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"Cognitive decline before the onset of dementia: A large population study spanning 20 years"

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This paper revisits questions addressed by Amieva, et al. (2014) that studied the role of Cognitive Reserve (CR) on cognitive decline before dementia diagnosis using 20 years of longitudinal data on a sample of individuals from Bordeaux, France in which education was the primary proxy for CR which is regarded as an unobserved latent variable. This paper addresses these questions using nationally representative longitudinal data that contains measures of cognitive status from the Health and Retirement Study (HRS) that span 20 years in ten waves of HRS from 1998 to 2018. However, the main contribution of the paper lies in theoretical, methodological and substantive innovation.

First, we propose to quantify the theory of Cognitive Reserve by showing that a baseline measure of cognitive performance in HRS provides is a sufficient statistic for cumulative effects, on average, of individual life histories from conception including genetic inheritance and education through late mid-life when individuals enter the HRS. This quantification is scientifically significant for several reasons. It provides a metric by which CR differences can be measured in cross-sections of individuals and changes in CR over time can be measured longitudinally.

Second, we specify a quasi-experimental case-control model. We treat the onset and trajectory of cognition of individuals prior to dementia as an event study in which the event is the unobservable latent onset of neuropathology that causes an individual to experience abnormally rapid cognitive decline relative similar individuals who do not become demented. Cases are identified using imputation of an individual's dementia status using the cognition measure supplemented by proxy reports of participants who will not or cannot take the cognitive tests. (Langa, Kabeto and Weir, 2009, 2020)

Third, following Békés and Kézdi (2021, Ch.24), we organize the data to create a quasi-experimental case-control design. In this design, dementia cases are defined using imputed dementia status from Langa, et al. (2020). Event time is defined by a clock that is zero at the time of dementia and ranges from t-2 to t-20 in the years before dementia. Controls for each value of the clock from a pool of over 60,000 person-years of potential never-demented individuals who are exactly matched on baseline cognition, age, sex, race and education. This design allows us to estimate the cumulative causal effects of the unobserved neuropathology from onset to diagnosis and to analyze differences by education and sex as compared to exactly matched controls. We also estimate the degree to which cases are subjectively aware of their abnormal cognitive decline.

Fourth, recent research (e.g., Mosconi, et al. Nature Scientific Reports, 2021;) has shown that the sex hormones, estrogen and testosterone, have an important effect on brain function that may help explain why, because of menopause, women are twice as likely as men to be demented. Within our case-control model, a person's sex can be regarded as a random assignment of the y chromosome to a regime in which pathology causes greater brain damage per unit time to females than it does to men such that women require greater baseline CR than men to acquire the same protection as men. Because there is almost no sex difference in baseline CR, it follows that women need to enter old age with a greater quantity of CR than men in order to match the protection against pathologies that lead to dementia. We find clear evidence that this is the case in our case-control model.

argue that sex differences in this framework, identify the effect of a randomized assignment of the y chromosome by mother nature that is traced in recent literature to the male-female difference loss of hormones that affect the brain caused by menopause.

The analytic goal of this paper is to estimate the causal effects on cognitive performance of underlying latent neuropathologies that ultimately lead to a diagnosis of dementia and examine the degree to which cognitive reserve (Stern (2009) affects the timing of the onset and trajectory of abnormal cognitive decline before diagnosis of dementia. We use longitudinal data from 10 waves of the Health and Retirement Study (HRS) spanning 20 years from 1998 to 2018. Individual cognitive status is measured using scores on a 27-point scale drawn from the TICS (Telephone Interview of Cognitive Status, Brandt, et al., 1988) which is documented in McCammon (2022); we refer to it as Cog27 throughout this paper.

The HRS has pioneered the measurement of the cognitive performance of older adults in nationally representative probability surveys in the U.S. and around the world that also contain survey data and linked data on a rich set of measures of economic, social, psychological, geographic, genetic, biomarker. This paper builds on the use of the Cog27 measure to provide a means to study dementia in a context that permits generalization to the national population of individuals over age 50 or to specific subgroups within the total population using carefully constructed sampling probability weights.

In this paper, we design a quasi-experimental case-control model of AHRD dementia using cut points suggested by Langa-Kabeto-Weir (2009, 2020) that best correspond to in-person clinical assessments of the cognitive status of a subset of HSR respondents in the AHEAD study (Crimmins, et al., 2011). LKW assign three categories of cognitive status: dementia, CIND (i.e., cognitive impairment, not demented), and normal cognitive status. A dementia case is defined by the first survey in which a respondent scores 0-4 correct answers. In addition, LKW impute dementia status based on proxy reports for individuals who cannot or will not take the Cog27 tests.[1]
References:

Amieva, et al. (2014)
Békés and Kézdi (2021, Ch.24)
Gianattasio, et al. (2020)Langa, Kabeto and Weir (2009, 2020)
(Stern (2009)
Mosconi, et al. Nature Scientific Reports (2021)

[1] Gianattasio, et al. (2020) discuss alternatives to the LKW "algorithmic" dementia diagnoses and Hurd, et al. (???) argue that random noise in Cog27 scores suggests that it is better to estimate dementia status populistically. As we discuss later, the precision of assigning cases status is not very important in our case-control model. We do examine the emergence of early cognitive decline by estimating the probability of CIND in the years before diagnosis.