**Response to Invited Commentary**

**Glymour et al. Respond to “Is Cognitive Aging Predicted by Educational Level?”**

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We thank Dr. Sharrett for his thoughtful commentary (1). The progression of research findings on educational attainment and cognitive aging has been disappointing; this topic illustrates the difficult methodological challenges in identifying opportunities to prevent or delay cognitive decline. Similar challenges extend to research on clinical, behavioral, and even genetic risk factors. The difficulties include settling on relevant causal questions to identify modifiable risk factors, finding outcome assessments that are both valid and reliable, distinguishing determinants of attained cognitive performance from causes of cognitive decline, and avoiding bias from selective survival and dropout. Some theoretically plausible methodological problems in epidemiology turn out to introduce only trivial problems in real applications. However, many of the potential biases in neuroepidemiology could quite plausibly qualitatively reverse inferences.

In our view, we are not quite done nailing shut the coffin on the hypothesis that education delays or slows the rate of cognitive decline in healthy populations. The possibility of bias due to selective survival remains. In the present study (2), our efforts to account for this bias using inverse probability weighting did not reverse findings. However, this work, like all prior research, rests on the yet unverified assumption that we have adequately measured and modeled the common causes of the rate of change and death. Because of the potentially pervasive nature of this bias, we think assessing this assumption is a priority for future research. A related problem that is almost never addressed in current research is the possibility of selective survival before study enrollment (i.e., left-hand censoring).

A further concern is the possibility of noninterval measurement; equal declines in raw score may not connote the same disease progression in individuals with different baseline scores. This problem can be approached with statistical solutions, for example by improving the interval scaling of cognitive tests or using analytic methods robust to scaling problems (3–5). Incorporating naturally scaled biomarker outcomes into analyses is a potential alternative. Biomarkers do not fully solve the problem, however, if the association between the biomarkers and underlying disease is nonlinear (6).

Finally, there is substantial imprecision in our estimates of the rate of cognitive change. Even very small differences in rates of decline could accumulate over many years to the point of clinically relevant differences in function in the very old. Meta-analyses of the many previously reported small, nonsignificant associations could therefore be informative. Unfortunately, the longitudinal models adopted in various studies differ substantially (7). As a result, successful meta-analyses will likely require careful harmonization efforts.

These caveats aside, we think that at this point, the weight of the evidence suggests that educational level does not substantially influence the rate of cognitive change in elderly populations. This is most consistent with a passive model of cognitive reserve. Extensive observational and limited quasi-experimental evidence indicate that cognitive skills gained through education persist into old age; such skills are likely to delay the clinical manifestation of dementia. If education induces active compensation, this compensation should offset disease progression and manifest as a slower rate of decline in cognitive performance. Thus, current findings suggest that a higher level of education predicts a lower risk of dementia because in highly educated individuals, a greater accumulation of pathology is required to cross the cognitive impairment threshold for diagnosable dementia, at least when using traditional diagnostic criteria. Sharrett (1) raises a key question: Can behavioral or environmental conditions modify cognitive level even in older age to similarly delay clinical dementia? The growing availability of biomarker and neuroimaging measures of brain health expands opportunities to test some hypotheses more directly and quickly.

For the goal of understanding processes of accumulating pathology or dynamic resilience that influence the development of dementia, education does not look very promising. Even if education confers only passive reserve, however, this advantage is important. From a public-health perspective, the global increases in population educational levels achieved in the past several decades (8) could translate into tremendous benefits for the independence of our aging populations.
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REFERENCES