Brain Health & Dementia Risk Reduction

As preventative neurology becomes possible, it is worth providing risk reduction care to those at risk of Alzheimer’s disease dementia.

By Nabeel Saif BA, MS; George Sadek, BA; Sonia Bellara, MBBS; Hollie Hristov, FNP; and Richard S. Isaacson, MD

Introduction

More than 5.8 million people in the US have Alzheimer’s disease (AD) dementia, and this is projected to grow to 13.8 million by 2050. Considering that dementia affected 50 million people worldwide in 2015, its global effect on careers, families, communities, and societies has become an emerging public health crisis.

Although several pharmacologic strategies have been approved for the treatment of AD, therapeutic advances to delay disease progression has been a challenge. Recent setbacks in drug development may suggest that treatments have been initiated too late in the disease course, hindering the possibility for participants in trials to demonstrate improvements.

Age is the strongest known risk factor for cognitive decline; however, AD is not a natural or inevitable consequence of aging. In fact, pathology of AD begins decades prior to the onset of symptoms. Therefore, a shift in focus toward addressing modifiable AD risk factors, along with developing effective diagnostic tools for early detection of AD, is warranted.

Modifiable Risk Factors and Their Cognitive Effects

Many observational studies have identified a host of modifiable risk factors related to lifestyle (eg, physical inactivity, social isolation, and cognitive inactivity) and certain medical conditions, including hypertension, diabetes, hypercholesterolemia, obesity, and depression, play a vital role in AD risk. Several randomized controlled trials (RCTs) show that proactive risk-factor modification can positively affect patient cognition and health outcomes. The FINGER study, a 2-year large multidomain RCT, demonstrated that multimodal interventions, including dietary recommendations, physical activity, social activity, cognitive training, and metabolic/vascular risk monitoring, resulted in greater cognitive benefit when compared with receiving general health advice. The FINGER study was the first of its kind, and several other RCTs soon followed.

Given the overlap in cardiovascular disease (CVD) and dementia risk factors, the ENLIGHTEN trial focused on aerobic exercise (AE) and dietary approaches to stop hypertension (DASH) interventions in sedentary individuals over age 55. The greatest improvement in executive function came from combining AE and the DASH diet, rather than AE alone, DASH alone, or general health education.

The SPRINT trial and SPRINT-MIND substudy examined whether aggressive systolic blood pressure (BP) control (target BP < 120 mm Hg vs a standard goal of < 140 mm Hg) in participants over age 50 with hypertension could impact rate of developing probable dementia or mild cognitive impairment (MCI). Although there was no significant difference in the rate of probable dementia between the 2 groups, aggressive BP control resulted in a 19% decrease in MCI. The short study duration (3.3 years) may explain why no improvement was seen in the probable dementia outcome, considering the slow progression of AD.

Not all trials have shown positive results, however. The 3-year French MAPT trial failed to show that multidomain interventions (dietary counseling, physical exercise, and cognitive training), omega-3 fatty acid supplementation, or both were effective in mitigating cognitive decline, although this may be attributable to study design. Participants in MAPT were age 70 or more and worse at baseline than participants in FINGER and ENLIGHTEN, who had a lower average age. Additionally, the dietary recommendations were based on the French national nutrition and health program and not corroborated by more recent evidence (eg,
Mediterranean-style or MIND diets); the omega-3 fatty acid supplementation dose (800 mg) was lower than in other studies and not tailored based on participants omega-3 fatty acid serum levels. Similarly, the 2-year lifestyle interventions and independence for elders (LIFE) study, in which participants mean age was also higher and interventions not individually tailored, found that moderate-intensity physical activity (walking, resistance training, and flexibility) produced no difference in cognitive function when compared with health education.\(^\text{11}\)

**Emerging Clinical Practice Risk Reduction Paradigm**

Considering the evolving evidence and complexity of AD pathology, it is becoming more common for health care providers to engage in direct clinical care for AD risk reduction.\(^\text{12-14}\) Several clinics have focused on AD risk assessment and early intervention using an evidence-based approach, while also studying its clinical effectiveness.\(^\text{13,15,16}\) Each program has generally focused on brain-healthy lifestyle approaches and tailored interventions in an effort to optimize brain health and reduce AD risk. These personalized interventions also enhance management of other medical conditions.\(^\text{13-15}\) This approach is based on precision medicine, which is defined by the National Institute of Health (NIH) as an approach to patient care that accounts for each person’s genes, environment, and lifestyle to individualize disease treatment and prevention.\(^\text{13,17}\)

Recently, 2 Alzheimer’s prevention clinics published a structured framework to care for people at risk of AD using a clinical precision medicine approach (Box 1).\(^\text{13}\) Along with traditional patient care practices (eg, past medical history and physical/neurologic examination), a more comprehensive evaluation is suggested to effectively assess AD risk. These measurements constitute the ABCs of AD prevention and provide a framework for pharmacogenomic and nutrigenomic considerations essential for individualizing recommendations. Patients are followed longitudinally (every 6 months) to assess changes across their ABCs, and data from each follow-up assessment is used to further refine recommendations. Preliminary results have demonstrated significant improvements in cognitive performance from baseline to 6 months.\(^\text{18}\)

Although individuals without symptoms have been the majority of people seen based on the hypothesis that preventative measures may be most effective during earliest AD phases (eg, primary and/or secondary AD prevention) (Figure),\(^\text{3}\) persons who present with mild subjective complaints or MCI due to AD are also evaluated. From a practical clinical perspective, clinicians can apply this paradigm of clinical precision medicine to provide individualized, multidomain interventions for AD dementia risk reduction across a broad range of people.

**Useful Risk Evaluation Tools**

When a family member of a person with AD asks, “Is there anything I can do to reduce my Alzheimer’s risk?” there are several evidence-based precision-medicine principles that guide clinical practice. For clinicians interested in seeing patients specifically for AD risk reduction, a natural place to start recruitment is children of people with AD in an existing practice. For more comprehensive information on how this process can work, and the measures that are obtained and tracked, a free continuing medical education (CME) accredited course is available via www.AlzU.org/CME. This course includes free downloadable resources, patient

---

**Box I: Individualized Alzheimer’s Risk Reduction Assessment ABC’s**

A. Anthropometrics (body composition)
   - body composition measures (-%body fat or waist-to-hip ratio)
B. Blood biomarkers of vascular and AD dementia risk
   - lipid profile
   - inflammatory metabolic profile,
   - nutritional biomarkers
   - genetics (APOE, MTHFR)
C. Cognitive performance across relevant domains
   - memory
   - learning
   - executive function
   - processing speed
   - language

Abbreviations: APOE, apolipoprotein E; MTHFR, methylene-tetrahydrofolate reductase.
questionnaires, and extensive references. Herein, we provide initial guidelines on how to implement focused clinical assessments and personalized early intervention plans to reduce AD risk.

Expanded Clinical History

As part of a focused Alzheimer’s prevention clinical history, we recommend assessing a patient’s educational history. This includes high-school/college/graduate school performance/rank and standardized test scores, along with career achievements, all of which are thought to correlate with early brain development, a main component of AD risk assessment. The history should also include past and current lifestyle patterns that would be major targetable risk factors for intervention, including diet, exercise, sleep, hobbies, stress management, mood, hearing loss, and how these may have changed over time. Past medical history, a detailed family history, review of systems, and physical/nerologic examination can follow.

Anthropometrics

Although measuring vital signs is essential to help assess AD risk, measures such as body mass index (BMI) via height and weight may be an imprecise measure for both general as well as brain health. Considered a measurement for stored fat, BMI is nonspecific, whereas waist-to-hip circumference may be a better proxy for metabolic health. This is important as evidence suggests that increased abdominal circumference is associated with smaller hippocampal volumes. Objective measures of body fat distribution (eg, percent body fat and dry lean mass) can better inform clinicians of specific recommendations for individuals. Biometric devices can allow both clinicians and their patients to monitor subtle physical changes over time that may be related to AD risk. The cost range of bioimpedance devices is wide ($100-$15,000), and other more rigorous test means (eg, a dual-energy X-ray absorptiometry [DEXA] scan) can be considered if readily available. If a bioimpedance device is used, it is important to collect measurements in a standardized manner (eg, fasting, same device, same time of day) for more accurate longitudinal comparisons.

Blood Biomarkers and Genetics

Standard lipid markers are an essential component of measuring risk for developing AD, because elevated total cholesterol, low-density lipoprotein cholesterol, and triglycerides have been linked with long-term cognitive decline. Specifically, in people with the apolipoprotein E (APOE) ε4 allele, for example, low APO-A1 (a component of high density lipid [HDL]) is a marker of elevated AD risk. Additionally, metabolic biomarkers (eg, glycosylated hemoglobin [HbA1c], fasting glucose, and fasting insulin) are of special importance when assessing AD risk, as hyperinsulinemia can promote neuroinflammation and amyloid-beta (Aβ) deposition. Diabetes doubles a person’s risk of AD, and elevated fasting glucose can worsen cognition even in those without diabetes, making it a useful biomarker to track. Relevant nutritional biomarkers include serum omega-3/6 fatty acids, vitamin levels (B12 and D), and homocysteine to help guide a targeted plan with appropriate nutrition/dietary supplementation recommendations. Other plasma proteins that can be used to monitor risk include cystatin C, for which elevated levels are associated with increased 3-year risk of conversion from MCI to AD, and N-terminal probrain natriuretic peptide (NT-proBNP), which is associated with vascular dementia.

The ε4 variant of APOE is among the most well-established genetic risk factors for late-onset AD. Although people with APOE ε4 have greater risk of developing AD, recent research has shown they are also more susceptible to certain modifiable lifestyle factors. For instance, those with APOE ε4 who are sedentary, smoke, or consume alcohol have a higher AD risk compared with those without APOE ε4.

Methylenetetrahydrofolate reductase (MTHFR), which has a major role in folate metabolism, is implicated in late-onset AD pathogenesis. The 2 most studied polymorphisms of MTHFR, MTHFR-C667T and -A1298C, are associated with high serum homocysteine levels—a targetable AD risk factor. It is important to discuss potential risks and benefits of genetic testing, and careful judgement is needed by the clinician.

Cognitive Testing

Neuropsychologic testing can be an effective way for clinicians to measure the cognitive domains affected by AD, including memory, attention, processing speed, executive function, language, visuospatial function, and lexical ability. The cognitive tests suggested for use in an AD-prevention clinic should be sensitive to subtle changes in cognition that may not be noticeable in asymptomatic at-risk individuals. Computer-based testing combined with composite cognitive measures may hold the most promise.

Creating an Individualized Intervention Plan

Using the above clinical assessments (ABCs), clinicians can apply evidence-based precision medicine to target the modifiable AD risk factors for an at-risk individual. Both pharmacologic and nonpharmacologic recommendations may be prescribed when benefits outweigh any potential risk (Box 2). An example overview of how clinical assessments inform various interventions is in Table 1, based on previous publications.

Pharmacologic Interventions

Medications. Although lifestyle interventions are essential in managing a person’s AD risk, some modifiable risk factors are
better treated through pharmacologic means. Management of comorbidities (eg, diabetes, hypertension, hyperlipidemia, or depression) can generally be based on national evidence-based guidelines, which may include pharmacologic intervention. In these instances, risk factors should be addressed and managed in collaboration with a person’s primary care physician (PCP) or specialist, if warranted.

**Vitamins and Supplements.** Use of vitamins and supplements to treat any underlying deficiencies should be managed with a precision medicine approach. For example, when the serum homocysteine level is elevated (>10 mcmol/L), clinicians should take into account genetics, lifestyle patterns, cognitive function, and medical history of the patient to determine whether B-complex vitamins (B₁₂, 500 mcg; folate, 800 mcg; B₆, 20 mg) may be helpful. Although the evidence is yet unclear, in patients with a double mutation in the 677 and or/1298 MTHFR, who do not respond to B-complex therapy, methylated forms of B₁₂ and folate may be considered.

Another example is a person with vitamin D deficiency. Typically, a serum level of 30 nmol per L would be considered a target for treatment. Recent studies, however, have suggested a range of 50 to 70 nmol per L may be more beneficial. This is particularly important for APOE ε4 homozygotes (ε4/ε4), because higher levels of serum vitamin D in these individuals improved memory function, whereas nonhomozygotes showed no improvement. Further details of vitamin and nutritional supplements to consider, including omega-3 fatty acids, plant sterols, and curcumin, have been published.

**Nonpharmacologic Interventions**

**Exercise.** Nonpharmacologic interventions should be prescribed to address modifiable lifestyle risk factors. Although everyone should routinely engage in exercise, an individual’s ABCs evaluation can guide recommended physical activity. For example, someone with elevated percent body fat and insulin resistance may be instructed to focus on higher-intensity exercise at least 2 to 3 times per week, if tolerable, along with weight and resistance training at least once or twice a week. Recommendations should be tailored based on APOE genotype, as studies have shown that people with APOE ε4 see greater long-term benefits from increased exercise. Individuals should be directed to increase the amount and type of exercise as tolerated, and should always discuss changes with their primary care physician.

**Nutrition.** Dietary modifications can be tailored for each patient, but should generally follow the patterns of the Mediterranean and MIND diets, which emphasize lower glycemic carbohydrates, lean protein, and healthy fats. Clinicians can also tailor dietary advice based on genetics. For instance, people with APOE ε4 may be more susceptible to pesticide exposure, specifically dichlorodiphenyldichloroethylene (DDE) because this has been found to increase risk of AD. Because high levels of DDE can sometimes be found on fruits and vegetables grown outside of the US and Canada, people with APOE ε4 should be educated on where to buy organic produce, whenever possible.

**Sleep.** Sleep hygiene is an essential component of AD risk reduction, and 7 to 8 hours of uninterrupted sleep per night should be the optimal goal. Practical suggestions to help people sleep include avoiding caffeine consumption after 2 pm, restricting use of electronics approximately 30 to 45 minutes before getting into bed, and going to bed and waking up at the same time each day, along with several other techniques.

**Other Factors.** Other considerations include stress management, oral hygiene, cognitive engagement/training, and the risks/benefits of hormone replacement therapy.
Patient Education and Counseling

Clinicians have several resources to assist with patient education. In addition to individual counseling, there is an online course for the public at AlzU.org that has been shown to increase knowledge about AD prevention and willingness to participate in AD prevention clinical trials.35 This free tool includes interactive lessons, web-based cognitive assessments, and other resources for people at risk. If genetic testing is considered, genetic counseling beforehand is recommended. This discussion augments the content on AlzU.org and will better inform a person’s decision whether or not to have genetic testing and what their results could mean. Clinicians can advise people about ongoing clinical trials and refer for participation, if applicable. Evidence has shown that giving all possible information about ongoing trials helps individuals feel better equipped to make calculated decisions about their potential participation. This can also assist with low study recruitment rates which have slowed research progress.42

The importance of follow-up assessments should be stressed because routine follow-up visits enable both the clinician and patient to monitor progress. By observing assessment ABCs across multiple visits, a clinician can precisely refine the interventions accordingly. Follow-up visits also allow the clinician to assess adherence to treatment as well. In cases where a person encounters barriers to treatment, the clinician can work with her or him in partnership to devise solutions and alternate recommendations as needed.

Future Directions

Although preliminary results show that clinical precision medicine can significantly improve cognition in people at risk for AD, further research is needed to determine the comparative effectiveness of these interventions.13,14 As preliminary results are so far limited to 6-month follow-up, ongoing follow up is needed to assess longer-term effectiveness on cognitive performance, AD and cardiovascular risk, and development of AD dementia. Results from baseline to 18 months were presented at the American Academy of Neurology (AAN) and the Alzheimer’s Association International Conference (AAIC) in 2019. Considering the growing number of clinical sites providing AD risk prevention, coordination and collaboration between sites, although challenging, can help create a larger volume of clinical data and a network with potential to improve outcomes assessments. A consortium of practice sites has been created, and interested practitioners may contact the authors for more information. The initial goals of the consortium will be to

### TABLE 1. BIOMARKER-TO-INTERVENTION PARADIGM

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Anthropometrics</th>
<th>Blood Biomarkers</th>
<th>Genetics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Waist: hip % Body fat % Dry lean mass</td>
<td>Fasting glucose</td>
<td>Cholesterol</td>
</tr>
<tr>
<td>Vitamin B₁₂</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylated B₁₂</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPA/DHA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocoa flavonoids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plant sterols</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low carb/high fiber</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caloric restriction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omega-3 rich fish</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overnight fasting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refer to cardiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aerobic/resistance exercise</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Patients of the Alzheimer’s Prevention Clinic at Weill Cornell Medicine and NewYork-Presbyterian are given tailored recommendations based on the above findings. For example, a patient will be recommended a diet higher in omega-3 rich fatty fishes depending on their lipid panel results, serum fatty acid levels, and APOE gene status. Abbreviations: APOE4, apolipoprotein E4; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HbA1C, glycosylated hemoglobin; HDL, high-density lipid; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipid; LDL-p, low-density lipid-phosphorylated; MTHFR, methylenetetrahydrofolate reductase; O, optional; SR, strongly recommended; R, recommended.
develop a philosophy of care, harmonize measures collected, cultivate and conduct multicenter clinical precision medicine research projects to advance practice, and commit to better understanding gender and precision medicine-based differences in care.

### Conclusion

Considering the morbidity of AD, public health impact, and growing acceptance that preventative neurology can be applied to outpatient care, it is worthwhile for clinicians to consider providing risk reduction care to tens of millions of patients in need.

---


---

**TABLE 2. DIETARY PATTERN RECOMMENDATIONS**

<table>
<thead>
<tr>
<th>Food Choice</th>
<th>Examples</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green leafy vegetables</td>
<td>Kale, dark greens, spinach, romaine</td>
<td>6 or more servings/wk</td>
</tr>
<tr>
<td>Other vegetables</td>
<td>Pepper, carrots, broccoli</td>
<td>6 or more servings/wk</td>
</tr>
<tr>
<td>Berries</td>
<td>Strawberries, blueberries</td>
<td>2 or more servings/wk</td>
</tr>
<tr>
<td>Other whole fruit</td>
<td>Pears, apples, oranges</td>
<td>7-14 servings/wk</td>
</tr>
<tr>
<td>Plant-based fats</td>
<td>Avocado, seeds, hazelnuts, almonds</td>
<td>5 or more servings/wk</td>
</tr>
<tr>
<td>Legumes</td>
<td>Beans, peas</td>
<td>5 or fewer servings/wk</td>
</tr>
<tr>
<td>Whole grains</td>
<td>Steel cut oats, quinoa</td>
<td>1-2 servings/day</td>
</tr>
<tr>
<td>Fish (not fried/not shell)</td>
<td>Wild salmon, fatty fish, sardines</td>
<td>2-4 servings/wk</td>
</tr>
<tr>
<td>Poultry (not fried)</td>
<td>Chicken, turkey</td>
<td>4 or more servings/wk</td>
</tr>
<tr>
<td>Eggs</td>
<td></td>
<td>4-8/wk</td>
</tr>
<tr>
<td>Unprocessed red meat and pork</td>
<td>Choose grass-fed when possible</td>
<td>2 or fewer servings/wk</td>
</tr>
<tr>
<td>Regular cheese</td>
<td>Choose grass-fed when possible</td>
<td>4 or fewer servings/wk</td>
</tr>
<tr>
<td>Plain yogurt</td>
<td>Live/active cultures</td>
<td>4-6 servings/wk</td>
</tr>
<tr>
<td>Butter, cream, mayonnaise</td>
<td>Choose grass-fed when possible</td>
<td>Less than 1 Tbsp/day</td>
</tr>
<tr>
<td>Beverages</td>
<td>Coffee, tea, dark cocoa</td>
<td>2 or more servings/day</td>
</tr>
<tr>
<td>Dark cocoa powder</td>
<td></td>
<td>5-7 servings/wk</td>
</tr>
<tr>
<td>Wine, other alcohol</td>
<td>Women: 1/day</td>
<td></td>
</tr>
<tr>
<td>Desserts</td>
<td>Pastries, sweets, ice cream</td>
<td></td>
</tr>
<tr>
<td>Fast fried foods</td>
<td>French fries, fried chicken</td>
<td>2 or fewer servings/wk</td>
</tr>
<tr>
<td>Extra virgin oil</td>
<td>Primary oil used</td>
<td>1 Tbsp/day</td>
</tr>
<tr>
<td>Overnight fasting</td>
<td>12-16 hours, 16 hours preferable</td>
<td>5 nights maximum/wk</td>
</tr>
<tr>
<td>Total carbohydrates</td>
<td>≤ 120 g/day</td>
<td>Daily</td>
</tr>
</tbody>
</table>

---

(Continued on page 104)


NS, GS, and SB contributed equally to this manuscript.

Disclosures
The authors report no disclosures.