

Physical exercise and activity may be important in reducing dementia risk at any age

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Neurology® 2019;92:362-363. doi:10.1212/WNL.0000000000006935

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Page 370

Lifestyle interventions such as physical exercise may provide inexpensive and effective ways to delay the onset of cognitive decline and dementia. If we are able to reduce Alzheimer neuropathology in the future as now appears possible,¹ combining pharmacologic and lifestyle interventions will likely provide the best prevention for cognitive decline and dementia. In this respect, prevention of dementia and cognitive impairment would be similar to current preventive treatments for diabetes and vascular disease, where both types of interventions are used.

Numerous observational studies have provided support for an association between physical exercise and reduction in cognitive decline and dementia.² The mechanisms underlying this association remain unclear. The results of randomized trials of physical exercise^{3,4} suggest that exercise leads to increases in brain tissue, including in the hippocampus, where atrophy is an early and important finding in Alzheimer disease (AD). One of these trials showed that aerobic exercise resulted in increased levels of brain-derived neurotrophic factor (BDNF) in association with increased hippocampal volume.³ Other studies suggest that higher *BDNF* gene expression may have a role in slowing cognitive decline.⁵ Alternatively, physical exercise itself might reduce brain pathology. Studies in animal models of AD have shown that higher levels of physical activity reduce the accumulation of Alzheimer pathology.⁶ In a recent human study, Alzheimer biomarkers were reduced in dominant AD mutation carriers with high vs low physical exercise.⁷ Another recent study suggested that even moderate exercise might be beneficial in reducing Alzheimer pathology.⁸

Given the current interest in sharpening terminology,⁹ it is important to consider the mechanisms that potentially underlie the beneficial effect of physical activity. Clearly, physical activity could increase brain maintenance: the effect of genetics or lifestyle on reduced development of age-related brain changes and pathology. The observations reviewed above regarding the improvement of brain volume by physical activity, as well as the upregulation of important neurotrophic factors, are consistent with this idea. In addition, exercise might also contribute to cognitive reserve: the adaptability (i.e., efficiency, capacity, flexibility) of cognitive processes that helps to explain differential susceptibility of cognitive abilities or day-to-day function to brain aging, pathology, or insult. For this to be the case, evidence that physical activity influences functional processes over and above the brain substrate is useful. For example, aerobic exercise has been associated with greater connectivity of the default mode network¹⁰ as well as allocation of brain resources.¹¹ Thus, physical activity can both promote brain maintenance and cognitive reserve.

In the current issue of *Neurology*®, Buchman et al.¹² provide evidence for beneficial effects of total daily physical activity on cognitive performance that is independent of a variety of brain lesions including AD pathology. Building on a large longitudinal study with autopsy follow-up, they examined the association between total daily physical activity derived from wrist accelerometer recordings an average of 2 years prior to death and cognition. After adjusting for the severity of a variety of brain lesions, including quantitative measures of AD pathology, individuals with higher levels of total daily physical activity continued to have significantly better cognitive function. The authors attributed this finding to increased cognitive reserve associated with better physical and motor function.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the editorial.

Because the data from this study are cross-sectional, causal inferences cannot be drawn. An alternative explanation for the results is that at least some of the association resulted from reverse causality, i.e., that lower cognitive function led to less physical activity. Some support for this view is provided by a large reduction in the strength of the association between physical activity and cognition when participants with dementia were excluded from the model, suggesting that as individuals become demented they may reduce their physical activity. Consistent with this view, unadjusted comparisons of physical activity in those who had dementia vs those who did not showed a significant reduction in physical activity among the participants with dementia. It is important to emphasize that this does not imply that physical activity does not increase reserve against cognitive decline, only that the effect may be more modest among those with better cognition. What is needed to establish causation are longitudinal studies of physical activity and cognition with brain imaging to document the influence of pathology on this association.

Studies that have documented benefits of physical exercise on cognition have generally focused on strenuous or aerobic exercise in earlier life. It is unclear how the effects of physical activity as measured by a wrist-worn accelerometer in late life are related to those of aerobic or other types of exercise throughout the life course. One of the only studies that examined physical activity over the life course reported low to moderate correlations between childhood, age 30, age 50, and late-life exercise.¹³

Although important questions remain, currently available data suggest that promotion of an active lifestyle in late as well as early life that includes regular physical activity and exercise may be beneficial in reducing the risk of dementia, both through increases in reserve and reduction of Alzheimer neuropathology. The fact that physical exercise and activity

have few if any downsides makes them an attractive target for the prevention of cognitive impairment and dementia.

Study funding

No targeted funding reported.

Disclosure

The authors report no disclosures. Go to Neurology.org/N for full disclosures.

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Neurology 2019;92:362-363 Published Online before print January 16, 2019

DOI 10.1212/WNL.0000000000006935

This information is current as of January 16, 2019

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