Preventative medicine and Alzheimer's disease: is Alzheimer's disease risk reduction achievable?

Benjamin Sinyor*, Richard Isaacson, Christopher Ochner

Alzheimer's disease (AD) has a multifactorial etiology that has eluded scientists and clinicians for decades. This incomplete understanding of the causal factors likely contributes to the dearth of effective therapeutics available to treat this growing pandemic. Cholinesterase inhibitors such as galantamine, rivastigmine and donepezil are considered frontline treatments but these medications merely treat some of the symptoms associated with AD, rather than curing or even slowing the progression of the disease. This has caused some investigators and clinicians to start exploring the potential to prevent AD. However, the concept of AD has gained widespread acceptance in the clinical community, with many stating that the prevention of AD is impossible. While we would concede that reducing the likelihood of AD development to zero is impossible, these authors argue that significant reduction of the risk of developing AD, particularly in patients at an elevated risk for AD development, is achievable today, and can save many lives and life years.

The focus of this piece is on primary prevention of AD, which we consider to be reduction of the likelihood of individuals to develop AD in the future. However, there is evidence to suggest that some of the same preventive measures recommended for risk reduction in asymptomatic individuals may work for secondary prevention [e.g., slowing or halting the progression from preclinical AD to mild cognitive impairment (MCI) to AD] and perhaps even tertiary prevention (i.e., maintaining and/or restoring some cognitive functions in individuals with MCI due to AD) as well. Because these interventions require an investment (i.e., time, effort, cost) and because it is easier to study the efficacy of prevention interventions in at-risk samples, our discussion and the supportive evidence presented will focus on risk reduction in individuals with risk factors for the development of AD. These risk factors include age, a family history of AD, a history of traumatic brain injury, heart disease, diabetes, stroke, high blood pressure, high cholesterol and known presence of one or two Apolipoprotein E (APOE) ε4 alleles, a genetic variant of the APOE gene on chromosome 19.

Growing evidence shows that inflammation, a process which can be mitigated by changes in a diet and lifestyle, could be a major factor contributor to AD development. Pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin 1 beta (IL-1β), and interleukin 6 (IL-6), are upregulated in the brains of individuals with AD, which leads to an accumulation of amyloid B plaque aggregates and tau hyperphosphorylation resulting in neuronal loss (Jack et al., 2018). However, there is a limited window for analyzing cytokines, plaques, neurofibrillary tangles, and tracking constant MRI changes. Given this, early identification of risk factors can be challenging and costly so clinicians should be on the lookout for risk factors that may be determined quickly through the patient's chart and/or reported medical history (e.g., advanced age with a history of heart disease, diabetes, stroke, high blood pressure and/or high cholesterol, with a family history of AD). Presence of some or all of these risk factors may be sufficient for the patient to take preventative action and/or request more in-depth risk assessment from an AD prevention specialist, a growing clinical area.

Genetic and imaging data suggest that through the spectrum of disease, amyloid accumulates initially, followed by tauopathy, and this eventually causes enough microglial activation and neuroinflammation to lead to symptoms (Jack et al., 2018). In "resilient brains", abundant amyloid plaques and tangles can be seen at death with no cognitive deficits, and the reason is likely the same – a lack of neuroinflammation (Cable et al., 2020). Patients can have plaques and tangles but if neuroinflammation is not triggered, it is believed that one would not lose enough neurons to develop cognitive symptoms, and thus addressing the "initiating" proteinopathy (plaques and tangles) decades in advance may hold the most promise for success.

Evidence for primary prevention: Several studies suggest nutritional interventions may be effective in delaying AD onset. The role of antioxidants in AD treatments may be integral in reducing the long term risk of AD. Turmeric has been known to have anti-inflammatory and antioxidant effects in the body. Macrophages have been shown to increase uptake and phagocytosis of beta-amyloid plaques in patients with AD. Turmeric has been shown to reduce the release of reactive oxygen species by increasing neutrophil count and decreasing the levels of pro-inflammatory cytokines such as TNF-α and interleukin 1 beta (IL-1β). As a result, there is a decrease in cytokine inflammation, which is beneficial for patients with AD. Additionally, turmeric exposure also decreased the levels of pro-inflammatory cytokines IL-1, IL-6, and TNF-α. A study done *in vitro* showed increased production of anti-inflammatory cytokine IL-4 in cultured microglia from mice that were treated with turmeric extract, which has been shown to hinder microglia activation and overall lower inflammatory mediator assembly such as TNF-α (Yang et al., 2005).

Other antioxidants such as vitamin E can possibly slow the dementia pathogenesis in AD. Alpha tocopherol transfer protein (alpha-TTP) or vitamin E concentration has been shown to be increased in the brains of patients with neurodegenerative diseases, demonstrating that vitamin E is an essential antioxidant factor for neuronal protection. A 2014 and 2018 meta-analysis concluded that AD is associated with a low concentration of serum vitamin E (Dong et al., 2018). A Randomized, Clinical Trial of Vitamin E and Memantine in Alzheimer's Disease (TEAM –AD), one of the largest trials known for AD treatment, showed that 2000 IU/day of vitamin E significantly delayed the clinical progression of AD symptoms (Dysken et al., 2014). Vitamin C, a potent antioxidant, also aids to combat oxidative stress, a proposed pathophysiological mechanism of AD. Additionally, the Mediterranean-DASH Diet Intervention for Neurogenerative Delay (MIND) diet which is a combination of the Mediterranean, DASH and increase intake in vegetables was statistically significant with a lower risk of developing AD by 53% (HR = 0.47; 95%CI: 0.29, 0.76) in the top tier group compared with participants in the lowest tier group (Morris et al., 2015). This confirms that antioxidants such as vitamin E and turmeric, as well as the MIND diet indeed play a significant role in decreasing inflammation, which has been associated with the pathogenesis of AD.

Possible mechanisms of action to explain the efficacy of prevention interventions: One of the largest randomized trials testing a lifestyle intervention for AD was the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial. This 1200 person study analyzed cognitive performance (executive functioning, complex tasks) in patients with cognitive decline and increased risk of dementia (Ngandu et al, 2015). The intervention group was offered a combination of nutritional advice and exercise, cognitive training, and other various vascular and metabolic risk factors. Persons in the control group receive regular health advice. The intervention group showed a significant increase in executive functioning, complex memory tasks, processing speeds and a lower risk of cognitive decline (Ngandu et al., 2015). The primary outcome was a change in cognitive performance measured with an NTB total score, a composite score based on results from 14 tests which measures memory and executive function. NTB is a valid, reliable measure that analyzes change of cognition in patients with mild to moderate Alzheimer disease. The results of the NTB measured with a Z score, showed that at 2 years the Z score was 0.20 (SE = 0.02, SD = 0.51) in the intervention group and 0.16 (SE = 0.01, SD = 0.51) in the control group (Ngandu et al., 2015). This means that after 2 years the NTB total score was 25% higher in the intervention group than in the control group, improving significant beneficial effect on cognitive outcome. This highlights that not only dietary factors play a key role in AD, but also non-dietary lifestyle modifications are beneficial as well.

Effect of prevention interventions may depend on genetic predisposition: Using genome-based technologies to diagnose pathology has accelerated in the past 20 years and has been recently adopted into routine clinical practice today. Berkowitz et al. (2018) demonstrated that individuals with the APOE genotype may display a greater significant response to various lifestyle interventions. For example, individuals with ε4 alleles can show more dramatic changes in total cholesterol, low-density lipoprotein, and high-density lipoprotein in response to reductions in dietary fat, whereas individuals without an ε4 allele might express greater cognitive function from the Mediterranean diet (Berkowitz et al., 2018). Aside from specific genes, there are single nucleotide polymorphisms (SNPs) that are associated with an increased risk of AD: CLU, CR1, and PICALM (Berkowitz et al., 2018). These genes are not available to sequence commercially, but do respond to the dietary input and change due to the Mediterranean diet (Isaacson et al., 2019). This reinforces the idea that modifiable risk factors such as diet can effectively alter our genome and mitigate the progression of AD.

Precision medicine may be helpful in assessing and reducing risk for AD development: The idea of sequencing one's genome to tailor their diet

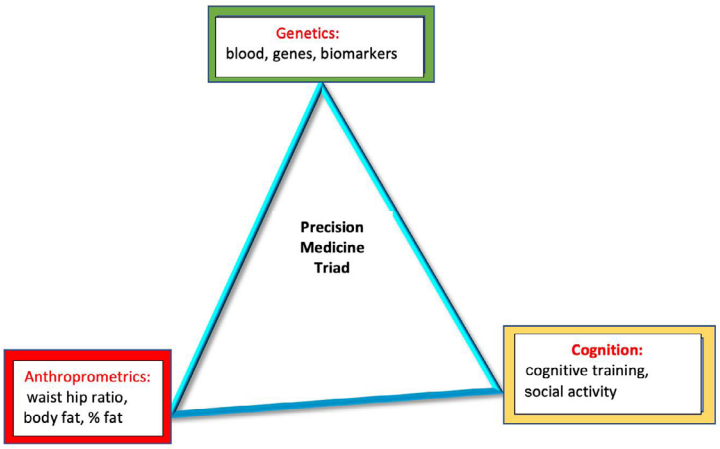

Figure 1 | **Certain markers that can help investigate and mitigate a person with Alzheimer's disease.**

and lifestyle is a concept within reach. Precision medicine, a potential means of primary and/or secondary prevention, is the acquisition of the multifaceted characteristics encompassing a human being. Clinical history, neurodevelopment, academic history, past and current lifestyle habits, environmental exposures, and life events are analyzed. Past medical history, including physical/neurological examination are studied and then interpreted as well. Anthropometrics, the study of the proportions of the human body (body mass index, waist to hip ratio), and blood biomarkers with genetic analysis are performed. In conjunction with the physical examination, a cognitive assessment is also obtained and, along all of this invaluable information, allows us to practice "deep phenotyping", or in other words gathering individual data about each person (**Figure 1**). One key study published by Isaacson et al. (2019) showed that individualized AD risk factor management may improve cognitive function which may be related to AD pathology. Several AD-risk biomarkers such as high-density lipoprotein cholesterol, high-sensitivity C-reactive protein, adiponectin, and 25-hydroxy-vitamin D were improved when a tailored individual regimen was applied to patients who are at risk for AD (Isaacson et al. (2019). These modifiable risk factors can be prioritized to specific treatments and towards an individual approach with prevention.

Summary: Until recently, AD was not regarded as conceivably preventable and more so considered a devastating disease that is poorly understood. Identifying this disease or at least a preliminary AD diagnosis at a younger age may lead to $7 trillion in savings in the US alone, by potentially shortening the time of extensive medical management. Additionally, the mental health burden on families can potentially be spared immensely. Through continued collaborative efforts across medical specialties, the next logical step is to replicate AD risk reduction in clinical practice in additional cohorts globally (Kivipelto et al, 2020). From a clinical perspective, recognizing these processes with precision medicine and an incorporation of antioxidants will allow for definite results in the effort to reduce risk and improve patient outcomes. Clinical trials with the emphasis on the pre-clinical stage can emphasize critical risk reduction and target cognitive decline. The FINGER trial was met with such a positive response that World-Wide FINGERS (WW-FINGERS) was launched in 2017 and included over 25 countries. This conglomerate includes multiple preventative and risk reduction trials. Large RCTs such as the MIND-CHINA, U.S. POINTER, CANADA—CAN-Thumbs-UP, India FINGER, and many more trials are being researched with a parameter placed on each trial (Kivipelto et al, 2020).

A shift of focus on risk reduction and preventative measures should also be ongoing and possibly utilized in the clinical setting. Since there is no cure for AD, patients who are at high risk could benefit from early risk detection to possibly reduce the likelihood of developing AD. Given mounting evidence supporting the effectiveness of preventive measures, clinicians have an obligation to educate themselves and council their patients on different options for AD prevention. It is the hope of these authors that this manuscript encourages more primary care clinicians to: 1. look for AD risk factors and/or early signs of cognitive decline; 2. remember that AD risk reduction is possible, and; 3. feel confident in suggesting that at-risk patients take relatively benign steps towards AD risk reduction by emphasizing a healthy diet by the Mediterranean diet and/or MIND diet. Increasing dietary antioxidant consumption (especially Vitamin E, Vitamin C, and Turmeric) may help decrease inflammation in the brain, and alter our genome to help snare the process of AD. Non-dietary lifestyle modifications such as increased exercise and social interaction can be beneficial, may sharpen cognitive performance and improve executive function. In addition, we hope this piece encourages further investigation, both in the clinic and in the research laboratory, into AD risk reduction regimens tailored to particular individuals. Until there is a cure, clinicians must use all available tools to help patients fight the battle against AD.

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