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EDITORIAL COMMENT

Childhood Cardiovascular Risk Factors and Midlife Cognitive Performance

Time to Act on Primordial Prevention*

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The traditional cardiovascular disease (CVD) risk factors have long been associated with cognitive function in later life (1). To date, the vast majority of studies have focused on middle-age risk factor levels and cognitive outcomes in older age (2–4). The newer concept of "cardiovascular health" in young adulthood was only recently shown to have significant associations with cognition up to 25 years later among participants of the CARDIA (Coronary Artery Risk Development in Young Adults) study (5). It is increasingly being recognized that loss of ideal cardiovascular health and exposure to elevated cardiovascular risk factor levels at young ages, and the accumulated burden of these risk factors, is a major contributor to health outcomes in later life. In fact, the top global research priorities for the next decade in dementia research call for a focus on prevention (6); however, until recently, it has been unclear at what ages this accumulated burden starts to accrue and when prevention efforts should begin.

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The study by Rovio et al. from the YFS (Young Finns Study) in this issue of the *Journal* (7) provides some of the first information about how childhood risk factor levels and their accumulation over time may affect cognitive performance in middle age. The investigators estimated the cumulative burden of risk factors including blood pressure, serum lipids, and smoking during 3 life periods: childhood (6 to 12 years), adolescence (12 to 18 years), and young adulthood (18 to 24 years) among 2,026 participants of the YFS. They then examined the relationship of these measures of cumulative burden on midlife (age 34 to 49 years) cognitive performance as defined by 4 domains including the paired associates learning test (visual and episodic memory and visuospatial associative learning), rapid visual information processing test (recognition, visual processing, and sustained attention), the spatial working memory test (working memory), and the reaction time test.

They found that early life cumulative exposures of systolic blood pressure and total cholesterol were associated with worse midlife visual and episodic memory and visuospatial associative learning. Individuals in the highest tertile of cumulative systolic blood pressure and cholesterol exposure were 8.4 and 6.6 years, respectively, older (worse) in terms of their "cognitive aging" compared with the lowest tertile. These effect sizes are large and worrisome for adults who are still relatively young. The impact of cumulative measures of smoking and body mass index were weaker (or nonsignificant), nor were there any major findings with outcomes of sustained attention and visual processing. Of importance, when the investigators examined the impact of elevated risk factor levels early in life as compared with elevations in middle age, the early life exposures were more strongly associated with later life cognitive function. Also of note, adjustment for early life socioeconomic factors and (to the extent possible) academic performance did not fully attenuate these associations. These findings extend our prior understanding on the accumulation of cardiovascular risk and cognition back into childhood and suggest that the adverse impacts on later-life health begin accruing very early in life.

The YFS is uniquely positioned to address these scientific questions, and is strengthened by the detailed phenotyping, high retention, and long-term follow-up of the Young Finns Cohort; however,

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similar to previous studies, this one is limited by a single measure of cognitive performance. It remains unclear whether differences identified between quartiles of cumulative risk factor burden are the result of baseline differences in cognitive performance, which could indicate that poor cognitive function leads to worse cardiovascular health instead of the reverse. Indeed, it is quite plausible that those with lower cognitive function early in life may be less resilient and less able to avoid unhealthy behaviors that in turn would lead to worse risk factors and further declines in cognitive function. A growing body of literature suggests that early life neurodevelopment and the context of social environmental factors may play key roles in determining health behaviors and susceptibility to risk factors and chronic diseases of aging. As follow-up of the Young Finns Cohort continues, the investigators can address some of these issues with a second round of cognitive testing, thereby allowing for a longitudinal analysis. Even better data could come from longitudinal cohorts that have baseline cognitive function testing beginning early in life. Despite this limitation, the current YFS provides an important focus on the impact that risk factor levels as early as age 6 may have on cognition in middle age. The impact of disparities in cognition during middle age is likely to have major long-term ramifications for individuals as they pursue their careers and social/family obligations. It will be interesting to see how these differences translate to later life decline and incidence of clinical diagnoses, such as dementia and Alzheimer's disease.

The mechanisms underlying the association between early life cumulative exposures and cognitive health in midlife have not been fully elucidated. There are 2 prevailing theories on the relationship between cardiovascular risk factors and cognitive health. The first is that prevalent CVDs (including myocardial infarction, heart failure, and stroke) mediate the relationship between risk factor levels and cognitive health. Given the young age of the YFS participants and the low prevalence of CVD events, this mechanism is unlikely to explain the findings. A second proposed mechanism is that long-term, elevated risk factor levels promote the development of microvascular (and even macrovascular) disease through subclinical ischemia, structural changes to the brain, and atrophy. Although the exact mechanism needs further study, what is clear is that these effects may be happening much earlier in life than we previously thought and may be producing measurable manifestations by middle age.

This study and others contribute to the growing recognition that early life exposures exert a long-lasting influence on health. Although treating risk factors once they develop is likely to produce benefits in long-term health, the greatest contribution to reducing future burden of disease will be in preventing the loss of ideal risk factor levels (i.e., primordial prevention) from early life. Clinical trials have shown that treating hypertension, hypercholesterolemia, and diabetes will reduce future disease risk; however, at the point a clinical diagnosis is made, individuals have already experienced a long preclinical elevation in risk factor levels and thus already accumulated substantial vascular and target organ injury. For example, even individuals with well-controlled blood pressure on antihypertensive medications are at substantially higher CVD risk as compared with individuals who maintained ideal blood pressure levels throughout young adulthood (8). It is likely that these findings translate to cognitive health given the shared risk pathways. In contrast to primary prevention, which focuses on treating the risk factors of a disease, primordial prevention aims to prevent the development of the risk factors themselves. Taken together, the current findings highlight the increasing importance of primordial prevention in improving long-term health. And they provide a path to more positive messaging as well, for although worse risk factor exposures in childhood are associated with worse midlife cognitive function, the reverse is also true: that maintenance of ideal cardiovascular health factor levels is associated with retention of cognitive function into midlife.

Because elevations in risk factor levels including blood pressure and lipids occur early in life, to truly intervene before risk is accrued, intervention efforts need to begin in childhood and perhaps even preconception. Clinical pediatric guidelines and scientific statements from the American College of Cardiology and American Heart Association are increasingly focused on addressing early life elevations in cardiovascular risk factors (9). Rovio et al. (7) show compelling data on how influential very early life exposures are on long-term health. They highlight how crucial it is to focus our efforts on primordial prevention in childhood so we can help current and future generations remain in both ideal cardiovascular and cognitive health.

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REFERENCES

1. Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective. Alzheimers Dement 2015;11:718–26.

2. Debette S, Seshadri S, Beiser A, et al. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. Neurology 2011;77:461–8.

3. Knopman D, Boland LL, Mosley T, et al. Cardiovascular risk factors and cognitive decline in middle-aged adults. Neurology 2001;56:42–8.

4. Obisesan TO, Obisesan OA, Martins S, et al. High blood pressure, hypertension, and high pulse pressure are associated with poorer cognitive function in persons aged 60 and older: the Third National Health and Nutrition Examination Survey. J Am Geriatr Soc 2008;56:501–9.

5. Yaffe K, Vittinghoff E, Pletcher MJ, et al. Early adult to midlife cardiovascular risk factors and cognitive function. Circulation 2014;129:1560–7.

6. Shah H, Albanese E, Duggan C, et al. Research priorities to reduce the global burden of dementia by 2025. Lancet Neurol 2016;15:1285–94.

7. Ruvio SP, Pahkala K, Nevalainen J, et al. Cardiovascular risk factors from childhood and midlife cognitive performance: the Young Finns study. J Am Coll Cardiol 2017;69:2279–89.

8. Liu K, Colangelo LA, Daviglus ML, et al. Can antihypertensive treatment restore the risk of cardiovascular disease to ideal levels? The Coronary Artery Risk Development in Young Adults (CARDIA) Study and the Multi-Ethnic Study of Atherosclerosis (MESA). J Am Heart Assoc 2015;4:e002275.

9. Steinberger J, Daniels SR, Hagberg N, et al. Cardiovascular health promotion in children: challenges and opportunities for 2020 and beyond: a scientific statement from the American Heart Association. Circulation 2016;134:e236–55.

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