

# Lifestyles and Cognitive Health

## What Older Individuals Can Do to Optimize Cognitive Outcomes

Sudeep S. Gill, MD, MSc; Dallas P. Seitz, MD, PhD

**Loss of cognitive function** and the development of dementia are among the greatest concerns confronting older individuals. As populations around the world age, the global prevalence of dementia is predicted to increase substantially from an estimated 35.6 million in 2010 to 65.7 million in 2030, and 115.4 million in 2050.<sup>1</sup>

In the United States in 1990, Alzheimer disease ranked 25th in terms of disability-adjusted life-years lost. In 2010, it ranked 12th, with the greatest median percentage change of any of the leading 30 diseases.<sup>2</sup> The burden of mild cognitive impairment (MCI) is even larger.<sup>3</sup> Discussions between physicians and patients about strategies to prevent cognitive decline and dementia have become commonplace, and there is great interest in new evidence of lifestyle modifications that might improve cognitive aging and prevent the onset of dementia. These lifestyle modifications include exercise, dietary changes, cognitive training (ie, “brain games”), and multimodal treatments. A meta-analysis of observational studies found that the modifiable risk factors that have most consistently been associated with a reduced risk of dementia include higher educational attainment, increased physical activity, and avoidance of smoking.<sup>4</sup>

In this issue of *JAMA*, results from 2 high-quality studies evaluate the influence of lifestyle interventions on cognitive outcomes. Both studies are secondary analyses of randomized clinical trials (RCTs) involving older persons. In the Lifestyle Interventions and Independence for Elders (LIFE) trial, results show no cognitive benefits from structured exercise.<sup>5</sup> In the Age-Related Eye Disease Study 2 (AREDS2), results show no change in cognitive function scores with supplements of either long-chain polyunsaturated fatty acids (LCPUFAs) or lutein combined with zeaxanthin when compared with placebo.<sup>6</sup>

The LIFE trial recruited 1635 community-dwelling, sedentary adults aged 70 to 89 years, and randomized them either to a structured, moderate-intensity physical activity program (n = 818) that included walking, resistance training, and flexibility exercises or to a health education program (n = 817) of educational workshops and upper extremity stretching.<sup>5</sup> The primary cognitive outcomes were measures of psychomotor speed, attention, and memory (Digit Symbol Coding task and Hopkins Verbal learning tasks). Additional neuropsychological tests and rates of incident MCI and dementia were also evaluated. After 24 months, data on the 1476 (90.3%) participants with follow-up cognitive data found there were no dif-

ferences in the main analysis between the moderate-intensity physical activity program as compared with the health education program on global or domain-specific cognitive measures or on the risk of incident MCI or dementia.

The AREDS2 trial enrolled older adults at high risk of progressing to late age-related macular degeneration, and was able to capture follow-up cognitive function testing on 3501 (83%) of 4203 study participants. This trial evaluated supplementation with LCPUFAs alone, lutein/zeaxanthin alone, their combination, or placebo along with varying amounts of vitamin C, vitamin E, beta carotene, and zinc for up to 5 years. Cognitive outcomes included assessment of the change in a composite of several neuropsychological measures over the course of the 5 years of the study. Overall, none of the dietary supplements under investigation were associated with any significant differences on the primary composite cognitive outcome or any of the component tests.<sup>6</sup>

How can the negative results of these analyses from the LIFE and AREDS2 trials be reconciled with existing literature on exercise and diet interventions to prevent cognitive decline and dementia? In contrast to the results from the LIFE trial, some studies have demonstrated that exercise interventions can improve cognition. For example, another well-designed RCT evaluated a 6-month exercise program that was supplemented by a behavioral intervention to enhance adherence. This RCT recruited 170 older adults who had reported cognitive concerns or who met diagnostic criteria for MCI. The trial demonstrated statistically significant although clinically modest benefits with the exercise program when compared with outcomes in an education and usual care group over an 18-month follow-up period.<sup>7</sup> The outcome measure in this study was the ADAS-Cog (Alzheimer’s Disease Assessment Scale—Cognition), a measure used in RCTs of many pharmaceutical interventions for dementia that may be more sensitive to change than outcome measures assessed in the LIFE trial.

Observational studies have also demonstrated that daily physical activity energy expenditure was associated with decreased risk of cognitive impairment and reduced risk of developing Alzheimer disease.<sup>8,9</sup> Sink and colleagues discuss a variety of possible explanations for the apparent conflicting results of studies examining the relationship between exercise and cognitive function; further studies designed to examine primary cognitive outcomes will be required to clarify the effectiveness of exercise interventions in older adults. The effects of exercise on cognition also may differ in older adults

without cognitive concerns (as was the case in the LIFE trial) when compared with individuals with cognitive concerns, MCI, or dementia. In addition, different neuropsychological test batteries may be more or less sensitive to specific cognitive changes that are likely to be influenced by exercise.

Unlike studies of exercise, investigations evaluating the relationship between specific dietary supplements and cognitive decline have had more consistently negative findings. Although severe nutritional deficiencies are known to contribute to cognitive impairment in older adults (such as vitamin B<sub>12</sub> deficiency and niacin deficiency), RCTs have failed to demonstrate benefits from nutritional supplementation to improve cognition or prevent dementia. For example, vitamin E has not been shown to protect against the development of dementia in RCTs of individuals with MCI.<sup>10</sup> Even though specific dietary supplements may not be efficacious, results from the the PREDIMED trial<sup>11</sup> demonstrated that consumption of a Mediterranean diet supplemented with olive oil or nuts was associated with improved cognitive function. Epidemiological evidence has also suggested that adherence to a Mediterranean diet may be associated with a reduced risk of dementia, with this effect possibly mediated by beneficial cardiovascular effects.<sup>12</sup> Thus, long-term adherence to a balanced, heart-healthy diet may have greater cognitive benefits than more narrow focus on supplementing specific micronutrients.

Although the well-designed RCTs presented by Sink and colleagues<sup>5</sup> and Chew and colleagues<sup>6</sup> failed to demonstrate significant cognitive benefits, these results should not lead to nihilism involving lifestyle factors in older adults. It is still likely that lifestyle factors such as diet and physical activity have important roles in the prevention of cognitive decline, dementia, and performance of the activities of daily living. The FINGER trial<sup>13</sup> reported results of a multifaceted intervention that included diet, exercise, cognitive training, and vascular risk moni-

toring compared with provision of general health advice in participants aged 60 to 77 years who were at risk of developing dementia. At 2 years, the intervention was associated with significant benefits on a comprehensive neuropsychological test battery. Also, there is encouraging epidemiological evidence suggesting that the incidence of dementia among more recent cohorts of older adults may be declining.<sup>14</sup> These data are ecological in nature but provide evidence of a potential reduction in dementia risk that may be at least partly attributable to reductions in cardiovascular risk factors (also major risk factors for dementia), cardiovascular treatments such as aspirin and lipid-lowering therapy, and increasing educational achievement. It is likely the biggest gains in reducing the overall burden of dementia will be achieved through policy and public health initiatives promoting primary prevention of cognitive decline rather than efforts directed toward individuals who have already developed significant cognitive deficits.

Physicians should encourage patients of all ages to optimize physical activity levels throughout their life, which may help to reduce the risk of developing dementia and many other adverse health outcomes. An active lifestyle throughout the lifespan may be more effective in preventing cognitive decline than starting physical activity after the onset of cognitive symptoms. Similarly, adherence to Mediterranean or heart healthy diets throughout life are likely to be most beneficial in preventing cognitive decline or the onset of dementia in contrast to isolated nutritional supplements initiated late in life. Although the direct cognitive benefits of lifestyle interventions will require further confirmation, there is clear evidence that physical activity and a healthy diet contribute to improvements in a wide variety of health outcomes. These interventions are safe and widely available, but to be effective will require sustained efforts from older individuals and encouragement from their physicians.

#### ARTICLE INFORMATION

**Author Affiliations:** Department of Medicine, Queen's University, Kingston, Ontario, Canada (Gill); Department of Psychiatry, Queen's University, Kingston, Ontario, Canada (Seitz).

**Corresponding Author:** Sudeep S. Gill, MD, MSc, Department of Medicine, Queen's University and St Mary's of the Lake Hospital, 340 Union St, Kingston, ON, Canada, K7L 5A2 (sudeep.gill@ices.on.ca).

**Conflict of Interest Disclosures:** Both authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Gill reports being a paid member of the Committee to Evaluate Drugs, an independent advisory group on drug-related issues for the Ontario Ministry of Health and Long-Term Care. Dr Seitz reports receipt of an advisory board honorarium from Eli Lilly, Canada outside the submitted work.

#### REFERENCES

- Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia. *Alzheimers Dement*. 2013;9(1):63-75.
- US Burden of Disease Collaborators. The state of US health, 1990-2010. *JAMA*. 2013;310(6):591-608.
- Petersen RC, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L. Mild cognitive impairment. *J Intern Med*. 2014;275(3):214-228.
- Beydoun MA, Beydoun HA, Gamaldo AA, et al. Epidemiologic studies of modifiable factors associated with cognition and dementia. *BMC Public Health*. 2014;14:643.
- 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*. doi:10.1001/jama.2015.9617.
- Chew EY, Clemons TE, Agrón E, et al. Effect of omega-3 fatty acids, lutein/zeaxanthin, or other nutrient supplementation on cognitive function: the AREDS2 randomized clinical trial. *JAMA*. doi:10.1001/jama.2015.9677.
- Lautenschlager NT, Cox KL, Flicker L, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease. *JAMA*. 2008;300(9):1027-1037.
- Middleton LE, Manini TM, Simonsick EM, et al. Activity energy expenditure and incident cognitive impairment in older adults. *Arch Intern Med*. 2011;171(14):1251-1257.
- Buchman AS, Boyle PA, Yu L, et al. Total daily physical activity and the risk of AD and cognitive decline in older adults. *Neurology*. 2012;78(17):1323-1329.
- Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med*. 2005;352(23):2379-2388.
- Valls-Pedret C, Sala-Vila A, Serra-Mir M, et al. Mediterranean diet and age-related cognitive decline. *JAMA Intern Med*. 2015;175(7):1094-1103.
- Lourida I, Soni M, Thompson-Coon J, et al. Mediterranean diet, cognitive function, and dementia. *Epidemiology*. 2013;24(4):479-489.
- 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). *Lancet*. 2015;385(9984):2255-2263.
- Matthews FE, Arthur A, Barnes LE, et al. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England. *Lancet*. 2013;382(9902):1405-1412.