

Is Alzheimer's Prevention Possible Today?

In the absence of disease-modifying therapies, clinicians face an urgent need to be aware of potential interventions to reduce risk of, delay onset of, and at least in some cases prevent Alzheimer's disease (AD). Although there is no "magic pill" to prevent AD, evolving evidence can assist in answering a common question from patients: "Is there anything that I can do to reduce my risk?"^{1,2} In *The Prevention of Alzheimer's Disease: Lessons Learned and Applied*, Galvin eloquently and comprehensively provides a practical scientific overview for clinicians whose patients will inevitably ask how they can protect their brain health over time. Galvin appropriately makes the case that, while the field waits for successful pharmacological interventions, it is prudent to apply interventions that influence the multiple genetic, pathological, and biological pathways that may lead to AD while testing hypotheses related to risk reduction and mitigation. Based on the evidence to date, efforts to slow cognitive decline and prevent dementia may be more successful with multimodal interventions directed toward at-risk individuals based on their personal health profiles, rather than the more-common "one size fits all" approach.

As Galvin makes clear, a common methodological constraint of randomized controlled trials, even those that have demonstrated positive outcomes, is their experimental focus on homogeneous study cohorts that make it difficult to generalize results to the individual sitting in front of a clinician. Confirmation studies in real-world clinic settings are needed to test the efficacy and ecological validity of modifiable risk factor-reduction strategies in at-risk individuals, especially those at the asymptomatic preclinical stage of AD.

To this end, over the last few years, it has become more common for clinicians to practice in the field of AD prevention. Aligned with Galvin's rigorous, evidence-based, comprehensive, personalized framework, there are several clinics in United States that focus on AD risk assessment and early intervention. In 2013, the Alzheimer's Prevention Clinic (APC) at New York-Presbyterian Weill Cornell Medical Center was founded, providing direct clinical care to asymptomatic individuals with a family history of AD.³ In 2014, the Alzheimer's Risk Assessment and Intervention Clinic at the University of Alabama in Birmingham was established, followed by the Alzheimer's Prevention Program at Cedars Sinai Medical Center in Los Angeles in 2015, and the Alzheimer's Prevention Clinic and Research Center in San Juan, Puerto

Rico, in 2016 (in research collaboration with Weill Cornell). Similarly, the Cardiology Cognitive Clinic at the Rush Heart Center for Women in Chicago maintains the same philosophy of early care to protect brain health. These programs have applied the best available evidence in varied ways to provide care and educate people in the absence of definitive preventative treatments, and several have used novel strategies in an effectiveness-proven online AD prevention course (www.AlzU.org) to communicate a sound, balanced message to individuals and family members.⁴

From a practical clinical perspective, applying lessons learned from observational studies can help to target a range of modifiable risk factors.^{1,2,5} Population-attributable risk models estimate that one of every three cases of AD may be preventable (5). Considering that AD pathology begins in the brain decades before cognitive decline (1), pre-symptomatic risk factor management may be an important component of both primary and secondary AD prevention. In one report, the projected effect of risk factor reduction on AD prevalence found that a modest (10–25%) reduction in seven risk factors (diabetes mellitus, midlife hypertension, midlife obesity, smoking, depression, cognitive inactivity or low educational attainment, and physical inactivity) could prevent as many as 1.1 million to 3.0 million AD cases worldwide and 184,000 to 492,000 cases in the United States.⁶

Clinicians and patients have two options: to face the challenges of AD passively or to intervene based on the mounting scientific evidence for a direct relationship between lifestyle and vascular-related risk factors and future dementia. Most of these changes are balanced in terms of risk versus benefit and, especially when under physician supervision, grounded in safety,⁷ yet there remains substantial confusion for practicing physicians. With each passing week, more studies are published on either side of the fence, which can help and hinder. Most commonly in medical practice, treatment plans are designed for the "average patient" based on the best-available evidence, incorporating a broad spectrum of data from heterogeneous cohorts that may, or may not, be directly applicable.⁸ It may be most practical to provide each person with an individualized, detailed plan (fortified with qualifiers) for reducing the risk of dementia after an extensive evaluation of his or her medical history, lifestyle factors, body composition, and laboratory and cognitive assessments. Physicians can apply this framework rather than adhere to the concept that AD prevention is not possible, which could be interpreted to mean, "There is

This Editorial comments on the article by James E. Galvin

DOI: 10.1111/jgs.15060

nothing you should do. You don't have to exercise; you don't have to eat healthy; you don't have to engage your brain; you don't have to socialize because it won't help your brain."

Some of the most-robust and -applicable evidence comes from the landmark Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER). Published in the *Lancet* in 2015, this large, 2-year study established that an evidence-based program combining a brain-healthy diet, exercise, cognitive training, and vascular risk monitoring helped improve or maintain cognitive function in elderly people at risk of AD.⁹ Different effects have also been reported in carriers and noncarriers of the apolipoprotein (APO)E ϵ 4 gene, with the multidomain intervention being more effective in APOE ϵ 4-positive subjects.¹⁰ Conversely, the Multidomain Alzheimer Preventive Trial (MAPT) did not find significant effects of multimodal lifestyle interventions, omega-3 docosahexaenoic acid (DHA) supplementation, or a combination of the two on episodic memory.¹¹ It is instructive to postulate why the FINGER and MAPT studies had different outcomes. Considerations include the cognitive outcomes selected, or the older age, greater frailty, more-impaired baseline cognitive function, and a nutrition pattern that was considerably higher in carbohydrate intake in MAPT subjects. In addition, using a "one size fits all" approach with respect to supplementation with the omega-3 fatty acid DHA without first assessing red blood cell DHA levels in MAPT is one example of an intervention inconsistent with a customized approach.

Along these lines, according to the National Institutes of Health, precision medicine is defined as "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person".¹² The most-accurate term to describe a prudent way forward toward AD prevention may be what has been termed clinical precision medicine, whereby the use of an expanded clinical history (e.g., neurodevelopment, academic trajectory, past and current lifestyle patterns, environmental exposures, life course events) is combined with past medical history and physical and neurological examination and then interpreted in conjunction with anthropometric measures, blood biomarkers (including genetics), and cognitive performance.^{3,13} A comprehensive, multimodal management plan can then be carefully crafted by cross-referencing each point of data, and the person is followed longitudinally to evaluate the effectiveness of this clinical precision medicine intervention. Galvin suggests conducting these types of "N of 1" trials to evaluate the effectiveness of targeted evidence-based intervention strategies in an effort to validate this approach in a real-world clinical setting.

In the end, much of the argument may come down to a matter of semantics. Is it really possible to absolutely prevent a heart attack or a stroke? No. But decades of evidence favors the potential for significant risk reduction.^{14,15} Although the totality of the evidence in AD prevention is not as robust, the opportunities to apply emerging evidence in the clinic today are burgeoning. Preliminary results from the APC cohort have shown that the

clinical practice of AD prevention is feasible, and significant improvements in cognition and laboratory markers of AD risk have been demonstrated over time.¹³ Based on the totality of evidence and early experiences in the clinical management of AD prevention, we anticipate the continued growth of this medical specialty. Further research is warranted, and Galvin provides a roadmap for like-minded individuals to follow.

Richard Isaacson, MD
Department of Neurology, Weill Cornell Medicine,
New York, NY

ACKNOWLEDGMENTS

Conflict of Interest: The author serves on the scientific advisory boards for Lilly, Neurotrack, and 23 and Me and fully discloses that he has no other financial interests or potential conflicts in the 3 years before submission of the manuscript.

Author Contributions: The author is solely responsible for this work.

Sponsor's Role: The manuscript was funded by UL1TR00457 by the National Center for Advancing Translational Sciences.

REFERENCES

- Galvin JE. The prevention of Alzheimer's disease: Lessons learned and applied. *J Am Geriatr Soc* 2017; DOI: 10.1111/jgs.14997.
- Smith AD, Yaffe K. Dementia (including Alzheimer's disease) can be prevented: Statement supported by international experts. *J Alzheimers Dis* 2014;38:699–703.
- Seifan A, Isaacson RS. The Alzheimer's Prevention Clinic at Weill Cornell Medical College / New York—Presbyterian Hospital: Risk stratification and personalized early intervention. *J Prev Alz Dis* 2015;2:254–266.
- Isaacson RS, Haynes N, Seifan A et al. Alzheimer's prevention education: If we build it, will they come? *J Prev Alz Dis* 2014;1:91–98.
- Norton S, Matthews FE, Barnes DE et al. Potential for primary prevention of Alzheimer's disease: An analysis of population-based data. *Lancet Neurol* 2014;13:788–794.
- Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol* 2011;10:819–828.
- Sabayan B, Farzaneh S. Reducing risk of dementia in older age. *JAMA* 2017;317:2028.
- Caplan LR. How well does "evidence-based" medicine help neurologists care for individual patients? *Rev Neurol Dis* 2007;4:75–84.
- 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): A randomised controlled trial. *Lancet* 2015;385:2255–2263.
- Health Interventions Boost Cognition—But Do They Delay Dementia [on-line]? Available at www.alzforum.org/news/conference-coverage/health-interventions-boost-cognition-do-they-delay-dementia Accessed July 1, 2017.
- Vellas B, Carrie I, Gillette-Guyonnet S et al. MAPT study: A multidomain approach for preventing Alzheimer's disease: Design and baseline data. *J Prev Alzheimers Dis* 2014;1:12–22.
- What is precision medicine [on-line]? Available at <https://ghr.nlm.nih.gov/primer/precisionmedicine/definition> Accessed July 1, 2017.
- Schelke MW, Hackett K, Chen JL et al. Nutritional interventions for Alzheimer's prevention: A clinical precision medicine approach. *Ann N Y Acad Sci* 2016;1367:50–56.
- Clinical Practice Guidelines for Prevention [on-line]. Available at https://professional.heart.org/professional/ScienceNews/UCM_457211_Clinical-Practice-Guidelines-for-Prevention.jsp Accessed July 1, 2017.
- Guidelines and Statements [on-line]. Available at <http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&cy=&t=1084> Accessed July 1, 2017.