

# Prevention of dementia presents a potentially critical platform for improvement of long-term public health

Michal Schnaider Beeri, PhD

With the aging of the population, Alzheimer disease (AD) has become an epidemic and a major public health threat. Hundreds of molecules tested in clinical trials in the last decade to treat AD have failed, moving the field to examine the clinical and neurobiological value of prevention of cognitive decline and AD. This short review describes recently finished or currently ongoing clinical trials for prevention of AD, both their main outcomes and secondary outcomes. In addition, the potential modifying effects of age and of genetics as important factors that may affect the design of future clinical trials is discussed. Finally, we discuss the development of new molecular imaging and of digital technologies as a means to disclosure of dementia-related risk and disease progress, and their potential importance as contributors to adherence to healthy lifestyle for the prevention or delay of AD onset.

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## Introduction

After several decades without successful dementia drug discovery, prevention or delay of cognitive decline is a public health priority. Findings from numerous prospective longitudinal observational studies have identified seven major, potentially modifiable, risk factors that show consistent association with Alzheimer disease (AD) (midlife diabetes, midlife hypertension, midlife obesity, physical inactivity, depression, smoking, and low educational attainment).<sup>1</sup> The combined population-attributable risk for these modifiable risk factors is 30%,<sup>1</sup> which suggests that prevention or good control of these risk factors may postpone the onset and reduce substantially the incidence of dementia. Postponement of AD onset by 5 years has been estimated to decrease its prevalence by up to 50% in 50 years,<sup>2</sup> effectively targeting these risk factors may have a major public health benefit. Assuming

that there is a causal relationship between the risk factors and dementia, and that they are treated in midlife, when evidence suggests they affect brain health most, it is estimated that relative reductions of 10% per decade in each risk factor could reduce the prevalence of AD in 2050 by 8.3% globally.<sup>1</sup> If no effective interventions are developed, about 130 million individuals will suffer from dementia worldwide. An 8.3% reduction in prevalence concretely translates into preventing 11 million individuals from developing dementia.

The focus of this short review will be multidomain clinical trials that target the most well-established risk factors associated with cognitive decline, AD, and dementia, and on factors that might affect the potential effectiveness of such clinical trials. Dementia is a disease of multiple etiologies, but the currently available diagnostic and prognostic tools are not able to pinpoint the etiologies for a

**Author affiliations:** The Joseph Sagol Neuroscience Center, Sheba Medical Center, Tel HaShomer, Israel; Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York NY, USA. **Address for correspondence:** The Icahn School of Medicine at Mount Sinai, Department of Psychiatry, One Gustave Levy Place Box 1230, New York, NY 10029, USA. (email: [michal.beeri@mssm.edu](mailto:michal.beeri@mssm.edu))

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particular individual. Thus, multidomain prevention interventions provide a broader opportunity for targeting at least some of the etiologies of individuals at high dementia risk, thus slowing the disease process.

## Clinical trials for the prevention of Alzheimer disease

There have been numerous single domain randomized clinical trials for the prevention of cognitive decline, including the OPAL,<sup>3</sup> ACTIVE,<sup>4</sup> LIFE,<sup>5</sup> and IHAMS<sup>6</sup> studies and some with promising results, such as the ACTIVE trial, where the improvements of the targeted cognitive function (reasoning, speed of processing, and memory) were retained after 5 years.<sup>4</sup> However, a recent extensive literature review of randomized control trials on single lifestyle interventions for AD yielded inconsistent results<sup>7</sup> (in the ACTIVE trial itself, incident dementia after 5 years did not decrease in the intervention groups<sup>8</sup>). The positive results of the multidomain lifestyle model FINGER<sup>9,10</sup> study (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) brought some optimism which was accompanied by the disappointing results of the multidomain pre-DIVA<sup>11,12</sup> (Prevention of Dementia by Intensive Vascular Care) and MAPT<sup>13,14</sup> (Multidomain Alzheimer Prevention Trial) studies, raising concerns regarding the multidomain approach.

### A summary and discussion of results of each of the prevention trials

#### *FINGER*<sup>9</sup>

This double-blind controlled trial enrolled 1260 individuals between the ages 60 and 77 with a CAIDE (Cardiovascular Risk Factors, Aging and Dementia) Dementia Risk Score of at least 6 points (ie, excluding individuals with very low dementia risk based on this scoring system) and cognition at mean level or slightly lower than expected for age. The intervention targeted several domains (diet, exercise, cognitive training, and vascular risk monitoring) through meetings with relevant professionals who provided specific guidance and information,

and lasted 2 years. For example, the nutritional intervention included three individual meetings with a nutritionist and nine additional group sessions. The control group received general health advice. The primary outcome was cognitive decline. The intervention group had significantly less overall cognitive decline than the control group. The main cognitive drivers for these differences in decline were executive functions and processing speed but not episodic memory. The FINGER study results suggest that a multidomain intervention approach may be effective in delaying the onset of the disease for individuals with high dementia risk due to a relatively high load of dementia-related risk factors. Several replication trials around the world have been launched.<sup>15</sup> Such multidomain recommendations are already applied in the cardiovascular disease field.<sup>16</sup> Beneficial results remaining consistent and similar to those of the original FINGER study would strongly suggest the need for significant involvement of public health decision-makers and policies to broaden multidomain recommendations to delay the onset of dementia.

## The impact of midlife risk factors on dementia risk is stronger than the effect of late-life risk factors

policies to broaden multidomain recommendations to delay the onset of dementia.

#### *preDIVA*<sup>12</sup>

This was a prevention randomized clinical trial with a 6-year follow up of 3700 participants between the ages of 70 and 78, assessing the effect of nurse-led intensive vascular care to decrease dementia incidence and reduce disability. The intervention included treatment of hypertension, hypercholesterolemia, and diabetes; reduction of weight and smoking; and stimulation of physical activity. The intervention consisted of visits every 4 months for 6 years (18 visits) to a nurse in general practice, who assessed the participant's cardiovascular risk factors (smoking habits, diet, physical activity, weight, and blood pressure), and gave individually tailored lifestyle advice. The primary outcomes were incident dementia and disability score. The only exclusion criteria were dementia and other disorders likely to hinder successful long-term participation in the study, such as terminal illness and alcoholism, so the study did not specifically recruit individuals with a high profile of cardiovascular risk factors related to dementia. The intervention did not reduce the incidence of

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all-cause dementia. However, secondary analyses showed a beneficial effect for a subgroup of individuals who had untreated hypertension at baseline, raising the possibility that for those carrying risk factors, such an intervention may confer dementia risk benefit. Interestingly, the intervention was associated with decrease in white matter hyperintensities (WMH) volumes in those initiating the study with high (but not low) volumes of WMH.<sup>17</sup>

## *MAPT*<sup>14</sup>

This randomized placebo-controlled superiority trial of 1680 participants had four arms:

- 1) Multidomain intervention (43 group sessions and three preventive consultations integrating cognitive training, physical activity, and nutrition) plus omega 3 polyunsaturated fatty acid (two capsules a day for a total of 800 mg decosahexaenoic acid and 225 mg eicosapentaenoic acid)
- 2) Multidomain intervention plus placebo
- 3) Omega 3 polyunsaturated fatty acids alone
- 4) Placebo alone. Intervention was for 3 years

Participants were 70 years of age or above, all non-demented community dwelling, who reported either subjective memory complaint, limitations in one instrumental activity of daily living (such as ability to use the phone or shop) and slow gait (below 0.8 m/s, ie, more than 5 seconds to walk 4 meters). The primary outcome was change from baseline to 36 months in a composite z-score combining four cognitive tests covering episodic memory, orientation in time and space, speed of processing, and verbal fluency. There were no significant differences between any of the three intervention groups compared to the placebo group. However, posthoc analyses combining groups showed significantly less decline in the combined multidomain intervention groups compared with those who did not receive multidomain intervention. In addition, in secondary analyses of the orientation cognitive domain, the combined multidomain intervention groups declined significantly slower than the placebo group. Moreover, among participants with a CAIDE score of 6 or greater, the combined multidomain intervention groups had less cognitive decline than the placebo group. Importantly, a subsample (n=269) of the MAPT study underwent amyloid PET scan. Among those who had a positive amyloid scan, slower cognitive

decline was found in the combined multidomain intervention groups, as well as in multidomain intervention plus placebo, than in placebo alone.

## *HATICE*<sup>18</sup> (*Healthy Ageing Through Internet Counselling in the Elderly*)

In addition to these studies that have ended, the ongoing HATICE study aims at improving the cardiovascular profile of 2500 community dwelling participants above the age of 65 who are at increased risk for cardiovascular disease due to two or more cardiovascular risk factors (hypertension, dyslipidemia, overweight, active smoking, lack of physical exercise). The intervention is for 18 months and focuses on promoting awareness and self-management of these risk factors. Participants on the treatment arm will be exposed to a supportive, interactive, internet-based coach platform. Participants can set personal goals for lifestyle change through the platform, make action plans, monitor goals by entering data such as blood pressure, and communicate with a trained coach through messaging within the platform. Control participants will be exposed to a static platform providing general health information. The study is taking place in Finland, France, and the Netherlands. Its overall aims are to optimize the self-management of cardiovascular risk factors, improve the cardiovascular risk (CVR) profile, and reduce the risk of cardiovascular disease, cognitive decline, and dementia.

Although the FINGER study raises some optimism in the potential value of multidomain interventions to delay the onset of dementia by slowing cognitive decline, the overall negative results of the other trials raise concerns about the benefits of the approach. This is apparently surprising as there is a large body of observational<sup>19</sup> and animal model<sup>20</sup> evidence supporting the potential effectiveness of such an approach. It seems that one common characteristic of the three prevention trials is that the focus has to be on individuals who are at high dementia risk, primarily cardiovascular high risk per se: the preDIVA secondary results for less incident dementia in those with untreated hypertensive participants, and the MAPT secondary results of beneficial effects of the multidomain intervention in those with a CAIDE score above 6 support such an argument. However, to complicate matters, in the preDIVA study, the LIBRA modifiable dementia risk score (an index that includes depression, hypertension,

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obesity, diabetes, smoking, renal dysfunction, physical inactivity, alcohol use, age, and education) did not identify a high-risk group for whom the multidomain intervention was effective in preventing dementia or cognitive decline.<sup>21</sup> In addition, although in a small subsample, the MAPT results on AD neuropathology suggest that a multidomain intervention may have a better chance to maintain cognition among individuals whose brain has already some neuropathological compromise. Similarly, the preDIVA study suggests that the intervention could be effective in persons with high WMH volumes.<sup>17</sup> Such results support the view that the intervention affects the disease biology thereby benefiting cognition.

Two additional important factors may have affected the results of these clinical trials—age and genetic background.

### Age is a major modifier of associations of cardiovascular risk factors with cognitive outcomes

The impact of midlife risk factors on dementia risk is stronger than the effect of late-life risk factors. A recent study showed that two or more cardiovascular risk factors in midlife (but not late life), predicted amyloid aggregation.<sup>22</sup> In fact, in the oldest old, many of the associations are “reversed,” such that high levels of the risk factors (eg, hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>),<sup>23</sup> cholesterol,<sup>24</sup> homocysteine<sup>25</sup>) are associated with lower risk for dementia and cognitive impairment. Additionally, the neurodegenerative changes in AD begin decades before its clinical manifestations<sup>26</sup> suggesting that if preventive interventions benefit cognition through the biological mechanisms underlying dementia, such interventions should be initiated in midlife in order to delay dementia-related neuropathologies, and consequently, delaying dementia per se. Understandably, clinical trials of participants who are at midlife may be prohibitively expensive, as dementia and even cognitive decline in that age range is rare; consequently, very large sample sizes would be required, and the intervention would be very long. That said, with current developments of sensitive biomarkers for very early identification of biological outcomes—that are becoming available for observation much earlier than dementia symptoms—a prevention clinical trial for middle-aged high-risk individuals may become practical.

### Genetic background affects associations of risk factors with cognitive outcomes

Simplistically, an intervention should address a disease as a whole, irrespective of the patient’s genetic background. However, genetic background is a critical component in the choice and the effect of medications. The choice of breast cancer medications and treatment protocols, for example, are defined according to the type of breast cancer the patient has, and specifically whether or not the woman is a carrier of a *BRCA* mutations.<sup>27</sup> Theoretically, the ultimate personalized medicine model adapts the intervention according to each person’s genetic background. In the context of cognition and AD, much scientific progress is needed for this approach to become relevant and effective.

The associations of several modifiable risk factors with cognition, and with brain-related outcomes associated with AD, are stronger (or exclusively significant) among *APOE4* genotype carriers. These include obesity,<sup>28</sup> type 2 diabetes,<sup>29,30</sup> glycemic control,<sup>31</sup> blood pressure,<sup>32,33</sup> and physical activity.<sup>34,35</sup> In contrast, some studies suggest associations of cholesterol<sup>36</sup> and physical activity with AD-related cognitive outcomes among *APOE4* noncarriers, but no associations among *APOE4* carriers. Additionally, some evidence suggests that treatments for certain cardiovascular risk factors have a beneficial effect on cognition of *APOE4* noncarriers, with no effect on *APOE4* carriers—for example, angiotensin-converting enzyme inhibitors,<sup>37</sup> the insulin sensitizer rosiglitazone,<sup>38</sup> and intranasal insulin.<sup>39</sup> A few studies (ref 40 provides a good example) did not find a modulating role for the *APOE4* genotype on the relationships of modifiable risk factors with cognitive and brain outcomes related to AD.

*APOE4* is the most consistently found and replicable risk genotype for AD, and the large body of evidence for differential effects in observational studies, as well as in clinical trials strongly suggests that it should be accounted for in prevention clinical trials as well. Supporting this view are the results of the FINGER study, where the effect of the multidomain lifestyle intervention for prevention of cognitive decline was stronger (albeit not statistically significantly) in *APOE4* carriers than in noncarriers.<sup>41</sup> The (non-significant) trend was the same for the MAPT study.

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Beyond effects of *APOE4*, there are recent findings suggesting that for specific conditions that increase the risk of dementia, such as type 2 diabetes, related genes may modulate the effect on dementia. For example, haptoglobin, a gene whose effects on diabetes complications have been well-established,<sup>42</sup> have been recently associated with poorer cognitive functioning<sup>43</sup> and greater cognitive decline among elderly individuals.<sup>44</sup> Moreover, the haptoglobin genotype modulated the association of glycemic control with cognition<sup>45</sup> and with hippocampal volume<sup>46</sup> in cognitively normal type 2 diabetic elderly, such that among those carrying the 1-1 genotype, these associations were strong, while among noncarriers, they are essentially nonexistent. This implies greater susceptibility of the brain of haptoglobin 1-1 carriers to the deleterious effects of poor glycemic control and the potential of this subgroup to benefit from glycemic control-related interventions. These results suggest investigating the potential effects on outcomes of dementia-related genes other than *APOE*.

## Dementia-related risk disclosure and digital technologies may become important contributors to adherence to healthy lifestyle for the prevention of dementia

Another issue of substantive relevance to dementia-related clinical trials is the identification of the factors enhancing adherence to the intervention. Risk disclosure may become a critical factor. For example, there is initial evidence individuals who proactively seek AD genetic risk assessment use results to inform behavior changes.<sup>47</sup> Risk disclosure of the *APOE4* genotype was associated with greater intake of dietary supplement in *APOE4* carriers—but not in noncarriers—in the REVEAL trial.<sup>48</sup>

Importantly, disclosure of *APOE4* genotype does not seem to increase distress.<sup>49,50</sup> The disclosure of amyloid PET results is only now evolving, so little evidence is available on behavioral/lifestyle effects. One small study<sup>51</sup> has shown that disclosure of PET amyloid status did not significantly impact mood, but that subjects with increased amyloid burden were more likely than those whose amyloid PET scan was negative to make positive changes to their lifestyle, such as engaging in more exercise and changing their diet. Disclosure of amyloid status was not a barrier to recruitment in preclinical AD clinical trials.<sup>52</sup> The combination of little emotional distress, improved recruitment, and improved response to intervention suggest the potential of risk disclosure as an important contributor to better outcomes in prevention clinical trials.

Finally, the massive development of wearables and smartphone applications may open new prospects for lifestyle improvements and better long-term adherence to these changes. Speech-to-text capabilities may improve participants' adherence, as "talking out loud one's own risk factors" might increase awareness and improve engagement in the intervention process. Furthermore, in contrast to "classic" clinical trials, where intermittent "little data" is collected sporadically, use of mobile technologies can create "big data" of continuous risk factor management. Mobile phones are used by most adults, even in developing countries, so preventive intervention using mobile technology to maintain long-life cognitive health should be investigated. ■

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