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Cardiorespiratory Fitness and Brain Volumes

The role of exercise and brain health has been a very popular topic of discussion in recent years. The National Academies of Sciences concluded that aerobic exercise may be useful in slowing cognitive changes in aging, and the Lancet Commission similarly reported the value of aerobic training and cognitive outcomes.[1,2] In addition, the World Health Organization endorsed exercise as a means of intervening on the progression of cognitive impairment.[3] In an evidence-based medicine review of the literature, the American Academy of Neurology concluded that exercise may be useful in slowing clinical progression from mild cognitive impairment to dementia.[4] This topic is of great interest to the field.

While numerous bodies of literature have suggested that exercise is beneficial, there have been few studies analyzing what exercise measures might be indicative of a benefit. The implicit assumption has been that exercise leads to improved cardiorespiratory function (CRF), yet precise data have been lacking. However, a recent study from Norway evaluated participants' CRF at two points in time to evaluate if changes in physical fitness would have an impact on cognitive outcomes and mortality.[5] They found that change in CRF was an independent risk factor for incident dementia and dementia mortality. They estimated that participants who increased their estimated CRF over time gained 2.2 dementia-free years, and 2.7 years of life when compared with those who remained unfit at the two assessments.

Wittfeld et al[6] from the German Center for Neurodegenerative Diseases reported cross-sectional analyses of the association of CRF and global and local brain volumes on magnetic resonance imaging in the current issue of *Mayo Clinic Proceedings*. They found that CRF was positively associated with gray matter (GM) and total brain volumes in certain brain regions; and interestingly, the associations were in regions of the brain coupled with particular cognitive functions and not motor functions. These data suggested that CRF has a positive association with cognition particularly in regions of the brain noted to be involved with cognitive decline and aging. White matter (WM) changes were not observed.

The strength of the study is derived from the data sources: two large population-based cohorts that lend credence to the validity of the results. There have been several smaller studies supporting an association between exercise and brain health, but this study involved 2103 participants. A popularly cited study on exercise training suggested that aerobic exercise may increase the size of the hippocampus and improve spatial memory.[7] This study involved 120 older adults, and the authors speculated about the role of brain-derived neurotropic factor on neurogenesis in the dentate. However, the sample selection and the size of the sample make generalizations challenging, whereas the study from Wittfeld et al[6] appears more representative, and the findings with age are particularly encouraging.

The particular GM regions involved suggest areas that may be clinically relevant for cognitive changes in aging, namely, hippocampal formation, parahippocampal gyrus, temporal gyrus, fusiform gyrus, cingulate, and orbitofrontal cortices; these findings align with some of the regions of interest described in various magnetic resonance imaging studies of aging and cognitive impairment. Some of the regions of interest of GM described in this study do coincide with similar areas involved in Alzheimer disease; however, one must be careful not to suggest that CRF correlations will have any impact on Alzheimer disease pathophysiology, but the regional associations are interesting.

Two additional caveats should be mentioned. First, the unilateral nature of most of the positive associations between CRF and brain volumes is difficult to

Mayo Clin Proc. ■ January 2020;95(1):6-8 ■ https://doi.org/10.1016/j.mayocp.2019.11.011
www.mayoclinicproceedings.org ■

explain. One might expect homologous brain areas to respond similarly to an external exposure such as CRF; actually, given the systemic nature of CRF, one might expect similar associations across all brain areas, not just a few. The fact that the associations were not replicated across most of the significant homologous brain regions should be factored into the interpretation of the results. Second, the authors used intracranial volume (ICV) as a single regressor for all brain regions. This can be problematic because the relationship between ICV and volume is not the same for different brain regions. This is further complicated by the fact that, on average, men have larger head sizes than women, and thus the errors in ICV adjustment in the regression analyses may be propagated into the sex adjustments.

The lack of association between CRF and WM is curious because much of the literature suggests exercise effects on cerebral connectivity patterns. However, as the authors note, diffusion tensor imaging may have been a better measure of WM integrity than the ones used here, and consequently, this lack of association must be cautiously interpreted.

An interesting and potentially important observation in this study was the finding of an interaction of age with peak oxygen uptake (VO2) and maximimal power output (Wmax) on hippocampal volume. These data suggest that the effect of CRF may be stronger in those individuals aged 45 years and older. This is encouraging because hippocampal atrophy and a decline in recent memory are commonly observed features of aging.[7] Larson et al[8] have shown that exercise may be associated with the delay in onset of cognitive aging and perhaps dementia in persons aged 65 years and older. If some of these aging changes could be counteracted by lifestyle changes, this would send a positive message to older individuals. Of note, in observational studies of healthy middle-aged individuals who become more fit, there is a clear mortality benefit,[9] but the impact on cognition is not known. However, cognition in more than 1 million young male Swedish military conscripts is related to fitness based in large part on environmental versus genetic factors,[10] and low fitness at age 18 years is associated with early-onset dementia.[11] These data tend to counter the argument that cross-sectional assessments of phenotypes and behaviors including fitness, walking speed, and physical activity are merely surrogate markers of intrinsic biology that may not be modifiable.

The primary limitation of this study, as the authors note, involves its cross-sectional nature and, consequently, one must be cautious against over-interpreting the data. It is tempting to suggest a causal relationship, but that would be inappropriate given the nature of the data. The real validity of the results suggested here would come from longitudinal follow-up results of the populations. It would also be interesting to know if behavioral exercise patterns of the participants correlated with the CRF findings. Along these lines, a major challenge with interventional exercise and lifestyle studies is that most are only months or perhaps 1 year in duration. In this context, very-long-term studies on topics related to an exercise intervention and brain health will be costly and logistically challenging to conduct. Nevertheless, these data are encouraging, intriguing, and contribute to the growing literature relating to exercise and brain health. The correlations of CRF and certain brain structures are unique.

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Potential Competing Interests: The authors report no competing interests.

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Mayo Clin Proc. ■ January 2020;95(1):6-8 ■ https://doi.org/10.1016/j.mayocp.2019.11.011
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