Dementia Prevention in Clinical Practice

Kellyann Niotis, MD[1] Kiarra Akiyoshi, BA[1] Caroline Carlton, BA[1] Richard Isaacson, MD[1,2]

[1] Department of Neurology, Weill Cornell Medicine and New York - Presbyterian, New York, New York
[2] Department of Neurology, Florida Atlantic University, Charles E. Schmidt College of Medicine, Boca Raton, Florida

Address for correspondence Richard Isaacson, MD, Department of Neurology, Weill Cornell Medicine and New York - Presbyterian, 428 E 72nd St, New York, NY 10021 (e-mail: rii9004@med.cornell.edu).

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Abstract

Over 55 million people globally are living with dementia and, by 2050, this number is projected to increase to 131 million. This poses immeasurable challenges for patients and their families and a significant threat to domestic and global economies. Given this public health crisis and disappointing results from disease-modifying trials, there has been a recent shift in focus toward primary and secondary prevention strategies. Approximately 40% of Alzheimer's disease (AD) cases, which is the most common form of dementia, may be prevented or at least delayed. Success of risk reduction studies through addressing modifiable risk factors, in addition to the failure of most drug trials, lends support for personalized multidomain interventions rather than a "one-size-fits-all" approach. Evolving evidence supports early intervention in at-risk patients using individualized interventions directed at modifiable risk factors. Comprehensive risk stratification can be informed by emerging principals of precision medicine, and include expanded clinical and family history, anthropometric measurements, blood biomarkers, neurocognitive evaluation, and genetic information. Risk stratification is key in differentiating subtypes of dementia and identifies targetable areas for intervention. This article reviews a clinical approach toward dementia risk stratification and evidence-based prevention strategies, with a primary focus on AD.

Keywords

- Alzheimer's disease prevention
- dementia prevention
- precision medicine

Dementia is a neurodegenerative disease with a significant impact on the lives of patients affected, their caregivers, and society. Dementia is an umbrella term for a range of conditions characterized by progressive cognitive impairment and behavioral changes that interfere with daily functioning. Neurodegenerative dementias such as Alzheimer's disease (AD) are most common, followed by microangiopathies such as vascular dementia (VaD) and Lewy body dementia (LBD), with mixed pathology often seen.

As of 2021, more than 55 million people were living with dementia, but with an aging population, dementia is an increasingly prevalent threat to population health with a projected 131 million people affected by the disease by 2050.[1–3] This will continue to pose a significant threat to domestic and global economies, with disease-related costs estimated at $200 billion per year in the United States (expected to rise to two trillion by 2030) and $600 billion worldwide.[4–6] Given this emerging public health crisis, the search for effective treatments has increased with urgency, as current treatment approaches are "symptomatic" without altering the underlying pathological course of the disease, and approved therapies have shown limited efficacy with considerable side effects.[7–10]

The pivot toward primary and secondary prevention strategies—before irreversible neuronal loss and clinical dementia—has been motivated by discouraging results from pharmaceutical trials in AD in addition to growing evidence that modifiable risk factors provide an opportunity for early intervention. According to the Lancet Commission 2020 Report, these modifiable risk factors account for approximately 40% of dementia cases worldwide.[11] Findings from projection models estimate that delaying AD by just 1 year would reduce the total worldwide number of cases in people older than 60 years in 2050 by 11%, and others have

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shown that medical advances aimed at delaying disease onset for 5 years or longer would result in a 41% lower prevalence and 40% lower cost of AD in 2050.[12,13] Therefore, investing resources and efforts in prevention may be a more fruitful and actionable path in clinical practice today toward decreasing dementia incidence and socioeconomic impact.[14]

In this article, we review the current clinical approach to dementia risk stratification and early detection as well as evidence-based prevention strategies, with a primary focus on AD, the most common neurodegenerative dementia.

Alzheimer's Disease Overview

In 2021, an estimated 6.2 million Americans were living with AD, and that number is projected to increase to 13.8 million by 2050.[15] While the cause of AD is not fully understood, a combination of genetic (nonmodifiable) and environmental/lifestyle (modifiable) factors likely contribute (as well as a host of other comorbid diseases that have their own unique modifiable and nonmodifiable risk factors). AD is associated with abnormal deposition of amyloid-beta (Aβ) proteins accumulating in amyloid plaques, and hyperphosphorylated tau (p-tau) proteins resulting in neurofibrillary tangles and, hence, is referred to as a tauopathy. AD preferentially affects the hippocampus which is responsible for the first symptoms of amnestic cognitive decline.

AD is a heterogeneous disease and may present and progress differently depending on the person and individual factors leading to the disease pathology. To this end, various models of subtyping AD based on a criterion such as disease phenotypes, pathological findings, and other biomarkers have been proposed.[16–19] While these are important steps toward characterizing early individual disease variation, using a single biomarker to determine disease risk and clinical trajectory may not provide a complete picture of the potential factors contributing to AD pathology. Furthermore, the coexistence of multiple pathologies (i.e., microangiopathic changes, alpha-synuclein deposits, and tau aggregates) on an individual level suggests a strong overlap between these neurodegenerative processes. As such, we advocate for a practical approach to AD and dementia risk stratification using individual clinical attributes and biomarkers. This also more optimally allows for personalized care based on modifiable risk factors and specific underlying disease pathology.

Approach to Risk Stratification

When applying dementia prevention methods in cognitively normal patients, proper risk stratification is imperative to allow for pathology-specific interventions. ►**Table 1** summarizes the clinical domains considered in dementia risk stratification. Often, family history of AD or dementia is the primary motivator for patients to seek risk reduction management.[20,21] As AD is responsible for 60 to 80% of all dementia cases, and significant overlap between clinical presentation exists, other less common forms of dementia are often misdiagnosed as AD.[22–24] It is necessary to diligently investigate any family history of diagnosed AD, other dementias, or undiagnosed symptoms of cognitive impairment—especially in first-degree relatives—along with the age of onset and clinical presentation for any affected relatives. For example, dementia onset at age <65 years (yet more likely with onset in 40s–50s) in multiple relatives may suggest involvement of highly penetrant autosomal dominant genes. These include *amyloid precursor protein (APP)*, *presenilin 1 (PSEN1)*, and *presenilin 2 (PSEN2)* in the appropriate clinical context and may warrant genetic testing for these variants after genetic counseling is performed. A family history prominent for psychiatric disease, anterolateral sclerosis (ALS), or autism spectrum disorder (ASD) may suggest frontotemporal dementia (FTD) is more likely.[25]

A dementia-prevention–focused clinical history including age, biological sex, medical history, and factors related to early life brain development (academic performance, class ranking, standardized test scores, and career achievement) should be performed. This expanded history should also include assessment of past and current lifestyle habits (exercise, diet, sleep, stress management) that would be targetable risk factors. A detailed review of systems for symptoms that may indicate alternate pathology should be included.[21] For example, the presence of REM sleep behavior disorder is strongly associated with the development of Parkinson's disease (PD) or other synucleinopathy (e.g., LBD).[26] The identification of conditions such as hypertension, hearing impairment, periodontal disease, obesity, depression, diabetes, alcoholism, and traumatic brain injury is of the utmost importance, as these conditions are some of the strongest risk factors for developing AD.[11] Physical and neurological exam should follow. Physical exam findings such as bradykinesia, myoclonus, orthostatic hypotension, and loss of the optokinetic reflex may suggest atypical AD or alpha-synuclein pathology. Although it is nonspecific, olfactory impairment is a common and early sign of neurodegenerative diseases corresponding to emerging pathologic processes in the olfactory system. While patients may report hyposmia or anosmia, objective testing is necessary to accurately determine olfactory function.[27]

Vital signs and anthropometric measurements are also essential. Collecting objective measurements of body composition including lean dry mass, skeletal muscle mass, and body fat percentage using tools such as bioimpedance devices or other more rigorous means (e.g., a dual-energy X-ray absorptiometry [DEXA] scan) should be performed in a standardized manner (e.g., fasting, same device, same time of the day) for more accurate longitudinal comparisons. Measurements such as body mass index (BMI) are imprecise and not as informative, whereas waist-to-hip circumference—which is associated with hippocampal volume—may be a better proxy.[28]

Additionally, blood biomarkers are an essential component of the risk stratification process and can aid in identifying modifiable risk factors. Since hypercholesterolemia and hypertriglyceridemia are associated with cognitive decline, advanced lipid and inflammatory panels more routinely performed by the preventive cardiology field should be considered.[29] Although clinical guidelines in the United

Table 1 Dementia risk stratification

Domain	Supports underlying, typical LOAD pathology	Supports underlying, typical vascular dementia pathology	Supports underlying, typical EOAD pathology	Supports underlying synucleinopathy (PD, DLB)	Supports underlying FTD pathology	Supports underlying atypical neurodegenerative disease (atypical AD, CBS, PSP)
Age	≥65[44]	≥65[310]	<65[311]	Variable but typically ≥60[312]	>40[313]	≥60[314]
Sex	Female > male[70,71]	Male > female[315]	Female > male[311]	Male > female[312,316]	Male > female[313]	Female = male[317–319]
Cognition	Amnestic Impairments in episodic memory and semantic function[320,321]	Impairments on attentional/executive function, semantic memory, and visuospatial skills[320]	Amnestic, frontal/executive function and visual memory impairment Apraxia/visuospatial dysfunction[322,323]	Non-amnestic (bradyphrenia, poor learning, logopenia) Impairments in visuospatial function and letter fluency[312]	Non-amnestic (language, behavioral, visual, or dysexecutive)[324]	Non-amnestic (language, behavioral, visual, or dysexecutive)[325]
Medical history	Vascular and metabolic conditions (e.g., heart disease, stroke, high blood pressure, diabetes, obesity)[209,225–227] Developmental and learning disabilities, head injury[319]	Vascular and metabolic conditions (e.g., heart disease, stroke, high blood pressure, diabetes, obesity)[310]		Cancers, especially melanoma; seborrheic dermatitis; constipation; apathy; visual changes and vertigo; changes to handwriting; exposures to pesticides/solvents; well water[312]		
Family history	Amnestic-type dementia Developmental and learning disabilities[319]		Early-onset dementia in multiple family members in autosomal dominant pattern[115]	Parkinsonian disorders Psychiatric disorders especially suicide Melanoma and other cancers[312,326]	ALS, ASD, substance use disorders, and other psychiatric disorders[324]	Learning disability or atypical dementia[327] non-amnestic dementia
Sleep	Sleep inefficiency[264–270]	Sleep apnea Sleep disturbances[328,329]	Sleep disturbances[330]	REM behavior restless leg syndrome Periodic limb movements of sleep[312]	Somnolence, narcolepsy-like attacks, insomnia[331]	Irregular sleep/wake behavior[332]
Mood	Late-life depression/anxiety Irritability Apathy[245]	Late-life depression, apathy, and psychosis[245,333]	Apathy, agitation, disinhibition, irritability[322,334]	Early-life depression/anxiety obsessive compulsive disorder Visual hallucinations[312]	Emotional blunting, mood changes, disinhibition[335]	Apathy Disinhibition Loss of empathy
Motor	Slowed walking (without parkinsonism)[336]	Parkinsonian-like gait disorder, dysarthria, and autonomic dysfunction[310]	Aberrant motor behavior[334]	Parkinsonism (bradykinesia, rigidity, tremor, stooped posture, gait changes, imbalance/falls) or autonomic dysfunction (constipation, urinary frequency, orthostatic hypotension, impotence)[312]	Parkinsonism, dysphagia[324]	Muscle twitching Muscle atrophy Myoclonus Dystonia Gaze paralysis Difficulty walking Eye movement difficulty[325]
Genetic	APOE4, TOMM40, APOC1, mitochondrial haplotype		APP, PEN1, PEN2, APOB[337,338]	APOE, SNCA, LRRK2, VPS35, PRKN, PINK1, DJ-1, GBA[331]	*C9orf72, GRN, MAPT*[339]	MAPT, *C9orf72*[340]

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; APOC1, apolipoprotein C1; APOE, apolipoprotein E-4; APP, amyloid precursor protein, PSEN1, presenilin 1; ASD, autism spectrum disorder; *C9orf72,* chromosome 9 open reading frame 72; CBS, corticobasal syndrome; EOAD, early-onset Alzheimer's disease; FTD, frontotemporal dementia; *GRN*, progranulin; LOAD, late-onset Alzheimer's disease; LRRK2, leucine-rich repeat kinase 2; *MAPT*, microtubule-associated protein tau; PD, Parkinson's disease, DLB, dementia with Lewy bodies; PSEN2, presenilin 2; PSP, progressive supranuclear palsy; REM, rapid eye movement; SNCA, alpha synuclein; TOMM40, translocase of outer mitochondrial membrane 40; VPS35, vacuolar protein sorting-35, PINK1, PTEN-induced kinase-1.

States advise on the use of low-density lipoprotein cholesterol (LDL-C) and non–high-density lipoprotein cholesterol (HDL-C) to guide cholesterol management decisions, the 2019 European Society of Cardiology/European Atherosclerosis Society Guidelines concluded that apolipoprotein B (apoB) is a more accurate measure of risk, especially in younger patients. Obtaining advanced lipid panels to better guide risk stratification and to monitor adequacy of lipid lowering therapy has been successfully deployed in AD prevention clinical practice over the last decade.[20,21,30,31] In *apolipoprotein E (ApoE4)* carriers, Apo-A1 (a component of HDL cholesterol) is a marker for increased AD risk, whereas N-terminal probrain natriuretic peptide (NT-proBNP) is a plasma protein associated with VaD.[32,33] Insulin resistance is associated with poor cognitive function and can promote neuroinflammation and amyloid deposition.[34,35] As such, metabolic metrics (e.g., glycosylated hemoglobin [HgbA1C%], fasting insulin, fasting glucose, and HOMA-IR) should be evaluated. Nutritional measures such as omega-3/6 fatty acids, vitamin levels (B_{12} and D), and homocysteine should be considered as they may guide the need for dietary modification or supplementation directly related to brain health outcomes.[21]

Neurocognitive evaluation using both computerized and more traditional individual tests (as well as preclinical focused batteries) to quantify global cognitive status, executive function, processing speed, language, verbal knowledge, and learning and memory may demonstrate early presymptomatic changes.[36–38] Although AD typically presents with episodic and associative memory dysfunction, language and executive dysfunction are seen in early FTD and visuospatial deficits are common in early LBD.[24,39,40] See ►**Fig. 1** for a comprehensive model of AD prevention management.

Though genetic information must be interpreted in the context of family and complete clinical history, it may be valuable for risk assessment in the appropriate clinical context and with adequate patient counseling. The *ApoE* gene—whose E4 allele is the most significant and well-studied genetic risk factor for AD—affects lipid homeostasis, especially in the central nervous system (CNS), and impedes Aβ clearance at the blood–brain barrier (BBB).[41] *ApoE4* carriers account for an estimated 40 to 65% of AD cases despite making up only around 20% of the general population.[42] While estimates vary among different studies, the *ApoE4* genotype incurs a 2- to 3-fold increased risk of AD in heterozygotes and an 8- to 12-fold increased risk in homozygotes as compared to *ApoE3* homozygotes.[15] The *ApoE2* genotype—present in only 5% of the population—is protective with carriers being two times less likely to develop AD.[43,44]

ApoE is not only an important mediator of AD risk, but it also may account for specific disease heterogeneity.[45] For example, *ApoE4* carriers may have greater memory impairment due to more tau deposition and brain atrophy in the medial temporal lobe, whereas AD patients without an *ApoE4* variant demonstrate greater executive, visuospatial, and language dysfunction due to more tau accumulation and atrophy in the frontal and parietal lobes.[45]

However, being a carrier of *ApoE4* does not ensure that an individual will develop the disease—its influence is variable across age, race, ethnicity, and biological sex, and can change

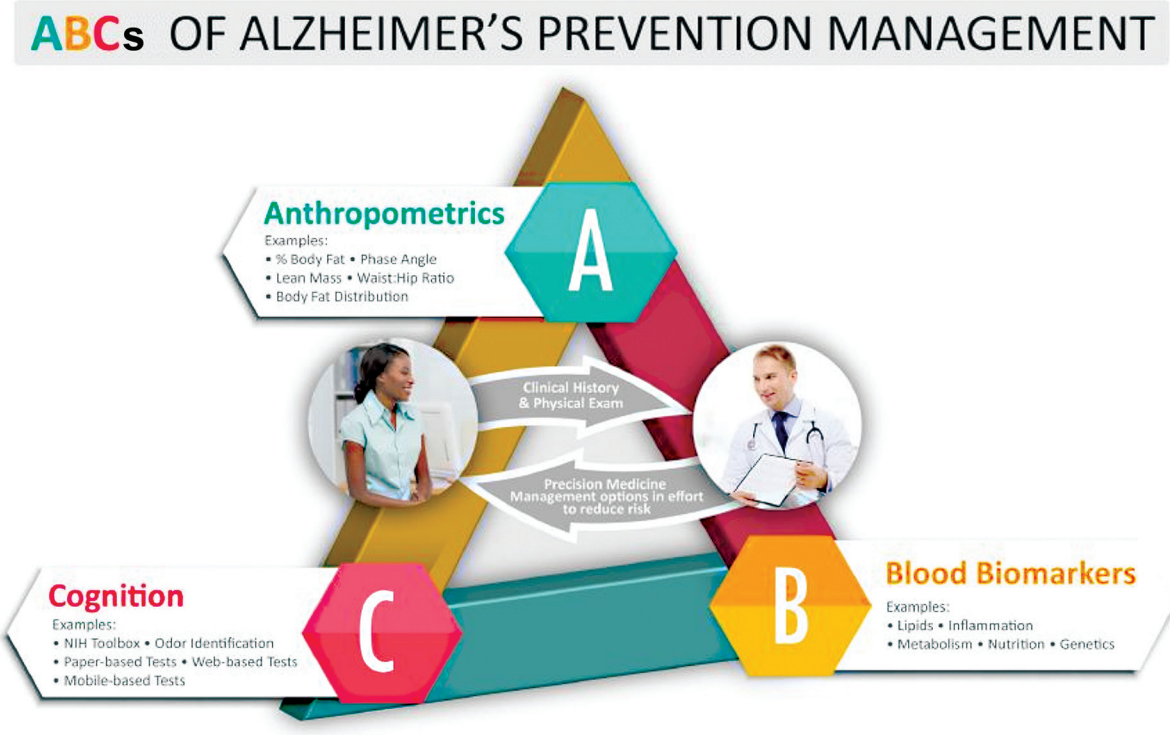

Fig. 1 ABCs of Alzheimer's prevention management. (Seifan A, Isaacson R. The Alzheimer's Prevention Clinic at Weill Cornell Medical College/New York - Presbyterian Hospital: Risk Stratification and Personalized Early Intervention. J Prev Alzheimers Dis 2015;2:254-266. Reprinted with permission of John Wiley and Sons.)

once modifiable risk factors are targeted.[21] It is further complicated by specific gene–gene interactions including other somatic and mitochondrial genetic variances/haplogroups that may alter the impact of *ApoE* by neutralizing, enabling, or synergizing its expression.[46–48] For example, KL-VS heterozygosity (KL-VShet)—having one copy of the *Klotho* gene—incurs a protective effect on *ApoE4* carriers and has been linked higher cognitive performance in adulthood.[49–52] Recent findings showed that a substantial portion of the approximately 15% of Americans carrying the *ApoE4* allele are protected by their KL-VShet status.[49,50] Given the complex genetic architecture of AD, a risk stratification methodology needs to be developed accounting for polygenic risk scores as well as additional clinical and genetic components that may directly modify ApoE expression or independently modify overall AD risk.

Until recently, invasive cerebrospinal fluid (CSF) biomarkers (Aβ1-42, T-tau, and P-tau181) and costly imaging studies (amyloid-PET, tau-PET, fMRI, etc.) were the only clinically available methods to diagnose preclinical AD. Advancements in blood-based biomarkers have opened the door to a new era of early detection and intervention.[53] PrecivityAD, a mass spectrometry-based plasma Aβ42/Aβ40 assay, is not only highly concordant with CSF biomarkers and amyloid PET scan in cognitively normal individuals, but it may be more sensitive in detecting preclinical AD. "False positives" were highly likely to convert to positive by CSF biomarkers (13-fold higher risk over an average follow-up period of 7.3 years) or amyloid PET (9-fold higher risk over an average follow-up period of 6.2 years), suggesting their superiority in detecting preclinical AD.

Risk Reduction and Prevention Overview

The pathophysiological changes of AD and other neurodegenerative disorders begin decades before clinical apparent symptoms, providing the opportunity for early intervention. Observational studies have identified several modifiable risk factors for AD that, if addressed, may prevent—or at minimum delay—a significant portion of AD cases.[11] A 2020 report by the *Lancet* commission added three modifiable risk factors—excessive alcohol consumption, traumatic brain injury, and air pollution—to the nine previously identified in 2017—less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, and low social interaction—which together account for approximately 40% of global dementia cases.[11] Other prospective studies have evaluated the effectiveness of AD risk reduction via addressing modifiable risk factors. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial, a large 2-year randomized clinical trial, demonstrated a decrease in AD risk at 24 months using multidomain lifestyle interventions including dietary and exercise recommendations, social activity, cognitive training, and metabolic/vascular monitoring when compared to general medical advice. The Exercise and Nutritional Interventions for Cognitive and Cardiovascular Health Enhancement (ENLIGHTEN) trial, which focused on aerobic exercise and dietary approaches to stop hypertension (DASH) diet, saw the greatest improvement in executive function in participants who received the combined intervention of aerobic exercise and the DASH diet rather than aerobic exercise alone, DASH alone, or general health education.[54] The Comparative Effectiveness Dementia and Alzheimer's Registry (CEDAR) study demonstrated that an individualized multidomain risk reduction approach improves cognitive function related to both AD pathology and changes more so characterized by cognitive aging, as well as reduced both AD and cardiovascular risk scores in both high- and low-compliance primary prevention and preclinical AD patients and high-compliance patients with MCI due to AD at 18 months.[55]

However, multidomain risk reduction interventions may be less effective in older patients and those with more advanced pathology. The nurse-led Prevention of Vascular Dementia by Intensive Care (PreDIVA) trial did not demonstrate a reduction in incident dementia with a multidomain cardiovascular risk factor reduction intervention in individuals aged 70 to 78 years.[56] The authors concluded that the intensity of care delivered might have been insufficient to induce the necessary effects on lifestyle change. The Multidomain Alzheimer Preventive Trial (MAPT) failed to demonstrate benefit on cognitive decline at 3 years with nutritional counseling, physical exercise, and cognitive training, omega-3 fatty acid supplementation, or both, though a post hoc analysis performed on participants with positive amyloid scans showed a significant benefit in favor of the interventions.[57] Defining appropriate recommendations based on the totality of evidence is imperative and may be in part responsible for these conflicting results. The French National Nutrition and Health Program (PNNS) guidelines were used to guide dietary recommendations instead of individualizing interventions based on more recent evidence (e.g., Mediterranean–DASH Intervention for Neurocognitive Delay [MIND] diet). The necessity of individually tailored recommendations may also be supported by the Lifestyle Interventions and Independence for Elders (LIFE) study, which failed to demonstrate positive cognitive benefit from moderate-intensity physical activity interventions (walking, resistance training, flexibility).[58] It is thought that the lack of benefit in this 2-year study stems from a higher mean age of participants and interventions that were not individually tailored.

Past studies suggest that personalized multidomain interventions may offer the greatest opportunity to decrease the incidence of, delay, or prevent AD and other dementias.[59] Individualizing risk reduction interventions requires accurate risk stratification based on both nonmodifiable and modifiable risk factors. Examples of risk factor and intervention considerations are described in ►**Table 3**.

Risk Factors and Interventions

Age

The most significant risk factor for AD is advanced age.[44] In fact, AD risk doubles every 5 years after the age of 65 years, and the number of Americans older than 65 years is projected to increase from 40.2 million in 2010 to 88.5 million in 2050.[60,61]

Although the aging process itself contributes to the risk of neurodegeneration, dementia is not a normal part of aging. As the brain ages, white matter volume decreases much more significantly than grey matter volume, but in those with AD, the rate of neuronal dysfunction, neuronal loss, and cognitive decline is accelerated.[62,63] There are many molecular and systemic hallmarks of aging that correlate with susceptibility to neurodegenerative disease such as genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, and mitochondrial dysfunction.[64] Aging is also characterized by cellular senescence and chronic, low-grade systemic inflammation—a process colloquially referred to as "inflammaging"—which is strongly associated with AD.[65,66] In acknowledgment of this theory, a recent study demonstrated the benefit of low/anti-inflammatory diet plans for older at-risk patients.[67] Other hallmarks of aging—deregulated nutrient sensing, stem cell exhaustion, altered intercellular communication—also correlate with susceptibility to neurodegenerative disease.[64]

Biological Sex

Research has suggested that the second most significant risk factor for AD is female sex. In fact, two-thirds of all AD patients are females, and postmenopausal women comprise over 60% of affected females.[68,69] Research continues to discern the reasons for this disparity, but statistical models have shown that women still possess twice the risk of men even when accounting for gender-dependent mortality rates, age at death, and differences in lifespan.[70,71] A growing body of evidence suggests differences in brain anatomy, function, and age-related morphological changes between women and men are involved.[71] The "estrogen hypothesis" posits that sex hormones, 17β-estradiol specifically, exert a neuroprotective effect on female brains. Estrogen dysfunction in the years leading up to and after menopause seems to exacerbate (or precipitate) the AD process in women in contrast to men of the same age.[72] Such research implicates the menopause transition (MT)—a midlife neuroendocrine transition state unique to females—in their higher risk for AD.[73] During the MT, the estrogen network uncouples from the brain's bioenergetic system, and the resulting hypometabolic state may serve as the substrate for neurological dysfunction. Women experiencing menopause may present neurological symptoms (disruption of estrogen-regulated systems like thermoregulation, sleep, and circadian rhythms), depression, and impairment in multiple cognitive domains.[74] Such unique circumstances for developing dementia warrant sex-specific recommendations when pursuing personalized risk reduction.

Research has been mixed as to the efficacy of hormone-replacement therapy (HRT) in protecting women from cognitive decline. Earlier studies generally showed a lack of benefit and even a potential harmful effect, whereas recent investigations indicate that the effectiveness of estrogen depends on multiple factors, such as the time of initiation of HRT, the individual's cognitive functioning at the time of HRT initiation, and the forms of hormones used.[75–84] Hypertension—a major risk factor for both cognitive decline and cardiovascular diseases—increases significantly in women after menopause, which suggests an additional need for female-specific cardiovascular interventions.[85]

Furthermore, insulin resistance and/or type 2 diabetes mellitus (DM2) may pose a higher risk for females than for males, thus warranting more aggressive management.[86] In patients with added risk due to physical inactivity, women seem to benefit more from a greater ratio of cardiovascular-to-resistance training than men, and both sexes should receive sex-specific nutritional counseling.[87–95] Women also face an added risk from suboptimal cognitive activity or reserve, for which they can be recommended adult education and cognitive training or second language or musical training.[96–99] While depression generally poses a higher risk for men, stress and anxiety pose a higher risk in women, and women may be more vulnerable to depression risk in the perimenopausal period.[100–104] For mental health purposes, both women and men may be recommended mindfulness training, meditation, periodic vacations, cognitive behavioral therapy, exercise counseling, and/or medication.[105–113] In a follow-up analysis to the CEDAR study, it was found that individualized multidomain interventions may offer equal cognitive benefits to both women and men when such sex-specific factors are employed, as well as better mitigation of calculated AD and CV risk in women compared to men.[114]

Genetics

The genetic architecture of AD is complex and an area of ongoing active investigation. While highly penetrant autosomal dominate mutations exist, they account for less than 1% of all AD cases and are associated with early-onset AD.[115] Late-onset AD has a more complicated etiology influenced by lifestyle factors, polygenetic heterogeneity, and epigenetic interactions.[116–118] Early risk reduction interventions, guided by risk stratification that considers genetics, allows for more personalized care.

As discussed, the *ApoE* gene is the most significant genetic risk factor. *ApoE* encodes a surface peptide found on plasma lipoproteins and is responsible for the transport, metabolism, and redistribution of lipids in the body, especially in the CNS.[41] The three *ApoE* variants have different affinities for lipoproteins and receptors, with *ApoE2* and *ApoE4* having a significant influence on lipid and lipoprotein levels.[119] In general, *ApoE4* is associated with an increase in LDL-C and *ApoB* and, therefore, a higher cardiovascular risk.[120–127] *ApoE2*, on the other hand, is associated with a three- to fourfold decrease in LDL-C compared to *ApoE4. ApoE4* carriers may also be more susceptible to certain modifiable lifestyle factors than noncarriers. For example, individuals with the *ApoE4* genotype who live a sedentary lifestyle, smoke, or consume alcohol possess a higher risk for developing AD than those who do not carry the *ApoE4* allele.[128,129] Given the propensity of *ApoE4* carriers to develop hyperlipidemia and atherosclerosis, early referral to a preventive cardiology specialist may be warranted based on individual factors, such as family history, serum lipid markers, and other evidence of early atherosclerotic changes. Statin therapy may provide a greater therapeutic efficacy in *ApoE4* homozygotes.[130]

Although *ApoE4* increases risk of AD, research indicates that *ApoE4* magnifies the impact of certain modifiable factors such as physical inactivity, obesity, tobacco use, alcohol consumption, and insulin resistance compared to those without *ApoE4*.[128,131,132] Addressing these factors may lead to a greater potential for success. Due to its differential effect on lipid metabolism, neuroinflammation, and glucose metabolism, *ApoE4* may provide a highly targeted and distinct approach to AD prevention interventions (see ►**Table 2**).[133] Optimizing insulin sensitivity through low-glycemic index or low-carbohydrate diets should be a priority. Additionally, fatty fish is rich in the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and consumption and/or supplementation is especially critical for *ApoE4* carriers. Higher doses of DHA may be required due to *ApoE4*-induced metabolic alterations and BBB dysfunction.[133–135] Studies show that the phenolic compounds oleocanthal and hydroxytyrosol found in extra virgin olive oil display anti-amyloid and anti-tau properties and may act on specific pathways adversely affected in *ApoE4* carriers.[136–139] *ApoE4* carriers may be more susceptible to pesticide exposure, specifically dichlorodiphenyldichloroethylene (DDE), and thus should be educated on the need to wash all produce properly as well as the potential benefits of buying organic. Other factors including hypertension, vitamin

Table 2 Example considerations for *ApoE4*+ carriers

Domains	Considerations	Benefits for *ApoE4*+ carriers
Dietary patterns[133]		
Low-glycemic index/ Low-carbohydrate diets	Regular dietary pattern	• Protects against insulin resistance • Lessens risk of Aβ degradation impairment by insulin • Reduces GSK3β-mediated hyperphosphorylation of tau • Ameliorates reduced cerebral blood flow • Protects against AGE formation and ApoE4 glycation, with consequences on cerebral lipid metabolism • Overall associated with reduced AD risk
Organic food	Regular substitution of non-organic foods	• Reduces body burden of toxins • Reduced exposure to certain pesticides that tend to effect ApoE4 carriers[341]
Extra virgin olive oil	1-2 Tbsp/day	• Anti-amyloid and anti-tau properties induced through phenolic compounds, oleocanthal and hydroxytyrosol • Increases levels of LRP1 • Inhibits CypA-NFκB-MMP9 • Increases ABCA1
Fatty fish	2–4 servings/week	• Inhibits NLRP3 formation • Inhibits CypA-NFκB-MMP9 • Improves amyloid and tau pathologies in animal models • Overall consumption associated with reduced AD risk
Alcohol	Limit alcohol consumption	• Reduced consumption overall associated with reduced AD risk
Biomarkers[133]		
Low RBC omega-3 (EPA/DHA)/ omega-3 index	Nutritional counseling + consider supplementation	• Possible improvements in memory reaction time in males • Improved attentional measures of cognition • Improved composite cognition scores
Low serum vitamin D (<30 nmol/L)	Consider supplementation and increase exposure to natural sunlight	• Possible improvement in cognitive function
Insulin resistance	Nutritional counseling, low-glycemic index or low carbohydrate diet; consider early referral to endocrinology; consider Zone 2 training, supplementation with cocoa flavanols	• Possible reduction in age-related cognitive dysfunction[173]
Hyperlipidemia (elevated ApoB, LDL-C, and/or LDL-P)	Early referral to preventive cardiology	• Management of dementia-related cardiovascular risk factors
Exercise		
Aerobic/Resistance training	Increased overall amount and intensity of exercise	• Helps counteract the increased clinical decline and brain atrophy in ApoE4 carriers
HIIT	Implementation of HIIT in regular exercise routine[195]	• Higher intensity exercise may protect against cognitive decline for ApoE4 carriers[342]

Abbreviations: ABCA1, ATP binding cassette subfamily A member 1; AD, Alzheimer's disease; AGE, advanced glycation end; ApoB, apolipoprotein B; Aβ, amyloid-beta; CypA-NFκB-MMP9, cyclophilin A-nuclear factor kappa B-matrix metallopeptidase 9; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GSK3β, glycogen synthase kinase-3β; HIIT, high-intensity interval training; LDL-C, low-density lipoprotein cholesterol; LDL-P, low-density lipoprotein particles; LRP1, LDL receptor-related protein 1; NLRP3, NOD-, LRR-, and pyrin domain-containing protein 3; RBC, red blood cell.

Table 3 Example risk reduction interventions

Risk factor	Individual factor	Intervention considerations	Servings
Diet[129]			
		Green leafy vegetables	6 or more servings/week
		Other vegetables	6 or more servings/week
		Berries	2 or more servings/week
		Other whole fruit (low glycemic)	7–14 servings/week
		Plant-based fats (i.e., avocado, seeds)	5 or more servings/week
		Legumes	5 or fewer servings/week
		Whole grains	1–2 servings/day
		Fish (not fried or shelled)	2–4 servings/week
		Poultry (not fried)	4 or fewer servings/week
		Eggs	4–8 or fewer/week
		Unprocessed red meat and pork (grass-fed when possible)	2 or fewer servings/week
		Coffee, tea	2 or more servings/day
		Dark cocoa powder	5–7 servings/week
		Wine, other alcohol	Women: 1 serving/day
			Men: 1–2 serving/day
		Extra virgin olive oil	Preferred over other monounsaturated fats
	Evidence of insulin resistance, elevated visceral body fat, or elevated waist:hip ratio	Time-restricted eating pattern	12–16 h ~5 d/wk
		Total carbohydrates	≤120 g/d daily depending on amount of regular exercise
		Fast fried foods	Limit intake
		Desserts, pastries, sweets	Limit intake
Nutritional biomarkers			
Low RBC omega-3 (EPA/DHA)/omega-3 index		Nutritional counseling +/− supplementation[343,344]	
Vitamin D deficiency		Cholecalciferol +/− daily, brief exposure to sunlight[345,346]	
Vitamin B12 deficiency	With absorption deficit[347]	Oral vs. IM B12 supplementation; nutritional counseling[163]	
	With absorption and/or potential genetic methylation deficit (e.g., MTHFR)	Methylated B12 or B complex	
	With elevated homocysteine	Consider methylated B-complex vitamins (folate, pyridoxine, cobalamin); TMG; NAC[347,348]	
Exercise			
	Female	Greater ratio of cardiovascular to resistance training[87–94]	
	Male	Equal-to-greater ratio of resistance to cardiovascular training	

Table 3 (*Continued*)

Risk factor	Individual factor	Intervention considerations	Servings
	Elevated visceral body fat	Cardiovascular exercises, such as fast walking (Zone 2, 65–70% of maximum heart rate), running, swimming, and cycling; HIIT	
	Low muscle mass	Resistance training to improve strength and endurance, often with use of weights	
	Insulin resistance	Zone 2 or steady-state cardiovascular training; HIIT	
Sleep			
Insufficient sleep/sleep disturbances		Maintain a consistent sleep schedule and optimize sleep environment	
		Careful review to identify sources of impaired sleep	
		Limit use of electronics and restrict food and alcohol use before bed	
		Avoid caffeine after ~1 pm	
		Avoid sleep aids such as Benadryl	
		Consider low-dose melatonin	
Sleep apnea	Type of apnea	CPAP or other treatment as indicated Refer to sleep specialist	
Education			
Suboptimal cognitive activity or reserve	May pose higher risk for females[96,97]	Adult education and/or cognitive training Second language training or musical training Puzzles, card games, mind games[98,99]	
Social interaction			
Social isolation	May pose higher risk for males[349–351]	Referral to social worker or geriatric care manager Encourage activity programs and social engagement[243,352]	
Mental health/stress			
Chronic stress, depression, and/or anxiety	Depression may pose higher risk in males[252]	Mindfulness training, meditation, periodic vacations, cognitive behavioral therapy, exercise counseling +/− medication[105–108,110–112]	
	Stress and anxiety may pose higher risk in females; Females may be more vulnerable to depression risk in the perimenopausal period[100–104]	As above May also benefit more from vacation and meditation[110,113]	
Management of other medical conditions			
Hearing loss		Management of hearing loss Introduction of hearing devices as per recommendation of primary care physician	

(*Continued*)

Table 3 (*Continued*)

Risk factor	Individual factor	Intervention considerations	Servings
Periodontal disease		Consistent oral hygiene through teeth brushing and flossing	
		Regular dental check-ups and teeth cleanings	
Perimenopause (<5–7 y after start of menopause transition)	Symptomatic age <65[353,354]	Careful consideration of risks/benefits of type, route, and dose of HRT for an individualized period of time[82,84]	
	Induced menopause[355]		
Hypertension	Midlife[173]	Systolic BP target of 120 mm Hg or lower and diastolic BP target of 70 or lower mm Hg.[212,213] Consider ARBs (especially candesartan and telmisartan) or ACE inhibitors[212–215] Avoid CNS-active beta-blockers[216]	
Insulin resistance/type 2 diabetes mellitus	With unhealthy lifestyle[173]	Lifestyle counseling	
	Already healthy lifestyle	Consider referral to endocrinology; exercise as above, supplementation with cocoa flavanols; TRE[173]	
	May pose higher risk for females[86]	As above Tighter targets for control	
Hyperlipidemia	Due to elevated sterol absorption	Ezetimibe Refer to preventive cardiologist[356]	
	Due to elevated sterol production	Hydrophilic statin therapy Refer to preventive cardiologist[357]	
	Refractory to monotherapy	May benefit more with combination therapy (e.g., statin and ezetimibe) Refer to preventive cardiologist to discuss PCSK9i[356]	
Elevated cystatin or reduced GFR		Early referral to internal medicine and/or nephrology[358]	
Elevated systemic inflammatory markers		Careful review of potential etiologies; consider supplementation with curcumin	

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blocker; BP, blood pressure; CNS, central nervous system; CPAP, continuous positive airway pressure; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GFR, glomerular filtration rate; HIIT, high-intensity interval training; IM, intramuscular; MTHFR, methylenetetrahydrofolate reductase; NAC, N-acetyl cysteine; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; RBC, red blood cell; TMG, trimethylglycine; TRE, time-restricted eating.

D supplementation, cognitive engagement, and physical activity may also warrant greater attention and more specific recommendations (see ►**Table 2**).[21,128,140,141]

Dietary Patterns

Several epidemiologic studies have reported an association between dietary patterns and risk for various forms of dementia, including AD.[142,143] There are sufficient data for the recommendation of a Mediterranean diet (MeDi) and Mediterranean–DASH Intervention for Neurocognitive Delay (MIND) diet to support cognitive function and reduce dementia risk.[144] The MIND diet, similar to the Mediterranean diet but with further focus on lowering blood pressure (BP), emphasizes plant-based foods and encourages eating green leafy vegetables, berries, whole grains, fish, poultry, beans, nuts, wine, and olive oil. Research supporting the MIND diet consists of evidence from 900 dementia-free older adults, showing an association with reduced AD risk and slower rate of cognitive decline.[145] Certain aspects of a MeDi, such as its emphasis on an intake of lower glycemic

carbohydrates, healthy fats, leafy vegetables, and lean proteins, are associated with delay in the onset of dementia and a decrease in AD risk.[146–149] Higher adherence to the MeDi is associated with reduced risk in developing MCI and reduced risk for conversion of MCI to AD, while lower adherence to the MeDi is associated with progressive AD biomarker abnormalities in middle-aged adults.[150,151] A meta-analysis of 26 different studies investigating different dietary habits and their subsequent AD risk showed that a healthy diet can decrease oxidative stress, inflammation, and accumulation of Aβ, therefore lowering AD risk.[152]

Inflammation is a risk factor for dementia and may be modulated by various nutritional patterns/interventions. As referenced prior, low inflammatory/anti-inflammatory diets are associated with a lower incidence of dementia.[67] Though restrictive and often difficult to adhere to, the ketogenic diet has been shown to decrease systemic inflammation and may have the potential to delay the progression of dementia.[153,154]

Time-restricted eating and intermittent fasting may also be neuroprotective by promoting the process of autophagy in the brain.[155,156] Studies report that intermittent fasting may attenuate the progression of dementia by improving cognitive dysfunction, inhibiting hippocampal neuronal damage against oxidative stress, reducing neuroinflammation, and increasing the production of neurotrophic factors.[157–159] However, the decision to recommend time-restricted eating or intermittent fasting needs to be based on individual factors such as comorbid conditions, body composition, and other personal needs and considerations.[160] Dietary recommendations are summarized in ►**Table 3**.

Dietary Components, Vitamins, and Supplements

The use of vitamins and other nutritional supplements may also be considered using a precision medicine approach. An additional risk for dementia is elevated total plasma homocysteine, an amino acid metabolite which induces oxidative stress. Those with elevated homocysteine levels (generally >10 µmol/L) may benefit from a B-complex vitamin which contains B_6, B_{12}, and folate. Additionally, higher levels of both vitamin B_6 and B_{12} have been associated with improved cognitive function in midlife and attenuated brain atrophy for those with elevated omega-3 fatty acid levels.[133,161] Methylenetetrahydrofolate reductase (MTHFR) plays a critical role in folate metabolism, and two polymorphisms in the *MTHFR* gene, MTHFR-C667T and -A1298C, are associated with high serum homocysteine levels.[162] Those with *MTHFR* polymorphisms and elevated homocysteine may benefit from supplementation with a methylated B vitamin complex to allow for better metabolism of homocysteine, though further investigation is needed.[21,163,164]

Furthermore, vitamin D deficiency is a known risk factor for AD and potential supplementation for AD risk reduction may be considered.[59,133,165,166] Generally, a vitamin D serum level of 30 nmol/L is considered a target for treatment, though recent studies have suggested a range of 50 to 70 nmol/L may be more beneficial.[167]

Omega-3 fatty acids (DHA and EPA) are essential polyunsaturated fats that support cardiovascular function, lower triglycerides, and reduce inflammation. By increasing cell membrane fluidity, they promote the synaptic plasticity essential for learning, memory, and other cognitive processes.[168] Regular consumption of fatty fish including salmon, albacore tuna, sardines, mackerel, lake trout, anchovies, and herring provides a rich source of omega-3 fatty acids, but for some supplementation may also be necessary. Most western diets are much higher in omega-6 compared to omega-3 due to consumption of plant oils like canola. Serum fatty acid balance tests can be used to guide treatment decisions with a target of a 4:1 ratio omega-3 to 6. Before recommending an omega-3 supplementation, risks and benefits should be discussed, and all patients on supplementation should be monitored for potential adverse effects, including bleeding and possible increased risk of atrial fibrillation based on some recent studies.[169,170]

Oxidative stress can contribute to neurodegeneration and, hence, dietary consumption of antioxidants including green leafy vegetables and berries is recommended.[165,171] Flavanols are another group of compounds with both antioxidant and anti-inflammatory properties that may have a role in delaying or preventing the onset of dementia.[172] Some dietary sources of flavanols include cocoa, kale, tomatoes, apples, blueberries, and tea. In a 2020 study, 921 cognitively normal elders were followed up for 6 years after which 220 participants (24%) developed AD.[172] Results showed that a higher flavanol intake was associated with a 48% decrease in risk for AD. Cocoa flavanols may also support memory function, BP regulation, and glucose metabolism, and supplementation may be considered based on these factors.[173–181]

Curcumin, also known as turmeric, is a polyphenolic compound with antioxidant, anti-inflammatory, and neuro- and chemoprotective properties that have traditionally been used as a remedy for many illnesses in India and China.[182,183] Animal studies have definitively shown beneficial effects of curcumin on a molecular and behavioral level, but clinical studies remain mixed as to its cognitive benefits.[182,184] Nevertheless, some evidence has shown that curcumin can improve cognitive functioning in patients with AD.[185] This benefit is thought to stem from curcumin's ability to cross the BBB and interfere with cellular signaling pathways and various molecular targets. Its antioxidant properties come from its ability to scavenge free radicals such as reactive oxygen species and reactive nitrogen species. Its anti-inflammatory benefits and other properties—decreasing Aβ plaques, delaying degradation of neurons, decreasing microglia formation—may also be responsible for any identified cognitive benefits.[185]

Alcohol

Light-to-moderate alcohol consumption has been associated with a decreased risk of AD, whereas heavy consumption may increase risk, and this relationship appears to be true for VaD as well.[186–189] Surprisingly, some evidence has also found abstaining from drinking to be associated with a higher risk of AD. In fact, one longitudinal study found nondrinkers and heavy drinkers both be twice as likely to have MCI in old age as light drinkers, and another saw an increased risk of dementia only in nondrinkers and those who consumed more than 14 servings per week.[190,191]

A meta-analysis conducted on participants with AD, VaD, and other types of dementia found drinkers to have a reduced risk of AD and dementia in general—but not a reduced risk of cognitive decline—when compared to nondrinkers.[186] A variety of positive effects of alcohol on the CNS have been suggested, most having to do with reduction of cardiovascular risk factors.[189] Further research is required, however, to identify the effects of alcohol on dementia pathogenesis and progression.

Despite the detrimental effects of heavy alcohol consumption on cognition being widely agreed upon, the benefit of light-to-moderate drinking does continue to receive debate.[189] Varying dosage definitions, ages of participants, and lengths of studies may lead to different outcomes in epidemiological studies concerning low-to-moderate alcohol consumption and dementia risk, so more standardized investigation is necessary.[189]

Future investigation should also focus on differing effects of alcohol consumption on dementia risk between women and men, across socioeconomic statuses, and between other subgroups. For instance, the relationship between alcohol consumption and dementia risk seems to be modified by *ApoE* genotype, as consumption of any amount or type of alcohol has been found to increase AD risk for *ApoE4* carriers.[132] One study conducted in individuals aged 65 and older without dementia at baseline found up to three servings of wine per day to be associated with a decreased risk of AD—but only for individuals without *ApoE4*.[188] This further emphasizes the importance of personalized interventions guided by accurate risk stratification.

Exercise

Several reviews and meta-analyses have concluded that regular physical activity has general therapeutic potential, but substantial variation exists in exercise benefits on cognitive health and dementia risk reduction at the individual level. As such, clinical evaluation and analysis of anthropometrics, biomarkers, and cognitive testing should be used to guide individualized recommended physical activity. For example, studies have shown that ApoE4 carriers see greater long-term benefits from increased exercise.[128] Such exercise interventions have shown to be more beneficial during the preclinical stage of AD than in later clinical stages.[192]

High-intensity interval training (HIIT), which entails short bursts of extreme exertion (85–95% maximum heart rate, depending on the protocol[193]) followed by recovery periods, has received increased attention in recent years thanks to its capacity for metabolic, cardiovascular, and pulmonary benefits coupled with the attraction of less time spent exercising.[194] It has been shown that HIIT may be more beneficial for *ApoE4* carriers than noncarriers, and it is especially beneficial for individuals with elevated homocysteine due to *MTHFR* mutations.[129,195] Furthermore, HIIT has the potential to decrease LDL, increase HDL, and improve insulin sensitivity more effectively than moderate-intensity aerobic training, and these factors carry influence on individual AD risk.[196,197]

Compared to HIIT, lower-intensity steady-state cardiovascular training (also called zone 2 training) is traditionally defined as a more moderate intensity (~65% maximum heart rate), longer duration aerobic exercise, but, on a cellular level, is defined as the range at which maximum ATP is produced in the mitochondria under aerobic conditions. The evidence seems to support the benefit of HIIT in improving aerobic capacity, but findings have been mixed as to whether HIIT or steady-state cardiovascular is more effective in improving VO_2max (maximum rate of oxygen).[198–201] It has been shown, though, that steady-state cardio is associated with more substantial decline in resting heart rate and body weight than HIIT due to a resultant increase in mitochondrial density and efficiency.[202] Therefore, while it should be a part of all exercise plans, it may be especially important on a regular basis (e.g., three times a week) and for longer durations (e.g., at least 45–60 minutes per session) in those with elevated visceral body fat. Other benefits include decrease in BP, lower risk of injury, and improvement in insulin resistance.[203]

Another commonly recommended type of exercise is resistance training (also called strength and weight training), which best improves lean muscle mass and metabolism. Resistance training has shown to reduce cardiovascular risk factors—which are associated with cognitive decline and dementia—and to promote neurotrophic factors that are beneficial for the brain.[204] The SMART (Study of Mental and Resistance Training) trial supported the positive impact of resistance training on cognition and occurrence of white matter lesions.[205] According to additional evidence, males may benefit from an equal-to-greater ratio of resistance to cardiovascular training, while females may benefit from a greater ratio of cardiovascular to resistance training, further highlighting the need for individualized and sex-specific exercise interventions.[206] The correct dose or amount of exercise, as determined by frequency, duration, and intensity, per patient should be informed by their comprehensive clinical evaluation. One randomized controlled trial conducted showed that resistance training three times per week for a total of 24 weeks significantly improved cognitive function among male seniors aged 65 to 75 years.[93] Another study found that once- and twice-weekly resistance training significantly improve executive functions in senior women.[92] Patients should be counseled on the need to consume adequate amounts of protein and carbohydrates surrounding strength training to mitigate the risk of losing rather than gaining muscle mass.

In all, physical activity reduces key cardiovascular and metabolic risk factors for dementia, such as hypertension (HTN) and insulin resistance, on top of providing benefits to cognitive health.[207,208] The recommended dose and type of exercise should depend on longitudinal anthropometric assessments, and the individual abilities and responses of each patient.[129]

Hypertension

Midlife stage 1 and stage 2 systolic HTN is associated with an 18 and 25% increased risk of AD, respectively, though HTN has also been linked to worse cognitive function, behavioral symptoms, and hippocampal glucose metabolism.[209] Additionally, elevated BP and pulse pressure is associated with Aβ

and p-tau deposition.[210] There are eight completed randomized controlled trials to date that have examined various approaches to BP lowering on dementia outcomes.[211] As of 2018, the data more collectively support a significant reduced risk of dementia with aggressive systolic BP lowering (at or below 120 mm Hg) compared to a standard systolic treatment goal (<140 mm Hg) with the results from the Systolic Blood Pressure Intervention Trial - Memory and Cognition in Decreased Hypertension (SPRINT-MIND) study.[212] Diastolic BP should also be targeted at or below 70 mm Hg based on this study. Although further study evaluating cerebrovascular-specific pathological endpoints such as MRI brain is needed, the totality of current evidence supports targeting a systolic BP of 120 mm Hg or lower without evidence of significant harm.[212,213] Optimal pharmacological agents are unknown and may depend on personal factors, but data support use of angiotensin II receptor blockers (ARBs) such as candesartan and telmisartan and ACE inhibitors over diuretics, and avoidance of CNS-penetrating beta blockers.[212–216]

Hyperlipidemia

The identification of *ApoE4* as the major genetic risk factor for AD helped elucidate the relationship between lipids and cholesterol and AD. Literature has confirmed the association between high LDL and dementia risk independent of the effects of *ApoE* status and some research suggests that midlife hyperlipidemia may be more impactful on AD risk later in life.[217–220] However, studies also show low total cholesterol in late life can be detrimental for neural function and memory suggesting a delicate cholesterol balance in the brain.[221,222] Desmosterol, a precursor of cholesterol, can be metabolized in the brain, and is important in the degradation of APP and has been shown to inhibit formation of Aβ. Lower desmosterol levels are found in plasma, brains, and CSF of AD patients compared to controls and this supports the emerging hypothesis that desmosterol may serve as a marker for cholesterol metabolism in the brain.[223] Statin use is associated with decreased risk of dementia in many studies and while inconclusive, some demonstrate a differential effect depending on pharmacodynamic properties. Few report that lipophilic statins may increase risk of dementia. At this stage, the mechanism of this increased risk is unknown but possibly may be due to increased penetration of the BBB, thereby blocking cholesterol production in the brain.[224] As statins therapy reduces desmosterol production, low levels of desmosterol may suggest that cholesterol synthesis is over-suppressed in the brain and could potentially guide treatment decisions.

Metabolic Comorbidities

The brain is a very highly metabolic tissue and depends heavily on glucose metabolism for neuronal synaptic transmission. Thus, alterations in glucose availability and utilization as found in conditions such as obesity, insulin resistance, and DM2 are postulated to lead to neurodegeneration and Aβ and tau protein phosphorylation.[225–227] The idea of glucose-mediated neurodegeneration has inspired investigation into the use of antidiabetic agents for treating AD. Specific interventions for those with insulin resistance and/or DM2 may include lifestyle counseling, pharmacological treatment with evidence supporting semaglutide and metformin, and supplements like cocoa flavanols.[173,228]

Education and Cognitive Engagement

Having more years of education is associated with lower risk of dementia.[229,230] This association is possibly due to the improvement of cognitive reserve with increased education but is also impacted by early life cognitive development (which is related to genetics, socioeconomic status, psychosocial, and other variables). Early life educational attainment was found to have a protective effect on total brain volume, specifically during the MCI stage of AD.[231] Consistent cognitive engagement throughout life such as learning a new language or how to play an instrument is associated with improved cognitive function.[98,99,232,233] Studies also show that those with a history of reading, writing, and playing games had lower levels of amyloid deposition on PET imaging suggesting that cognitive engagement may influence the onset or progression of AD.[234]

Social Interaction

Social isolation and loneliness—major sources of mental and psychosocial stress—are also risk factors for dementia. Research shows that social isolation may be associated with neuronal degeneration, while a rich social life may slow cognitive aging and be neuroprotective against AD.[235] Though the exact mechanisms linking isolation to dementia are not completely understood, it has been proposed that production of Aβ, the p-tau protein, and increases in oxidative stress and inflammation are involved.[236–238] Social enrichment in older adults has been associated with increased levels of BDNF, which increases neuroplasticity and promotes synaptic consolidation.[239] Several studies on the association between social support and dementia have shown that this association may differ between women and men. In one study, social activities were associated with less memory decline in men in their midlife and old age, but this relationship was not found in women.[240] In another, support from co-residing with family members and being married was protective among men, while community engagement was protective for women.[241] Social enrichment interventions may be most beneficial when they are also mentally engaging, associated with physical activity, or provide a sense of purpose and can even be technology-based.[242–244]

Mental Health and Stress

Findings suggest that depression, anxiety, and chronic stress are associated with dementia and AD development among asymptomatic patients. Stress raises cortisol and acutely may have a positive effect on cognition. However, prolonged cortisol elevation due to chronic stress and rumination leads to a detrimental effect on memory, may accelerate brain aging, and may contribute to neurodegeneration.[245] Depression-related symptoms in AD adults have been shown to affect dementia risk through neurodegeneration in AD-related brain regions;

however, this is shown independently of amyloid and p-tau risk.[246] Anxiety has shown to predict individual risk of both AD and VaD, and prolonged stressful experiences have been associated with conversion from MCI to dementia.[247,248] In one 35-year longitudinal study, risk of dementia increased in women who reported frequent or constant stress, and reporting stress at one, two, or three examinations correlated with a sequentially higher dementia risk in participants.[249] The relationship between stress and dementia is made even more evident by the possible twofold higher risk of dementia incurred by posttraumatic stress disorder (PTSD).[250,251] Research also shows depression-associated risk may be more substantial in males, while stress and anxiety-associated risk may be more substantial in females.[100–102,252,253] Decreasing the threat posed by these psychological conditions is yet another avenue for preventing or delaying the onset of dementia.[254,255] In addition to positive effects on mood, evidence suggests that some therapies (such as Lexapro) carry anti-amyloid benefits.[256] Individualized recommendations may include mindfulness training, meditation, periodic vacations, cognitive behavioral therapy, exercise counseling, and medication.[98,107,108,110–113,257–260]

Sleep

Evidence from several observational studies demonstrates that both too short and too long sleep duration are associated with cognitive decline and risk of dementia.[261–263] In older adults, changes in sleep duration and patterns are also associated with increased risk of dementia, but are also a marker for early AD pathology.[264–270] In a study of more than 2,800 participants, those who slept less than 5 hours per night were twice as likely to develop dementia—and twice as likely to die—compared to those who slept 6 to 8 hours per night.[271] Data from a 30-year Europe cohort of almost 8,000 participants showed a 30% increase in dementia risk in those who slept for 6 hours or less at ages 50, 60, and 70 years independent of other confounding factors and *ApoE* genotype.[272] Clearance of Aβ is ascribed to the glymphatic system which operates most efficiency during slow wave sleep.[273] In fact, in one study, Aβ accumulation imaging increased by 5% in healthy controls after a single night of sleep deprivation.[274] Others have demonstrated similar findings in the CSF.[275] Additionally, rapid eye movement (REM) stage sleep is essential for memory consolidation and reduction in REM sleep is associated with dementia risk.[276]

While sleep need is highly individualized, most healthy adults require 7 to 8 uninterrupted hours of sleep.[277] Guidance on good sleep hygiene practice should be provided including avoiding caffeine consumption after 1 pm; restricting food, alcohol, and the use of electronics before bed; maintaining a consistent sleep schedule every day; and optimizing sleep environment.[21] Anticholinergics, benzodiazepines, and z-hypnotics should be limited due to their associated dementia risk.[278,279]

Referral for management of comorbid conditions that affect sleep quality such as nocturia due to benign prostate hypertrophy may be required. Another highly prevalent and treatable condition is obstructive sleep apnea (OSA).[280] OSA is associated with increased AD risk with women suffering the adverse effects more than men despite the less frequent presentation of moderate-to-severe OSA in women.[280] In one study, patients with OSA were found to have a 1.70 times greater risk for dementia within 5 years of diagnosis compared to age- and sex-matched patients without OSA.[281] Another study conducted in 2021 found significant associations between OSA and brain white matter hyperintensities (WMHs)—commonly observed in older people and significantly associated with AD—which indicates a novel pathological mechanism linking OSA and dementia.[282] As such, screening for symptoms of OSA should be included as a part of a comprehensive AD risk reduction plan.

Other Medical Conditions

Other significant risk factors for dementia include hearing loss, past traumatic head injuries, and smoking. Hearing impairment significantly increases the risk of AD and other cognitive disorders (though this association is not causal and requires further investigation), and the progression of dementia is faster in those with hearing loss than without it.[283–285] As such, when applicable, audiometry evaluation should be considered. Furthermore, robust evidence indicates that approximately 30% of patients who die from traumatic brain injuries (TBIs) have Aβ plaques in their brains—the pathological hallmark of AD—signaling an association between head injuries and neurodegenerative disease.[286] While accidents are unavoidable, risk may be mitigated by wearing a helmet during high-risk activities and a seat belt in motor vehicles. Cigarette smoking also confers an increased risk of AD—an effect that has tended to be stable over time—and heavy consumption in middle-aged smokers can increase the risk of dementia by more than 100% compared to non-smokers.[287,288] For this and other adverse effects on overall health, smokers should be counseled on smoking cessation and provided other cessation support resources.

Periodontal disease affects 70% of adults 65 and older and is another modifiable medical condition that may be associated with dementia.[289–293] In a recent analysis by NIA scientists, gum disease was associated with the development of all-cause dementia and especially VaD.[291] It has been proposed that *Porphyromonas gingivalis*, the bacteria that most commonly causes gum disease, can lead to the production of Aβ. Inflammation may serve as another connecting link between periodontitis and dementia.[294–297] Patients should be educated on the importance of proper oral hygiene and following up regularly with their dentist. Bidirectional care integration between dental and medical providers may best help mitigate patient's risk. Further clinical research is needed in this emerging area, and this may be best served by collaborations among medical and dental providers and oral systemic health experts.[298]

Future Directions and Conclusion

Although the evidence supporting dementia prevention is substantial, many areas need further investigation. Individualized multidomain clinical care for AD prevention has

already demonstrated benefit, as can be seen with the Alzheimer's Prevention Clinic (APC) at Weill Cornell Medical College/New York - Presbyterian, which was founded in 2013. The APC framework applies evidence-based principles of clinical precision medicine to tailor individualized recommendations.[20,21] The National Institutes of Health defines precision medicine as "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person."[299,300] In adaptation of this approach for use in a clinical setting, *clinical* precision medicine informs risk stratification and personalized intervention via comprehensive and longitudinal assessment of patients' anthropometrics, blood biomarkers, cognition, genetics, and family and clinical history.[21]

Moving forward, the utility of the clinical precision medicine approach will benefit from the expansion of genomic sequencing and direct-to-consumer testing, as AD risk and clinical course is thought to be impacted by the polygenetic factors.[301] The interest in broader-scale genetic data to guide clinical decision-making has occurred in other medical specialties as well, and the comorbid risk factors for dementia have their own environmental and genetic contributors.[301–304] It is hoped that self-provided genomic data, including whole genome sequencing and other at-home commercial qualitative genotyping, can be incorporated more regularly into medical practice to better identify disease risk and inform individualized risk reduction strategies. It is important to recognize the limitations that persist in the field of precision medicine, as progress and accessibility continues to be constrained by high costs, fear of genetic discrimination, access and availability of genetic testing, and inadequate and unprepared infrastructure.[305,306]

Already many AD risk factors cluster around inequalities and inequities, which occur primarily in Black, Asian, Hispanic, and other marginalized ethnic groups and vulnerable populations.[11] To continue to progress within the field of dementia prevention, we must address these disparities. The differences in AD prevalence and pathophysiology between racial and ethnic groups are due to various factors, such as genetic variants associated with certain groups, but also with other environmental factors such as socioeconomic status, diet, or medical comorbidities, which are heavily influenced by inequity.[307–309] For instance, chronic health conditions that are associated with higher AD risk, such as cardiovascular disease and diabetes, disproportionately affect Black and Hispanic populations.[15] Worldwide, multisite research collaborations are required to construct a large and diverse cohort, and the APC framework may be applied. Further research is additionally needed to determine the comparative effectiveness of prevention interventions and ongoing follow-up is necessary to assess long-term effectiveness on the development of AD and other dementias.[21,59]

Preventive care for dementia has not been routinely integrated into clinical practice in the United States, largely because it is not covered by Centers for Medicare/Medicaid Services and, therefore, private insurance policies. Considering the economic burden of dementia, its public health impact, the emergence of blood-based amyloid biomarkers, and growth of preventative practices, it is worthwhile to invest in and expand clinical prevention efforts for the benefit of tens of millions of patients in need. In 2022, a consortium of six clinical research sites in the United States (Weill Cornell Medicine/New York - Presbyterian in New York City, NY; Florida Atlantic University in Boca Raton, FL; Cleveland Clinic Lou Ruvo Center in Las Vegas, NV; Norton Neuroscience Institute in Louisville, KY; Alzheimer's Prevention Clinic and Research Center in San Juan, PR; Atria Medical in New York City, NY) and three globally (McGill University in Montreal, Canada; Jersey Memory Service in Jersey, United Kingdom; University of New South Wales/University of Notre Dame, St. Vincent's Hospital in Sydney, Australia) formalized plans to harmonize measures collected and better accomplish this goal.

Conflict of Interest
None declared.

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