Desai et al. investigated whether engaging in physical activity moderated the association between concentrations of plasma neurofilament light chain (NfL) and cognitive function over time in adults aged 65 years or older who participated in the well-characterized Chicago Health and Aging Project. In their study, Desai et al. included 1158 participants, of whom 695 (60%) were African American and 463 (40%) were White (mean [SD] age, 77.4 [6.0] years). Physical activity was self-reported, and cognitive performance was routinely assessed. Participants were stratified by baseline NfL concentration (low [≤ 25.5 pg/mL] vs high [> 25.5 pg/mL]). The results showed that adults with a high NfL level, indicating neuronal damage and/or neurodegeneration, and low physical activity (0 minutes per week) were more likely to experience global cognitive decline, including declines in Mini-Mental State Examination scores, compared with those with low NfL levels and medium (> 0 to 150 minutes/week) or high (≥ 150 minutes/week) physical activity. Results were similar for episodic memory and perceptual speed. Their findings suggest that engaging in physical activity may mitigate at least some of the harmful effects of neuronal damage through unknown mechanisms. These results are consistent with those of a previous study that stratified groups based on low vs high levels of plasma total tau, also a marker of neuronal damage and/or neurodegeneration.

Owing to a rapidly aging global population, the number of people affected by dementia is expected to increase substantially during the coming decades, with most of the increase expected in low- and middle-income countries. The World Health Organization reports that by 2030, 17% of the world's population will be age 60 years or older. By 2050, the population of those 60 years or older will double, of whom two-thirds will be living in low- and middle-income countries. Intensive research efforts have been forged to delineate the underlying causes of dementia, and it is well-established that an intricate combination of genetic and lifestyle factors contributes. In the latest report by the Lancet Commission, it was stated that up to 40% of dementia cases can be prevented with appropriate management of modifiable risk factors. These risk factors are similar to those that have been identified for cardiovascular disease. One of these factors is physical inactivity, which may be associated with diminished cognitive reserve and increased metabolic (eg, obesity, diabetes) and vascular (eg, hypertension) risk. The multidomain World-Wide Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGERS) focuses on lifestyle factors in dementia prevention. These lifestyle factors include physical activity, cognitive training, dietary counseling, social activities, and monitoring and management of vascular and metabolic risk factors. However, studying the mechanism whereby these lifestyle factors may influence the underlying biology of dementia through the use of biomarkers has been limited to analyses of cerebrospinal fluid (obtained via an invasive and logistically challenging procedure) and/or brain imaging (usually costly, with limited access globally).

The rapid development of blood-based biomarkers reflecting pathophysiological processes in the nervous system has been one of the major scientific achievements of the 21st century. One of these, NfL, a biomarker of neuroaxonal injury, is an analytically robust, dynamic cross-disease biomarker that reflects both acute neuronal injury and neurodegeneration. In patients with Alzheimer disease (AD), higher levels of plasma NfL are observed, and longitudinally measured increases in NfL are associated with cognitive deterioration and neurodegeneration. These features pave the way to study NfL in epidemiological studies. In addition to the Chicago Health and Aging Project, other population-based studies, such as the Rotterdam Study, have reported that a higher
baseline NFL level was associated with a 1.5-fold increased risk of AD over a 14-year follow-up period and that an amplified rate of NFL increase began approximately 10 years before AD diagnosis.9

A caveat of population-based observational studies of lifestyle factors is that they cannot prove causation. Individuals who engage in a higher degree of physical activity may also be more likely to engage in other protective behaviors for cognition, for example, being more engaged in social activities and having a lower likelihood of depression. In addition, NFL levels have been shown to be altered in most neurological diseases affecting neurons in both the peripheral and central nervous systems and thus provide insights overall related to nerve damage.

Desai et al1 showed that any physical activity (vs no physical activity) was associated with slower cognitive decline in older adults when stratified by low and high neurological risk as measured by plasma levels of NFL. This observation paves the way for other biomarker studies in population-based settings that include lifestyle factors and interventions. An intriguing question still open for debate is whether the risk of AD can be mitigated by lifestyle interventions and whether that risk can be monitored using blood-based biomarkers. The advent of blood-based biomarkers that, unlike plasma NFL and total tau, are specific for AD-related processes, such as plasma phosphorylated tau (reflecting altered tau metabolism in response to amyloid plaques), the Aβ42/40 ratio (a biomarker of amyloid plaque formation), and glial fibrillary acidic protein (marking astroglial activation), remain to be adequately evaluated in observational studies, randomized clinical trials, and community intervention settings.7 As evident in the study by Desai et al,1 blood-based biomarkers have the potential to deepen the understanding of risk factor management alongside underlying pathophysiological processes that eventually lead to dementia.

REFERENCES

