors interact and accumulate over the life course, exposing individuals to a particular balance of benefit and risk and leading to disparities in later-life (Bauer 2014; Collins 2015; Diez Roux 2012; Montez and Hayward 2014; O'Rand and Hamil-Luker 2005; Schafer et al. 2013; Warner and Brown 2011; Weber and Parra-Medina 2003). More specifically to aging, the weathering hypothesis proposes that socially-disadvantaged individuals experience accelerated aging due to carrying higher "allostatic load"—the level of physiological dysregulation caused by chronic or recurring stressors (Geronimus et al. 2015; Geronimus and Korenman 1992; Juster et al. 2010; Seeman et al. 2010).

There is some evidence that people with more disadvantages experience worse cognitive function (Glymour and Manly 2008; Hale 2017; K. M. Mehta and Yeo 2017; Zhang et al. 2016). For example, Latinx and Blacks have 1.5 to three times higher risk of AD, as well as experiencing cognitive impairment at younger ages than Whites and spending a greater share of their life expectancy cognitively impaired (Garcia et al. 2018; Reuser et al. 2011; Zhang et al.

2016). It is not clear to what extent these disparities are driven by racially-patterned social factors, e.g., racial/ethnic disparities in education, comorbidities, or labor force participation (Fargo et al. 2009; Hale 2017; Kuh et al. 2003; Reskin 2012; Zhang et al. 2016). Neither is it clear whether those with multiple disadvantages experience faster cognitive decline.

Another challenge researchers have faced in trying to identify risk factors for dementia is that standard regression models can be thwarted by dynamic two-way pathways among, e.g., SES, labor force participation, social connectedness, and comorbidities, as well as the presence of non-linear mediators and outcomes (Adler et al. 2012; Bijlsma, Tarkiainen, et al. 2017; Jones et al. 2011; N. Mehta and Preston 2016). In fact, most longitudinal approaches are not appropriate for studying the direct and indirect effects of multiple time-varying determinants, as we propose to do (Bijlsma and Wilson 2017). Standard regression analysis is often used for life course research where models are treated as nested, and variables are added to the model sequentially in order of experience. For example, the base model might include race/ethnicity and sex, and the next model will include education, and then occupation, wealth, etc. Much epidemiological research has shown that this modeling strategy is inadequate when there are: 1) dynamic two-way pathways among these factors (e.g., depression ←→ employment (Bijlsma, Tarkiainen, et al. 2017)), 2) interactions between exposure(s) and mediator(s) (e.g., educational effects on cognition differ by race/ethnicity (Hale 2017)) or 3) mediator-outcome confounding (VanderWeele and Robinson 2015; Vanderweele and Tchetgen Tchetgen 2017).

The parametric g-formula, in contrast, offers transparency with regard to assumptions about observed and unobserved associations, applies flexible parametric models (e.g., variables can be modelled following any functional form, including interactions), and makes possible analysis of time-varying processes, while allowing for selection, reverse causality, and mediation (Bijlsma and Wilson 2017; Keil et al. 2014; Vanderweele and Tchetgen Tchetgen 2017; Wang and Arah 2015). These models also enable moving from modeling individuals to estimating population-averaged effects, important from a demographic or public health policy perspective (Bijlsma, Tarkiainen, et al. 2017; Lin et al. 2017; VanderWeele and Tchetgen Tchetgen 2017; Wang and Arah 2015). Therefore, an important use of mediation analyses is in simulating alternative scenarios, thereby offering policy-makers estimates of intervention effects (Bijlsma, Tarkiainen, et al. 2017).

Exploiting the rich, longitudinal data in the population-based, nationally-representative Health and Retirement Study, we will use the g-formula to model life course processes to identify pathways to dementia (Bijlsma, Tarkiainen, et al. 2017; Daniel et al. 2013; VanderWeele and Tchetgen Tchetgen 2017). Specifically, the objective of this paper is to identify 1) how educational attainment, labor force participation, and social connectedness interact to affect later-life cognitive function, net of childhood SES, health behaviors, and comorbidities and 2) what interventions (e.g., labor force participation and/or social engagement) predict the greatest reduction in dementia risk. For example, how much would dementia incidence be reduced by delaying retirement versus increasing social engagement, accounting for their interdependence?

Methods

Dataset

The **Health and Retirement Study (HRS)** (1992-ongoing; n≈30,000) is a longitudinal, biennial survey of U.S. residents (age 50+ spouses) that includes sociodemographic and health measures. The HRS uses a version of the Telephone Interview for Cognitive Status (TICS) that was specifically modified to be sensitive to pathological cognitive decline and to minimize ceiling effects.(Fong et al. 2009; Karlamangla et al. 2009) Important for our analyses, it has retrospective data on early-life environment, such as early-life health, parents' education, father's economic contribution to the family, and whether the family had to move or request aid due to financial hardship.

Key Study Measures

Cognitive Function. We extract a subset of questions from the HRS TICS interviews that represent fluid intelligence—a composite of cognitive domains thought to reflect neurophysiological health (e.g., short-term acquisition and retrieval) (Ghisletta et al. 2012; Ghisletta and Lindenberger 2004; Horn 1982). These measures are less correlated with education and cultural factors than crystallized intelligence (e.g., vocabulary) (Akshoomoff et al. 2013; Ghisletta et al. 2012). We have generated standardized scores for immediate and delayed word recall, "serial 7s" (counting backward from 100 by sevens), and counting backward from twenty (correct first time, correct second time, or incorrect). We averaged the four scores to generate cognitive function (Hale 2017).

Demographic factors. HRS reports a binary sex variable. Race/Ethnicity is Non-Hispanic White, African American/Black Hispanic, Non-Black Hispanic, and "Other." Age is exact age in years. We developed a categorical measure for practice effects (1^{st}, 2^{nd}, 3^{rd}-6^{th}, 7^{th}+) (Goldberg et al. 2015; Rabbitt et al. 2004; Vivot et al. 2016). We generated *Early-SES* from a set of HRS measures to form a more comprehensive picture of the early-life environment that includes self-reported early-SES, childhood health, parents' education, whether the family experienced economic hardship, and father's economic contribution to the family. We use categorical variables for *Educational Attainment* (less than high school, high school, some college, Associate degree or higher), *Occupation* (manual, service, farm/forestry/fish, professional, not in labor force), and *Later-Life Wealth* ($0-49,999K, $50-199,999K, $200-499,999K, $500K+). *Labor Force Participation* (LFP) is defined as full-time, part-time, unemployed, disabled, retired.

Behavioral factors and comorbidities. We also consider *Partnership Status*, *Exercising*, *Smoker* (never, former, current), *Alcohol Use*, body mass index (*BMI)*, and depressive symptoms (Center for Epidemiological Studies-Depression, CES-D). We will use both *Socializing with Neighbors* and an HRS module that includes participation in volunteer work, religious services, and other organized activities to build a "*Social Engagement*" measure. HRS also contains time-varying information on *Comorbidities*, including whether this year a respondent has been diagnosed with stroke, diabetes, heart condition, and/or high blood pressure/hypertension.

Analysis

We will model the association between cognitive function, as defined above, and life-course predictors, including early-SES, educational attainment, occupation, health behaviors, labor force participation, and social engagement. The parametric g-formula allows us to interpret causal effects, separate conditional and population-averaged effects, and adjust for intermediate confounders. We will contrast natural course and intervention scenarios for educational attainment, labor force participation, and social engagement.

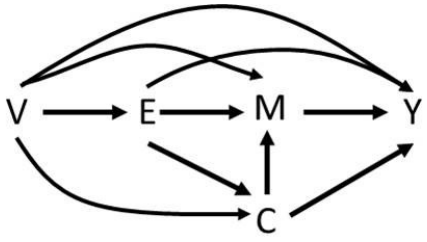

Figure 1 Conceptual diagram of life course pathway with intermediate confounding (VanderWeele and Tchetgen Tchetgen 2017)

In Figure 1, *V* represents the time-invariant baseline variables (e.g., race/ethnicity, sex, childhood SES); *E* is the time-invariant exposure of interest (e.g., education); *M* represents the

time-invariant and -varying mediators (e.g., labor force participation); and *C* represents mediator-outcome confounders that are also associated with the exposure *E* (e.g., comorbidities) (VanderWeele and Tchetgen Tchetgen 2017).

There are four steps to implementing this method. First, we will construct a causal directed acyclic graph (DAG), a diagram that portrays the interrelationships among the variables we will model. Second, using the DAG as guidance, we will estimate a series of multivariate models using the HRS data that model the mediators as outcomes, e.g., wherein we model educational attainment as a function of race/ethnicity and early-SES. Time-varying variables will be allowed to be affected by all control variables and, to limit assumptions on causality within a calendar year, by all time-varying variables in the previous year. Categorical variables will be modeled with sets of logistic regressions, operating together as a multinomial logistic regression. Third, we will choose mediation definitions and corresponding intervention scenarios (e.g., what happens if people retire later?). Fourth, we will use the parameters from this series of models to simulate the outcome of the interrelated processes described above. These four steps provide us with an estimation of the total effects of our predictors under alternative scenarios, a decomposition of the total effect into direct and indirect effects, and some sensitivity analyses of, for example, unobserved confounding (Bijlsma and Wilson 2017; VanderWeele 2013). The effect of exposures on mediating mechanisms and on cognitive function may depend on other social factors, such as race/ethnicity, so using interaction terms and subgroup analysis, we will also measure differences by subpopulation (Bijlsma, Tarkiainen, et al. 2017). By contrasting natural course and intervention scenarios, we will estimate the population-averaged impact of policy-relevant interventions (Taubman et al. 2009).

Preliminary results

Preliminary results suggest there are independent and interactive effects of life-course disadvantage on later-life fluid cognition, net of time-varying confounders like smoking, socializing, and exercise. For example, below we compare trajectories of cognitive decline from just one intervention scenario with the natural course. The natural course scenario means that life course processes continue as empirically observed. Because of dramatic social inequalities in the U.S., Black men would likely have lower educational attainment, more comorbidities, etc. than their White counterparts. In the intervention scenario, we compare this natural course with the

counterfactual that everyone, Blacks and Whites, has a college degree. In each of the panels in Figure 2, the y-axis is standardized fluid cognition, the x-axis is age, the lower line (blue) shows the population-averaged cognitive decline, and the higher line (red) shows the level and rate of decline if everyone in the population had a college degree. The dashed lines are 95% bootstrap confidence intervals.

As expected, an educational intervention would raise the level of cognitive function. Importantly, in that intervention scenario, the rate of decline is not quite as steep for the whole population. In examining disparities between Black and White men (the center and right panels), it is clear that in the natural course scenario (blue), Black men decline faster than White men. However, an intervention on education (red): 1) would significantly reduce the disparity in the level of cognitive function between Blacks with college (red) and the population-averaged White men (blue), 2) would significantly equalize rate of decline, but 3) if Whites and Blacks both had the intervention (both red), racial disparities would persist. In other words, educational attainment and our controls only partially explain racial disparities.

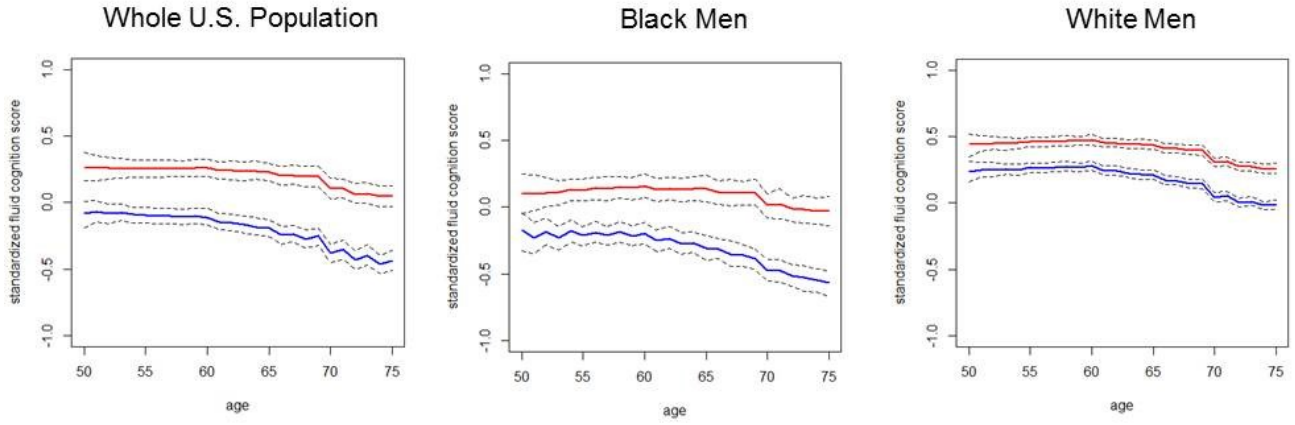

Figure 2 Natural course and intervention scenarios for trajectories of cognitive decline, net of early-SES, occupation, wealth, health behaviors, and comorbidities (blue = natural course; red = intervention wherein everyone has college degree)

Our next step in analysis is to explore interventions on labor force participation and social engagement, which is the primary focus of this paper we propose to present at PAA.

Discussion

With longer life expectancies and population aging, pathological cognitive decline will exact an increasing toll on families and health care systems. Alzheimer's disease (AD), the neuropathology causing most dementia, is particularly concerning as there is no treatment and no cure. Interdependent life-course processes influence cognitive function in terms of "achieved" cognition, as well as rate of decline. However, we do not know which exposures are the most significant, during which sensitive periods, how disadvantages may accumulate over the life course, or what interventions will have the greatest impact.

This shortcoming is related both to a lack of theorizing about how life-course factors are dynamically interconnected and a related methodological barrier. Most dementia research does not analyze how multiple risk factors over the life course interact to affect cognitive impairment. Furthermore, using standard regression methods, estimates of the association between exposure (e.g., education) and outcome are biased when intermediate confounders are present or when there are issues of reverse causality (VanderWeele and Robinson 2015). For example, multilevel logistic regression models show no or a counterintuitive negative correlation between early-SES and cognition once later-life factors are controlled, which is likely related to confounders (Hale 2017).

We will use the g-formula to consider time-variant and invariant risk exposures, intermediate confounders, and their reciprocal relationships with cognitive function (Bijlsma, Daniel, et al. 2017; Bijlsma, Tarkiainen, et al. 2017; Lin et al. 2017; VanderWeele and Tchetgen Tchetgen 2017; Wang and Arah 2015). Our more flexible modeling strategy should allow us to identify salient risk factors and key points of intervention (Imai et al. 2010).

This work has significant implications. By using advanced counterfactual modeling, we will be able estimate population-averaged effects of educational attainment, labor force participation, and social engagement, as well as which interventions are expected to result in the most significant decrease in dementia risk and burden, and at which critical periods in the life course.

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