

Aerobic exercise

A possible therapy for vascular cognitive impairment

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Cerebrovascular disease is the second most common cause of cognitive impairment and dementia and contributes to cognitive decline in the neurodegenerative dementias.¹ Vascular cognitive impairment (VCI) refers to all forms of mild to severe cognitive impairment associated with cerebrovascular disease. VCI is therefore heterogeneous not only because of the nature of the underlying lesions (associated with stroke or not) but also because of the various brain structures involved (damage to large or small vessels).² It is also heterogeneous clinically, the term encompassing all cognitive disorders from subtle cognitive impairment to dementia.^{3,4} Despite this heterogeneity, some common risk factors are associated with VCI; these include usual vascular risk factors, but also aging and low physical activity.⁵ Although better management of vascular risk factors is associated with a lower incidence of stroke, the effect on the risk of dementia is less clear.^{1,4} Further, while numerous studies have shown that physical activity is associated with a reduced risk of cognitive decline and progression to dementia, the evidence for trials of physical activity interventions are sparse and short-term.^{6–8} The benefits of physical activity are several-fold and may include a reduced risk of cardiovascular disease, but other more complex mechanisms, such as an increase of brain neurotrophins or an effect on neurogenesis, may be involved.⁴ To date, no trials have focused on the target group of patients with VCI.

In this issue of *Neurology*®, Liu-Ambrose et al.⁹ report the results of a single-blind randomized controlled trial comparing the effect of a 6-month progressive aerobic exercise training program against usual care plus education on cognitive function among older adults with mild subcortical ischemic VCI (SIVCI). The main objective was to provide a proof of concept for future study of the effect of physical activity on cognition. The choice of participants was appropriate, as autopsy studies have shown that people with dementia have a larger proportion of small subcortical ischemic lesions than cerebral multi-infarcts, with robust association of these small lesions with cognitive decline.^{2,10}

A total of 70 adults with a mean age of 74 years, with a diagnosis of mild SIVCI, were randomized to 2 groups: aerobic training (AT) or usual care plus education. The 3 prespecified primary outcomes included the Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-Cog), global executive functions as measured by the Executive Interview (EXIT-25), and activities of daily living as determined by the Alzheimer's Disease Cooperative Study (ADCS-ADL). At the end of the intervention period, the AT group only improved on performance of the ADAS-Cog compared with controls, with a mean –1.71-point difference ($p = 0.02$). However, this difference was no longer apparent 6 months later. Although the size of the effect on the ADAS-Cog was small, this study provides Class II evidence for effect of an aerobic exercise program in a population with mild SIVCI. The strengths of this study are not only its randomized design, but also that the study met its predefined feasibility criteria with a recruitment rate of 17%, a withdrawal rate of less than 15%, and an average exercise adherence of 68%.

However, the study outcome raises further questions. First, the mean difference between groups of 1.71 points on the ADAS-Cog (out of 70) was modest. Some have argued that an individual should demonstrate a 4-point difference to be clinically meaningful.¹¹ Second, only 1 of the 3 outcome measures was positive, which does not provide sufficient justification for this study to be considered as Class I evidence. Finally, it is surprising that this aerobic exercise program did not improve executive functions, as this would have been expected following several observational studies.⁴ However, physical activity may require a longer period to improve executive function, as it may exert its effect by lowering the diastolic blood pressure, as demonstrated in this study.

Despite these limitations, the results of this work provide a proof of concept of the effect of physical activities on cognition in patients with VCI and encourage further studies on larger groups of people with VCI.

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