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Invited Commentary

Invited Commentary: Lessons for Research on Cognitive Aging From a Study of Children

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As the population ages, the burden of disease from cognitive decline and dementing illness is rising. In the absence of treatments to reverse cognitive decline, prevention is a public health priority. Physical fitness and physical activity have emerged as prevention targets based on evidence of "neuroprotective" benefits in observational studies. However, observational studies linking active lifestyle with successful cognitive aging might be subject to bias from "neuroselection," in which adults with better cognitive functioning are more likely to engage in healthy behaviors and avoid unhealthy ones. In their analysis of longitudinal data on several thousand children from the United Kingdom's Millennium Cohort Study, Aggio et al. (*Am J Epidemiol*. 2016;183(12):1075–1082) revealed that this pattern of neuroselection is already apparent in childhood. However, they also report data that suggest there are cognitive benefits to engaging in certain types of active behaviors over and above this selection. Their findings argue for greater attention to confounding by neuroselection in research on cognitive aging, and they suggest the possibility that early interventions to promote certain health behaviors may instill a virtuous cycle with benefits that accumulate across the lifespan.

cognitive aging; confounding; human development; intelligence; life course; neuroprotection

The erosion of cognitive functions with advancing age damages quality of life and is a major source of morbidity and disability. As the population ages, the burden of disease from cognitive decline and dementing illness is rising (1). We currently lack treatments that can reverse cognitive decline. Prevention is therefore a public health priority, driving the search for so-called "neuroprotective" interventions. Physical activity and physical fitness have been promoted as intervention targets (2, 3). In laboratory experiments, rodents and humans have shown improved performance on some cognitive tests after exercise (4, 5). In observational studies, investigators found that compared with more sedentary and less-fit age-peers, active younger adults have better cognitive outcomes in their 50s and 60s (6–8), and active older adults develop dementia less often (9). Yet, no neuroprotective benefit has been found in randomized trials of interventions that increase physical activity (10, 11). These null findings raise questions for research on health behavior and cognitive aging. In this issue of the *Journal*, Aggio et al. (12) report on a study of children and suggests a few answers.

The authors reported data from the United Kingdom's Millennium Cohort Study, a population-based longitudinal study of nearly 20,000 children born in England, Scotland, and Wales during 2000–2002 and followed-up with repeatedly through age 11 years. Their aim was to understand whether naturally occurring variation in children's active and sedentary behaviors related to their cognitive functioning several years later. Results from laboratory and field experiments suggest that acute physical activity can boost children's performances on some cognitive tests (13). However, the relationship between long-term patterns of physical activity and cognitive functioning is less clear. Few long-term trials have been conducted. A further challenge is that the intervention procedures used to increase physical activity may have their own independent effects on cognitive function. For example, 1 recently published trial involved daily, 2-hour-long sessions of supervised physical activity and group play over the course of an entire school year (14). Observational studies can complement such field trials by testing whether the circumstances of active and sedentary behaviors modify their effects on the brain.

In their study, Aggio et al. (12) tested whether engaging in different types of active and sedentary behaviors at age 7 years predicted cognitive functioning 4 years later, at age

11 years. They analyzed data about children's activities reported by their mothers and also data from accelerometers worn by the children. Cognitive assessments were performed using the British Ability Scales. The authors found that children who engaged in more physical activity in clubs and classes at age 7 years scored higher on cognitive tests at age 11 years. In contrast, physical activity with family members at 7 years of age was not systematically related to cognitive functioning at 11 years of age. This result suggests that not all physical activity is equal with respect to effects on the brain. The content of sedentary time also mattered for interpretation of activity data. Initial analysis of the accelerometer data yielded the surprising result that more active children scored lower on cognitive tests. However, once the authors took into account how much time children spent reading, presumably a sedentary activity, the relationship disappeared. This result flags an important design consideration for future studies of activity levels and cognitive functioning. Finally, children's performances on baseline cognitive tests accounted for the majority of the simple associations between behavior at age 7 years and cognitive test performance at age 11 years. Notably, the relationship between club- and class-based physical activity and later cognitive test performance, although greatly reduced, remained statistically significant. Adding controls for children's socioeconomic circumstances did not change this result.

The main finding of the study was that associations of children's active and sedentary behaviors with their cognitive functioning are context-specific. In other words, it matters what the children are doing when they are active or sedentary; moving more is not, by itself, enough. This is a fair point. However, more work is needed before we may conclude that structured physical activities such as the club- and class-based activities measured in that study benefit brain development in children. One possibility not excluded by results from this study is that children with more rapid cognitive development also more often participated in club- and class-based physical activities. Future studies with repeated measures of the same cognitive tests across childhood years may investigate this possibility.

A secondary but possibly more important result is that children with higher baseline cognitive test scores spent their time in different ways than did their peers with lower test scores. The children with higher baseline scores did more of the behaviors associated with better cognitive outcomes and less of the behaviors associated with worse cognitive outcomes. Thus, the associations between behavior at 7 years of age and cognitive test performance at 11 years of age did not primarily reflect the causal effect of behavior on the brain. Instead, these associations reflected children's selective participation in different active and sedentary behaviors according to their cognitive functioning.

Both of these results are relevant for cognitive aging research into the potential neuroprotective benefits of health behaviors. Physical activity interventions aimed at achieving neuroprotective benefits in older adults may need to refine their targets, possibly by stimulating physical activity in ways that also engage the brain. In a recent successful trial of neuroprotective intervention, investigators combined physical activity with sedentary cognitive exercise and other lifestyle changes (15). Models are now being developed that elicit physical activity by involving older adults in socially and intellectually engaging tasks (16). Epidemiology can be used to help refine interventions by investigating in more detail the content of lifestyles linked with successful cognitive aging.

Epidemiology can also be used to help evaluate the potential of lifestyle interventions that deliver neuroprotective benefits by more aggressively testing for selection effects in observational studies. Selective participation in health behaviors according to cognitive functioning is likely to be as important a confounder in cognitive aging research as it is in studies of children, if not more so. The children in the study by Aggio et al. were presumably influenced in their allocation of time to active and sedentary behaviors by their parents. Yet, sorting into different behaviors according to cognitive functioning was still robust. In studies of adults, such sorting is presumably even stronger. The essential problem is that individuals with better cognitive functioning disproportionately select into healthier patterns of behavior, and this selection in turn confounds associations between behavior and cognitive outcomes in aging (17, 18). Thus, much of what is measured as neuroprotection in epidemiologic studies may actually reflect a process of "neuroselection," in which adults with better cognitive functioning are more likely to engage in more healthy behaviors and fewer unhealthy ones. Accounting for such neuroselection is essential to advance research on neuroprotective factors in aging.

If carefully conducted studies can be used to identify behaviors that benefit the brain, there is a third point in the study by Aggio et al. that may be useful to cognitive aging research: Earlier interventions may be the most effective. The deterioration of the body's systems that occurs with aging is a gradual and progressive process that is already underway by early adulthood (19). It may be easier to modify the rate of aging and its outcomes, including cognitive decline, by intervening earlier in the life course before substantial damage accumulates.

Researchers conducting life-course studies find that children who score higher on cognitive tests live longer, healthier lives than do their lower-scoring peers (20). Why this is the case remains poorly understood, although there are several hypotheses (21). The results in the study by Aggio et al. (12) hint at the possibility of a virtuous cycle: Better cognitive functioning leads individuals into healthier patterns of behavior (neuroselection), and these healthy behaviors in turn benefit cognitive functioning (neuroprotection). If such a virtuous cycle exists, early interventions will yield benefits that accumulate across the life course.

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REFERENCES

1. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2163–2196.
2. Reynolds G. Early fitness can improve the middle-age brain. *New York Times*. http://well.blogs.nytimes.com/2014/05/07/a-fit-body-at-25-a-fit-brain-at-50/. Published May 7, 2014. Accessed May 16, 2014.
3. US Centers for Disease Control and Prevention. Promoting active lifestyles among older adults. http://www.cdc.gov/nccdphp/dnpa/physical/pdf/lifestyles.pdf. Accessed December 14, 2015.
4. Hillman CH, Erickson KI, Kramer AF. Be smart, exercise your heart: exercise effects on brain and cognition. *Nat Rev Neurosci*. 2008;9(1):58–65.
5. Smith PJ, Blumenthal JA, Hoffman BM, et al. Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. *Psychosom Med*. 2010;72(3):239–252.
6. Defina LF, Willis BL, Radford NB, et al. The association between midlife cardiorespiratory fitness levels and later-life dementia: a cohort study. *Ann Intern Med*. 2013;158(3):162–168.
7. Reis JP, Loria CM, Launer LJ, et al. Cardiovascular health through young adulthood and cognitive functioning in midlife. *Ann Neurol*. 2013;73(2):170–179.
8. Zhu N, Jacobs DR Jr, Schreiner PJ, et al. Cardiorespiratory fitness and cognitive function in middle age: the CARDIA Study. *Neurology*. 2014;82(15):1339–1346.
9. Hamer M, Chida Y. Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. *Psychol Med*. 2009;39(1):3–11.
10. Sink KM, Espeland MA, Castro CM, et al. Effect of a 24-month physical activity intervention vs health education on cognitive outcomes in sedentary older adults: the LIFE randomized trial. *JAMA*. 2015;314(8):781–790.
11. Barnes DE, Santos-Modesitt W, Poelke G, et al. The Mental Activity and eXercise (MAX) trial: a randomized controlled trial to enhance cognitive function in older adults. *JAMA Intern Med*. 2013;173(9):797–804.
12. Aggio D, Smith L, Fisher A, et al. Context-specific associations of physical activity and sedentary behavior with cognition in children. *Am J Epidemiol*. 2016;183(12):1075–1082.
13. Verburgh L, Königs M, Scherder EJA, et al. Physical exercise and executive functions in preadolescent children, adolescents and young adults: a meta-analysis. *Br J Sports Med*. 2014;48(12):973–979.
14. Hillman CH, Pontifex MB, Castelli DM, et al. Effects of the FITKids randomized controlled trial on executive control and brain function. *Pediatrics*. 2014;134(4):e1063–e1071.
15. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet*. 2015;385(9984):2255–2263.
16. Carlson MC, Saczynski JS, Rebok GW, et al. Exploring the effects of an "everyday" activity program on executive function and memory in older adults: Experience Corps. *Gerontologist*. 2008;48(6):793–801.
17. Belsky DW, Caspi A, Goldman-Mellor S, et al. Is obesity associated with a decline in intelligence quotient during the first half of the life course? *Am J Epidemiol*. 2013;178(9):1461–1468.
18. Belsky DW, Caspi A, Israel S, et al. Cardiorespiratory fitness and cognitive function in midlife: neuroprotection or neuroselection? *Ann Neurol*. 2015;77(4):607–617.
19. Belsky DW, Caspi A, Houts R, et al. Quantification of biological aging in young adults. *Proc Natl Acad Sci U S A*. 2015;112(30):E4104–E4110.
20. Deary IJ, Weiss A, Batty GD. Intelligence and personality as predictors of illness and death: how researchers in differential psychology and chronic disease epidemiology are collaborating to understand and address health inequalities. *Psychol Sci Public Interest*. 2010;11(2):53–79.
21. Gottfredson LS, Deary IJ. Intelligence predicts health and longevity, but why? *Curr Dir Psychol Sci*. 2004;13:1–4.