Editorial

Is dementia a preventable disease?

Michael Davidson, MD; Florence Thibaut, MD, PhD, *Editor in chief*

There currently exists evidence of moderate quality that cognitive training, blood pressure management, and physical activity can delay onset or slow progression of AD.[1] All other preventive interventions have either produced negative and controversial results or are still under investigation. This issue will present reviews on both established preventive interventions and those under investigation.

The prospect of being affected by dementia, in general, and by Alzheimer disease (AD) in particular, is a source of worry for many of us as individuals and as a society. These worries are enhanced by knowing an affected individual whether genetically related to us or not and, by the self-realization that as we age the frequency of memory lapses increases.

Research during the 1980s and 1990s was dominated by the optimistic, yet biologically naïve notion that pharmacological enhancement of the activity of a single or a few neurotransmitters would ameliorate the ravages of AD. The ability to visualize with the help of position emission tomography (PET) the pathognomonic marker of AD, the amyloid deposit, has led to a plethora of trials since the beginning of 2000, targeting the amyloid deposits. However, like the neurotransmitter enhancing strategy, the anti-amyloid strategy yielded negative results. Since AD is characterized by progressive degeneration of neurons and synapses in key brain areas, a plausible explanation for these treatment failures would postulate that by the time the disease is clinically manifested, considerable tissue damage has already occurred; damage which cannot be reversed. Therefore, much of the current research efforts have been switched from treatment to prevention. If indeed the amyloid plaque and the tangles which are present 5 to 10 years before clinical manifestation are on the pathophysiological pathway to the disease and not just an innocent marker, then a wide window for prevention exists.

Like most diseases, AD is the result of genetic predisposition interacting with mutable factors, some of which have already been identified - hence, candidates for prevention. Prevention can consist of pharmacological/medical interventions and/or in risk-reducing lifestyle. However, to institute effective prevention programs, it is essential to accurately define the population at risk and to quantify the risk. Pharmacological/medical interventions must be safe and well-tolerated and lifestyle interventions must be readily applicable and nonintrusive. To prevent disappointment and subsequent noncompliance, it is essential to communicate clearly to the health professionals and to the public the experimental background supporting the available preventive interventions and their inherent limitations.

In our State of the art article, *Is Alzheimer disease a failure of mobilizing immune defense?* (p 7), Katsel and Haroutunian compare post-mortem data from a cohort of very old (>80 y/o) nondemented individuals with a cohort of demented individuals to explore the role of microglia modulation on the pathophysiology of AD. In a related article by Arad and Schwartz, *Potential immunotherapy for Alzheimer disease and age-related dementia* (p 21) the authors propose a treatment strategy by which the naturally occurring inhibitory mechanism of the immune system is blocked with the help of a systemically injected antibody. This in turn opens the blood-brain barrier, thus activating the central nervous system (CNS) "aging" immune system of AD patients. In turn, the CNS-activated immune system cleaves the plaques and other related debris and, in the AD-engineered rodent improves cognitive abilities. In sum, although we are far from full elucidation on which intervention is beneficial, there are some hints that

Author affiliations: Nicosia University, Cyprus (Michael Davidson); University Hospital Cochin (site Tarnier), Faculty of Medicine Paris Descartes (University Sorbonne-Paris Cité), INSERM U 894, IPN, Paris, France (Florence Thibaut). **Address for correspondence:** Florence Thibaut, University Hospital Cochin (site Tarnier), Faculty of Medicine Paris Descartes (University Sorbonne-Paris Cité), INSERM U 894, IPN, Paris, France. (email: florence.thibaut@aphp.fr)

lifestyle changes might reduce the risk for AD. Observational data collected over the last 5 years reveal a reduction in AD incidence which can be attributed to better lifestyle.[2,3] Due to the fact that drug development for AD currently is unsuccessful, validated targets and validated biomarkers are of utmost importance. Lewczuk et al[4] reviewed in 2017 cerebrospinal fluid and blood biomarkers for neurodegenerative dementias.

Jessen focuses on methodology in *What are we trying to prevent in Alzheimer disease?* (p 27) discusses the trial design, the functional and biomarkers outcome measurements, and the regulatory environment for prevention trials. In *Cognitive stimulation, training, and rehabilitation* (p 35), Kurz concludes, based on randomized controlled trials (RCTs), that nonspecific cognitive-enhancing activities or cognitive stimulation produce small benefits in healthy elderly, mild cognitive impairment (MCI), and early dementia. Cognitive training which is based on the repetition of a particular cognitive activity produces benefits on the specific activity, but it is not clear if the benefits translate beyond that specific activity. Cognitive rehabilitation focuses on task rather that a specific cognitive activity and when the benefit is achieved it can delay dependency and institutionalization. The reader is encouraged to scrutinize the claim of effectiveness advertised by some internet-based programs for proof of efficacy. In *Dementia treatment versus prevention* (p 43) and *Dementia prevention and reserve against neurodegenerative disease* (p 53), Perneczky reviews the mutable and immutable risk factors and elaborates on the notion that brain reserve might reduce risk for AD. Also, he reviews the interactions between life-long education, occupation, and genetics of IQ versus AD risk. Finally, he suggests that better education might reduce risk for AD. Lautenschlager et al, in *Physical activity for cognitive health* (p 61), assert that sedentary lifestyle increases the risk for dementia and that prospective trials indicate that physical activity (PA) benefits cognitive functioning in healthy elderly, MCI, and mild-to-moderate AD patients. They then review the impediments towards regular aerobic exercise in the elderly and provide specific guidelines on how to overcome the impediments. Scarmeas and Vlachos, in *Dietary intervention in MCI and dementia* (p 69) identify folate, vitamin E, Ω-3 fatty acids, and certain multi-nutrient formulations as potential additives benefiting dementia. However, the authors warn against a large number of potential confounders such as variability in supplement dosage and duration of administration, different chemical composition of the additive, previous and concomitant dietary habits to name only a few.

Bendlin in *Antidiabetic therapies and Alzheimer disease* (p 83) first reviews the observational studies linking type 2 diabetes (T2D) to AD clinical manifestation but not the amyloid deposits suggesting that antidiabetic medication might suppress the formation of the amyloid plaque, hence explaining the apparent discrepancy. However, observational studies of treatment with antidiabetic drugs produced inconclusive results ranging from benefits to no effect or damage. The large number of drugs used to treat T2D, variability in length of treatment, the effect of diabetic illness itself on AD, and the degree of the T2D control by the drugs are only some of the confounding variables that might explain the inconsistent results of the observational studies. Similar to observational studies, prospective trials have produced inconclusive and mainly negative results. Yet investigators continue to research brain insulin signaling and the effect of T2D on brain vasculature in an attempt to elucidate the undisputable link between T2D and risk for AD. Beeri, in *Prevention of dementia presents a potentially critical platform for improvement of long-term public health* (p 93) first provides a model to assess the impact of AD prevention/delay on public health. Then she lists the large multidomain prevention trials. Finally, she speculates on the effect of monitoring and disclosing the risk of AD on compliance with preventive activities.

Finally, in *Ethical issues in early diagnosis and prevention of Alzheimer disease* (p 101), Whitehouse discusses the ethical issues related to AD prevention, touching upon prevention in general, the role of science in society, and AD prevention versus the rest of the competing priorities in the provision of health care. ■

1. National Academies of Sciences, Engineering, and Medicine. 2017. *Preventing cognitive decline and dementia: A way forward.* Washington, DC: The National Academies Press. Available at https://doi.org/10.17226/24782. **2.** Wimo A, Sjolund BM, Skoldunger A, et al. Cohort effects in the prevalence and survival of people with dementia in a rural area in Northern Sweden. *J Alzheimers Dis.* 2016;50(2):387-396. **3.** 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: results of the Cognitive Function and Ageing Study I and II. *Lancet.* 2013;382(9902): 1405-1412. **4.** Lewczuk P, Riederer P, O'Bryant SE, et al. Cerebrospinal fluid and blood biomarkers for neurodegenerative dementias: an update of the Consensus of the Task Force on Biological Markers in Psychiatry of the World Federation of Societies of Biological Psychiatry. *World J Biol Psychiatry.* 2018;19(4):244-328.