Lifestyle Intervention and Alzheimer Disease

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BACKGROUND

Alzheimer disease (AD), the most prevalent type of dementia, represents the fastest-growing epidemic both in the United States and globally.[1] Currently, nearly 50 million individuals worldwide have been diagnosed with AD, and in the United States alone, there are more than 6.2 million who live with the diagnosis, with 1 new person diagnosed every 64 seconds.[2,3] Analysis projects an increase to 152 million diagnoses worldwide by 2050.[4] The emotional and financial costs of AD are staggering. In comparison, heart disease costs the US healthcare system approximately $120 billion, while AD costs $355 billion in direct costs and another $257 billion in indirect costs.[1] Furthermore, these costs are expected to grow to more than $1.1 trillion in the next 20 years, significantly affecting the healthcare system.[2]

Despite billions of dollars of investment over the last few decades for the treatment of AD, the US Food and Drug Administration (FDA) has approved only 1 drug—Aduhelm (aducanumab-avwa)—for disease course alteration. Due to its minimal demonstrated benefits and potential adverse effects, its approval has been controversial.[5,6] Yet our understanding of dementia etiology suggests that prevention or delay of onset of disease, through a comprehensive lifestyle intervention, may be a powerful option, as delaying symptoms by only 5 years may result in 41% fewer cases.[7,8]

To date, our myopic approach to AD has hindered a detailed look into cognitive decline and lifestyle.[9] Our focus has been on only 2 molecules, amyloid-beta (Aβ) peptide and hyperphosphorylated tau (p-tau), based on initial research demonstrating their role in the initiation and progression of disease.[10] Consequently, for the last few decades, the singular focus of research has been to block creation and accumulation of these proteins.[11] However, no drug targeting these proteins has demonstrated clinically meaningful results in AD treatment in clinical trials.[12] Yet there is plenty of research that implicates other factors in propagating or accelerating the disease process, including inflammation, oxidation, glucose dysregulation (insulin resistance/diabetes), lipid dysregulation, and direct toxic metabolic and traumatic processes.[13-17] Recognition of that has led to current interventional studies focusing on the effects of lifestyle intervention on individuals at risk of developing AD.[18,19]

RESEARCH ON PREVENTION

The results of 2 population studies concluded that, in individuals older than 65 years, "a healthy lifestyle as a composite score is associated with a substantially lower risk of Alzheimer's dementia." These studies, along with others, point to 5 fundamental lifestyle factors—nutrition, exercise, stress management, restorative sleep, and mental and social optimization—that can significantly affect one's risk of developing dementia.[7] An easy way to remember the core lifestyle elements is the acronym NEURO. In NEURO, N is for Nutrition, E stands for Exercise, U is for Unwind (stress management), R represents Restorative sleep, and O stands for Optimizing social and mental activity.

NUTRITION

Nutrition is an important lifestyle factor in dementia prevention. The brain, being a highly active organ, has a very high metabolic requirement and, consequently, is greatly affected by nutrition. Nutrition can have a positive or negative effect on glucose regulation, lipid regulation, inflammation, and oxidation.

Recent data on dietary intervention and dementia prevention show a variation on a single theme: a diet high in

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unprocessed plant-based foods; rich in phytonutrients, fiber, and polyunsaturated fats, especially omega-3 fatty acids; with or without fish; and low in processed foods—which are predominantly high in refined carbohydrates, saturated fats, and trans fatty acids—salt, and sugar, is protective and has been associated with a lower risk of AD and all-cause dementia.[20-24]

There appears to be a strong relationship between adherence to a Mediterranean diet (MD) and reduced risk of developing AD. Multiple observational studies have indicated that higher adherence to a MD is associated with reduced risk of AD and slower rates of cognitive decline.[25-27] In the PREDIMED (Prevención con Dieta Mediterránea) study, MD supplemented with nuts or olive oil produced improved cognitive function.[28] The Dietary Approaches to Stop Hypertension (DASH) diet is another dietary pattern which is also associated with improved cognitive outcomes.[29] Both MD and DASH dietary patterns have similar components, emphasizing a plant-predominant diet while limiting the consumption of red meat and other sources of saturated fats. MD is a cultural diet that specifically highlights daily intake of greens, beans, extra-virgin olive oil (monounsaturated fat), potatoes, and fish, along with some moderate consumption of wine, while DASH restricts intake of sodium, processed sweets, and saturated fat.[30]

A hybrid of the 2 aforementioned diets, the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND), was created by Martha Morris at Rush University, with modifications based on the evidence, to highlight foods that are protective for the brain.[31,32] The MIND diet uniquely specifies green leafy vegetables, as they possess the most potent neuroprotective qualities. Green leafy vegetables are rich sources of lutein, folate, vitamin E, beta-carotene, and polyphenols; these nutrients are related to brain health.[31,32] In the Rush Memory and Aging Project, the rate of decline among those who consumed 1-2 servings per day was the equivalent of being 11 years younger in age compared to those who rarely or never consumed green leafy vegetables.[31,32] Among fruits, only berries have been associated with slowing cognitive decline, in the Nurses' Health Study.[31,32] Other food components of DASH and MD included in MIND are extra-virgin olive oil, nuts, whole grains, and low-fat sources of protein, such as legumes and poultry on rare occasions.

Nevertheless, certain foods included in DASH and MD are not included in the MIND diet due to lack of evidence of their importance in brain health, including high consumption of fruits (3-4 servings in both DASH and MD), dairy (DASH), potatoes, and high fish consumption (2 servings per day and 6 fish meals per week in DASH and MD, respectively).[33] The MIND diet also recommends no more than 1-2 fish meals per week as sufficient to lower dementia risk, with no additional benefit from higher numbers of servings.[31,32] There is also evidence that the benefits of fish, often highlighted in MD, may be related to the higher concentration of omega-3, which may be found in fish or plant-based sources such as algae, quinoa, flax seed, hemp seeds, and even nuts like walnuts.[34]

A recent meta-analysis of 9 studies with 31,104 participants looked at the relationship between nutrition and cognitive impairment as well as dementia.[35] The meta-analysis revealed that increased consumption of fruit and vegetables was associated with a significant reduction in the risk for cognitive impairment and dementia (odds ratio [OR] 0.80; 95% confidence interval [CI]: 0.71-0.89). Further analysis demonstrated that a dose response effect was seen with incremental increase in consumption of 100 g per day of fruits and vegetables with a 13% (OR 0.87; 95% CI: 0.77-0.99) reduction in cognitive impairment and dementia risk.[35]

EXERCISE

The brain is significantly affected by exercise, as exercise has consistently shown beneficial effects on metabolic rates and processes, vascular health and vasogenesis, psychological processes such as anxiety and depression, and rapid proliferation of neuronal connections.[36-40] In the last 2 decades we have learned a great deal about the regenerative power of exercise on the brain. Moreover, it has become clear that not all exercise is equal. High-intensity aerobic exercise for longer durations is better, although there may be an upper limit to this.[41] For most of the population the upper limit should not be of great concern, as today a greater proportion of the population than ever before lives a sedentary life.[42]

Aerobic exercise is very important for general and brain health, as evidenced in a meta-analysis that included 16 studies with more than 160,000 participants, in which regular physical activity resulted in a 45% lower risk of developing AD (hazard ratio 0.55; 95% CI: 0.36-0.84; P=0.006).[43] A European multicenter study (LADIS: Leukoariosis and Disability) on the effects of exercise on 639 elderly subjects demonstrated a 40% lower risk of cognitive impairment and dementia, as well as a 60% lower risk of vascular dementia.[43] Baker et al studied the effects of intensive exercise vs stretching on those suffering from mild cognitive impairment (MCI), with the intensive exercise group demonstrating greater blood flow to the frontal lobe, increased brain size, better executive function, and protection against cognitive decline, despite strong genetic risk for AD.[44]

Furthermore, multiple studies have consistently demonstrated better brain health with strength training. In a 2010 meta-analysis of 15 studies, strenuous exercise resulted in a 38% reduced risk of cognitive decline.[45] Mavros et al dem-

onstrated that resistance training, over a 6-month period, in subjects experiencing MCI improved cognition to normal levels in 47% of individuals. These outcomes were maintained for 18 months, and greater leg strength had a much higher correlation with better brain health and size.[28]

In a meta-analysis that brought together 11 studies and looked at 3 different interventions (aerobic exercise, strength training, and multimodal exercise), it was found that exercise, aerobic exercise in particular, benefited global cognition in MCI patients. Yet a third factor that has emerged in the last few years is the fact that sedentary behavior, independent of exercise, has a powerful negative influence on health and cognition.[46] It is thus apparent that adding exercise and regular movement to a daily routine is critical for brain health.[47]

UNWIND: STRESS MANAGEMENT

There is evidence that persistent bad stress is associated with greater cognitive decline and smaller brains. Bad stress has been defined as the kind of behaviors, thoughts, and emotions that do not serve one's purpose, do not have clear directions, and do not result in clear, achievable successes. There is much research on the effects of bad stress on growth hormones, insulin resistance, thyroid function, sex hormones, and the immunologic system through the limbic, hypothalamic, pituitary, and endocrine system.[48-50] Bad stress also reduces brain-derived neurotrophic factor, inhibiting the growth of new connections between neurons.[51] Alternatively, stress, when well-defined, goal/purpose-oriented, and success-oriented, can promote cognitive and neuronal growth.[52] In a study by Lupien et al, elderly participants with increased stress-associated cortisol levels had a 14% reduction in hippocampal volume and impaired memory.[53]

Activities shown to reduce stress, such as meditation and mindfulness, have resulted in lower neural inflammation, reduced atrophy, and better brain function.[54] Harvard University researchers demonstrated that experienced meditators had thicker cortical volume and a larger cortex in regions of the brain associated with attention and sensory processing and this effect was more pronounced in older individuals, suggesting a greater effect of meditation on older individuals.[55,56]

RESTORATIVE SLEEP

The brain, which can consume up to 25% of the body's energy, is constantly working and gathering data, both passively and actively. Thus, it requires 7 to 8 hours of deep restorative sleep (4 to 5 cycles of different sleep phases, especially deep sleep and resting eye movement). This allows the brain to cleanse and organize thoughts and memories for better function.[57]

Rouch et al demonstrated that alteration of melatonin release, as seen in shift workers, may contribute to cognitive impairment. Further, in the VISAT study, male shift workers demonstrated lower cognitive function in a dose-response fashion, as those with greater periods of shift work had greater difficulty with memory, but had better cognitive function after halting shift work for at least 4 years.[58] In another study, sleep deprivation demonstrated cellular changes that led to microglia (the brain's janitors) starting to phagocytize normal brain tissue rather than performing their usual cleansing function. In the long term, this led to brain atrophy.[59] In a meta-analysis of 7 studies comprising more than 13,000 participants, sleep apnea increased the risk for developing AD by as much as 70%.[60] Although sleep medications may be helpful in the short term, there is evidence that some agents, such as benzodiazepines, may have negative long-term effects.[61,62] Of note, sleep hygiene and cognitive behavioral therapy can help resolve a significant number of sleep disorders influenced by environmental and psychological issues.[63]

OPTIMIZE (SOCIAL AND MENTAL ACTIVITY)

Currently, one of the most important factors contributing to redundancy of neuronal connections and neuroplasticity is the level of cognitive activity an individual has engaged in throughout their life. Each of the 87 billion neurons we possess can make as few as a couple, or as many as 30,000 connections,[64] and this number is determined by how one pushes, stresses, and challenges the brain around one's purpose.[65] Mental and social optimization has been shown to impart tremendous protection against degenerative diseases, an aspect called cognitive reserve, and this is probably the most important factor in risk reduction.[66]

Cognitive, social, and intellectual activity, jointly with higher education and occupational attainment, have been shown to decrease the risk of cognitive decline and dementia by increasing cognitive reserve (the capacity of the brain to resist the effects of neuropathologic damage).[67,68] Observational studies consistently show that people who engage in mentally stimulating activities are less likely to develop AD (risk ratio 0.54).[66,69-71] In a comprehensive review led by Barnes, it was demonstrated that approximately 19% of AD cases worldwide are potentially attributable to lower levels of education.[72] Developing cognitive reserves that enable individuals to continue functioning at a normal level, despite experiencing neurodegenerative and neurovascular changes, seems to have a high impact on disease onset. For example, the beneficial impact of bilingualism on brain reserve, and consequently on AD risk and cognition, has been highlighted recently. Studies suggest that lifelong bilingualism

may delay the onset of dementia by 4 years by contributing to cognitive reserve and, consequently, protecting against dementia.[73]

The protective power of lifelong cognitive activity was clearly demonstrated in a large-scale study of 678 Catholic nuns 75 to 107 years of age. Data captured from this population included early and midlife risk factors from archives, annual physical and cognitive testing in old age, and postmortem neuropathologic evaluation of the participants' brains. Postmortem evaluation of the brains of one group of nuns demonstrated significant pathology (neocortical neurofibrillary tangles), yet during life these nuns did not exhibit dementia. Another group of nuns demonstrated minimal postmortem brain pathology, yet they showed a greater incidence of dementia. Further analysis of contributing factors indicated that the main difference was that the cognitively protected group, despite much pathology, had developed greater cognitive reserve, demonstrated by the complexity of their language.[74,75] Other factors such as intelligence quotient and education have also been demonstrated to confer cognitive reserve.[64] Multiple studies have demonstrated that a decline in cognitive activity over the years consistently leads to cognitive decline and even brain atrophy, while stimulating brain activity can lead to greater reserve, cognitive capacity, and even brain size.[76-79]

Recently, there has been greater interest in knowing whether one can build cognitive reserve, capacity, and protection through video games. There is promising evidence that as the games become more sophisticated and personalized, they may provide a tremendous armamentarium of tools for building brain reserve and capacity. The 2014 ACTIVE (Advanced Cognitive Training in Vital Elderly) study examined the effects of cognitive training on 2785 healthy older adults. The study looked at 3 cognitive domains over several time periods (1, 2, 3, 5, and 10 years) after training. The results demonstrated long-term benefit in reasoning and processing speed, but not memory.[80]

The London taxi driver study revealed that involvement in complex activities like studying for a difficult visuospatial task (eg, learning the driving routes in London), resulted in greater cognitive capacity, as well as larger brain volume, specifically in the area dedicated to memory, the hippocampus.[81] The Wisconsin Registry for AD Prevention looked at the effects of lifetime job complexity on brain health and found that greater job complexity was associated with better cognitive performance and greater reserve.[82] In 2018, a meta-analysis of the effects of cognitive games/interventions in individuals with MCI revealed that focusing on a person's particular cognitive weakness (specific neuropsychological domain) led to improved cognitive function.[83]

COMBINATION OF LIFESTYLE FACTORS

Recently, the Lancet Commission on Dementia Prevention, Intervention, and Care, comprising scientists and psychiatrists, stated that as many as 40% of dementia cases could be attributed to modifiable risk factors including low education, midlife hearing loss, obesity, hypertension, late-life depression, smoking, physical inactivity, diabetes, and social isolation.[84]

The FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) interventional study analyzed the effects of comprehensive lifestyle intervention in 1260 individuals in their 60s and 70s at risk of developing dementia. The results demonstrated improvement in cognition in those receiving the comprehensive lifestyle intervention.[85]

Two similar studies in the Netherlands and France also demonstrated cognitive improvement in those at risk for developing dementia who had received a comprehensive lifestyle intervention.[86]

Currently, the only community-based intervention and research program at the national level is being conducted online at Brain Health Revolution. This is an innovative translational model that aims to inculcate healthy lifestyles into people's homes while measuring sustainable change.

ADDITIONAL RISK FACTORS

Some additional factors that have been shown to increase the risk for developing dementia are smoking, excessive alcohol use, other toxins (eg, lead, mercury, aluminum, carbon monoxide), head trauma, hearing loss, vitamin deficiency (B12, D), thyroid disease, and chronic inflammatory states. These factors can significantly contribute to increased risk of developing dementia, depending on the extent and duration of the risk factor.[83,87-91]

DISCUSSION

The research reported in this review includes many of the seminal studies that have looked at the environmental and lifestyle factors that contribute to the development and avoidance of dementia. To date, there is only 1 pharmaceutical treatment (Aduhelm) that has been shown to potentially slow down progression of early-stage AD, and it is not without controversy. Given that the evidence for the effects of comprehensive lifestyle intervention is significant, it is imperative that all healthcare providers, particularly family medicine physicians, are aware of the risk factors for dementia and the interventions that can positively affect cognitive decline.

Individual factors such as diets low in saturated fat, processed food, and processed sugar have been shown to reduce the risk of dementia by more than 50%.[32] Simple exercises can

reduce the risk of developing dementia by as much as 45%.[43] The same is true for stress management, restorative sleep, and cognitive activity. Importantly, when relevant changes to the aforementioned factors are made, the effects on brain health can be significant. Although the estimates vary greatly, there is agreement that between a 33% and 60% reduction in risk of AD is possible.[7] Based on our review of the literature, which demonstrated that the percentage of AD driven by high-penetrance genes such as presenelin-1 (PSEN1), presenelin-2 (PSEN2), and Alzheimer's precursor protein (APP) constitutes only 3% to 6% of all cases of AD, and that the majority of other cases are predominantly driven by lifestyle factors, we believe the number is closer to, if not higher than, 60% for those who diligently adhere to the NEURO approach.[7,92]

Given the potential benefits of the intervention on health in general and on dementia, even modest risk reduction would have tremendous effects on healthcare and the community in general. What is most empowering is that the influence on the outcome is not binary; rather, it falls along a spectrum depending on genetic risk and compliance with all the different lifestyle variables. Given that, to date, no single drug can influence the onset or course of dementia, any change in lifestyle can have significant public health consequences. What makes this approach to the "tsunami" that is dementia even more important is that it also has a positive effect on cardiovascular outcomes, cancer risk, and diabetes, as well as a tremendous effect on the greater cost of healthcare, given that the intervention is inexpensive and involves everyday life events.

BEST PRACTICES IN LIFESTYLE MEDICINE FOR AD PREVENTION

The authors' recommendation to family physicians is to make lifestyle education, resources, and intervention part of their clinical armamentarium for all patients, but especially those in midlife and of older age who are at greater risk for developing dementia. This includes information, resources, and a multidisciplinary approach to prevention as it pertains to management of metabolic risk factors (hypertension, high cholesterol, and insulin resistance/diabetes), inflammatory and infectious diseases, toxic contributors (alcohol, cigarette smoking, illicit drugs, heavy metals), traumatic brain injuries, sleep disorders, and psychiatric factors (depression, anxiety). Although all patients would benefit from this approach, given resource management, greater focus may be placed on those at imminent risk such as patients with early-stage memory and cognitive disorders. This means detecting cognitive deficits at their earliest stage using valid sensitive neuropsychological tools such as MoCA (Montreal Cognitive Assessment), Mini-Cog, CANTAB (Cambridge Neuropsychological Test Automated Battery), NEUROSpect, and others.

Furthermore, dementia should be approached similarly to cardiovascular disease, with as great an emphasis on prevention as on treatment. Family physicians and other primary care physicians ought to be first in line in moving toward this paradigm shift if we hope to make a difference.

AUTHORS' RECOMMENDATIONS

Nutrition:

- Reduce refined carbohydrates and processed sugars.
- Reduce saturated fat; consume polyunsaturated fat sources from plants.
- Reduce animal products (meat, poultry, and dairy), especially processed meats.
- Reduce processed foods.
- Consume more plants of all varieties (especially whole grains, green leafy vegetables, berries, cruciferous vegetables, spices, herbs, nuts, seeds, and green tea).
- Reduce salt consumption.

Exercise:

- Incorporate aerobic exercise, such as brisk walking, jogging, biking, swimming, dancing, etc for at least 150 minutes per week.
- Incorporate strength training, especially leg-strengthening exercises, 3 to 5 days per week.
- Create an environment where there is movement throughout the day.
- Add stretching and balance exercises to reduce injury.

Unwind (stress management):

- Identify one's good and bad stresses, specifically working toward increasing good (purpose-driven, success-oriented) stress and reducing bad stressors.
- Introduce meditation and mindfulness techniques: two 3-minute increments per day and increasing the duration as technique improves.

Restorative sleep:

- Introduce a regimented sleep pattern—going to bed the same time and waking up 7 to 8 hours later every day.
- Eliminate noise from sleep space, either by noise-reducing measures around the windows and doors, wearing earbuds, or presence of white noise during sleep.
- Eliminate blue light up to a half hour before sleep.
- Avoid eating at least 2 hours before sleep.

Optimize:

- Lead a purpose-driven life.
- Engage in complex real-life activities (involving mul-

tiple cognitive domains of the brain), such as playing musical instruments; learning to dance; learning languages; leading a project; being part of a book club; writing a blog, article, or book; etc.
- Consistently engage in cognitively challenging activities to continually push the brain to adapt.

Other recommendations:

- Abstain from smoking, eliminate or significantly reduce alcohol use (not more than 1 glass of wine per night), avoid head trauma (helmet use, seat belt use, and sport safety), and use hearing aids if experiencing hearing loss. ●

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