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EDITORIAL

Prevention of Late-Life Dementia: No Magic Bullet

In describing the biodemography of human aging, noted demographer James Vaupel wrote that half of the children alive in 2010 in countries with the highest life expectancies may live to celebrate their 100th birthday. He also wrote about a related public health imperative: the high rates of Alzheimer disease and related dementias (ADRD) in persons older than 85 years. Quoting Shakespeare's *As You Like It* ("sans teeth, sans eyes, sans taste, sans everything"), Vaupel called cognitive impairment and sensory deprivation, especially vision and hearing loss, the "two scourges of senescence" (1).

Since the early to mid-1980s, scientific attention and support for research on ADRD have increased. Although symptoms generally occur in late life, the underlying brain pathology probably develops many years earlier. Care and management of people with ADRD are improving, but we have no cures or even disease-modifying treatments; in any case, prevention is more attractive. Even delaying ADRD onset would have a profound effect on public health and individual lives.

The 4 evidence-based reviews (2–5) from the Minnesota Evidence-based Practice Center (EPC) published in *Annals* summarize findings from randomized controlled trials (RCTs) on the effectiveness of interventions to prevent cognitive decline, mild cognitive impairment, and clinical Alzheimer-type dementia. Because EPC systematic reviews inform the U.S. Preventive Services Task Force (USPSTF) and public health messaging, the process to generate them is stringent and standardized. These reviews were supported by the Agency for Healthcare Research and Quality and the National Institute on Aging to provide the evidence base for a recent National Academy of Medicine (NAM) report on preventing cognitive decline and dementia (6).

I served on the NAM committee that developed the report based on the Minnesota EPC reviews. I was also one of 24 international researchers involved in a Lancet Commission report (7), released at the same time as the NAM report, that covers "effective dementia prevention, intervention, and care." Aging patients and friends who expect to live to age 90 or older, when the prevalence of dementia increases to 50% or more, often say to me, "I sure hope I don't get Alzheimer's." How do the 4 EPC papers and the NAM and Lancet reports answer the questions these people have about preventing or delaying the onset of ADRD?

To put it simply, all evidence indicates that there is no magic bullet. Our NAM committee searched in vain for convincing evidence of effective preventive interventions from the RCTs reviewed by the EPC. Although we found some intriguing positive results for physical activity (8) (reviewed in Brasure and colleagues [2]), cognitive training (9) (reviewed in Butler and colleagues [5]), and possibly multifactorial interventions (10), nothing even approached the evidence level required for a USPSTF recommendation. The 2 other EPC papers, from Fink and colleagues (3) and Butler and coworkers (4), also found insufficient evidence to support medications or supplements for cognitive protection. Of the papers cited in the 4 reviews, the vast majority did not meet strength-of-evidence standards, offered little evidence of effectiveness, or both. For all the potential treatments considered during the past decades on the basis of observational studies or hypotheses about reducing neurodegeneration—from prescription medicines, to over-the-counter drugs, to vitamins—the evidence is insufficient to make EPC-based clinical recommendations.

Why is this so? In part, the lack of evidence reflects the challenge of studying prevention of a common chronic disease that originates well before symptoms occur. To see effectiveness, trials on preventive interventions may need to begin when participants are in midlife. Such lengthy trials would have huge logistic challenges, be costly, and be difficult to interpret because of probable selective attrition. Equally challenging, as pointed out in the NAM report, is that many of the most promising interventions, such as controlling hypertension, avoiding smoking, exercising, and treating diabetes and other vascular risk factors, are already goals of standard medical care. The need for randomization to control treatments would create ethical dilemmas.

Another reason for the disheartening findings of the EPC papers is that they reviewed only RCTs. The Lancet Commission on dementia took a different tactic in its prevention section. The report notes 2 interesting recent observational findings. First, the overall number of people with dementia is rising rapidly, primarily because of aging populations and an increase in dementia incidence in China and prevalence in Japan. However, some countries, including the United States, the United Kingdom, Sweden, the Netherlands, and Canada, have had an unexpected decline in age-specific incidence or prevalence of ADRD (7). The commission noted that this reduced dementia risk is probably related to lifetime exposure to more favorable socioeconomic, health, and lifestyle factors for persons born later in the 20th century. Second, the report acknowledged that dementia neuropathology is complex, and community-based autopsy studies have shown that plaques and tangles of Alzheimer disease often occur with other degenerative findings, including microvascular infarcts and Lewy bodies, which probably contribute to cognitive decline. Of even more importance, the report cites surprising results from community-based U.S. studies showing that some persons with advanced neuropathologic signs of Alzheimer disease do not

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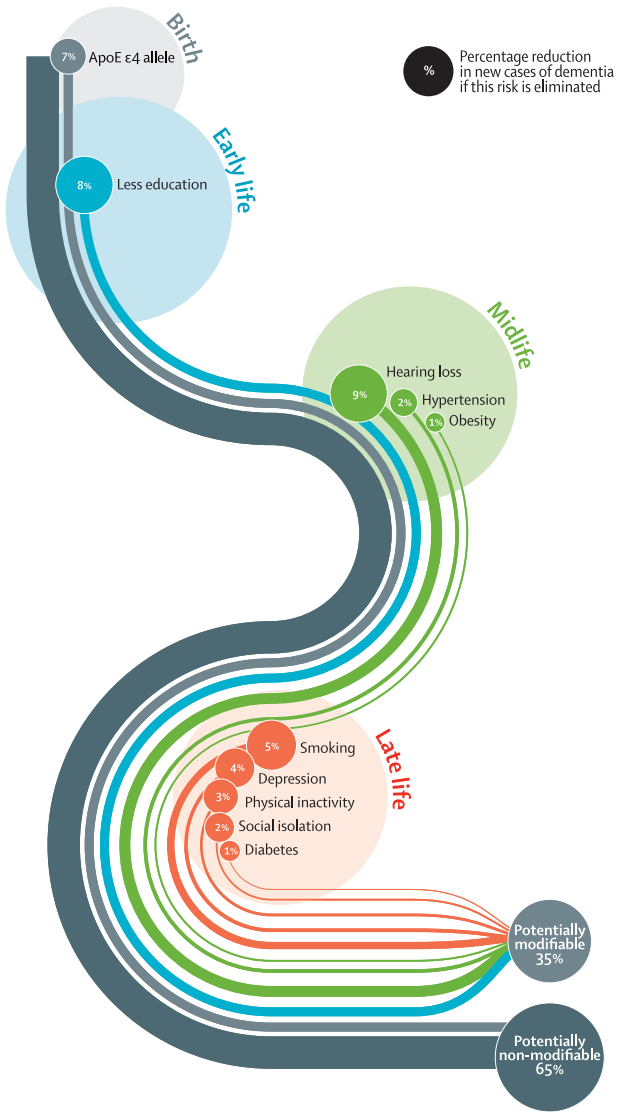
Figure. Risk factors for dementia.



The Lancet Commission's new life-course model, showing potentially modifiable–and nonmodifiable–risk factors for dementia. ApoE = apolipoprotein E. (Reprinted from *The Lancet*, 19 July 2017, Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al, Dementia prevention, intervention, and care, Copyright 2017, with permission from Elsevier).

have dementia but are resilient to showing its symptoms, even into very late life (11).

These 2 findings led the Lancet Commission to conclude that our best chance for preventing dementia is a "life course" approach, particularly toward suspected modifiable risk factors (**Figure**). This strategy acknowledges that factors throughout life influence ADRD development but may be modifiable and probably are susceptible to public health interventions and clinical care. In addition, improving risk factors will contribute to better general health and well-being.

The NAM report concluded that classes of interventions supported by encouraging, although inconclusive, evidence are cognitive training, blood pressure management, and increased physical activity. The Lancet Commission had a broader but overlapping list. The commission recommended promoting universal education to improve socioeconomic well-being, increasing physical activity, reducing or stopping smoking, and maintaining social engagement, as well as managing hypertension, obesity, hearing loss, depression, and diabetes. Like the 4 EPC papers, both reports highlight the scant data from RCTs. Both groups were encouraged that more evidence may come from ongoing research, such as studies of "combination therapies" that address several individual, modifiable risk factors.

When people ask me how to prevent dementia, they often want a simple answer, such as vitamins, dietary supplements, or the latest hyped idea. I tell them that they can take many common-sense actions that promote health throughout life and may help to avoid or delay ADRD, namely regular physical activity; control of vascular risk factors, including preventing or effectively managing diabetes; not smoking; and maintaining a healthy diet and weight. Engaging in cognitively stimulating activities and avoiding social isolation also are probably beneficial. As our patients age, we should do what we can to correct their vision and hearing loss and stay aware of drugs that harm the brain and increase dementia risk, such as chronic high doses of anticholinergics (12). Note that none of these recommendations has harmful side effects.

Thus, although we do not have a magic bullet to prevent ADRD, 2 recent, comprehensive reports emphasize that we have made progress in understanding the biology of the aging brain. Promising trials on dementia prevention are under way. The EPC papers and the NAM and Lancet reports provide a measured assessment of our current knowledge and a motivation to learn more ways to build resilience for a healthier late life (13).

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