STATE OF THE ART
REVIEWS

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Preventing Alzheimer's: Our Most Urgent Health Care Priority

Abstract: *Dementia is the fastest growing epidemic in the developed nations, and if not curtailed, it will single handedly collapse our health care system. The prevalence of dementia is 1 in 10 individuals older than 65 years and increases to 50% of all individuals older than 85 years. The prevalence of Alzheimer's dementia (AD), the most common form of dementia, has been increasing rapidly and is projected to reach 16 million individuals by the year 2050. Several prevailing myths about the science of dementia are discussed, such as that AD is inevitable and that it is exclusively a genetic disease. The fact is that AD is dependent on a multitude of genetic, epigenetic, and environmental factors that interact with one another. In fact, 4 core drivers represent 90% of what determines disease progression in AD. These are (1) glucose or energy dysregulation, (2) lipid dysregulation, (3) inflammation, and (4) oxidation. Lifestyle change can significantly alter the course of AD. The authors have created an acronym—NEURO—to help lifestyle practitioners and the public remember the most important lifestyle elements in the treatment and prevention of AD based on the evidence. "N" is for Nutrition, "E" for Exercise, "U" for Unwind (stress management), "R" for Restorative Sleep, and "O" for Optimizing mental*

and social activity. The evidence base for each of the components is reviewed.

Keywords: Alzheimer's, brain health, prevention, longevity, cognitive impairment

Background

We have learned more about the brain, this 3-pound organ that is the source of human consciousness, in the first quarter of the 21st century than ever before in

discovered that our brains may consist of around 86 billion neurons, potentially as many as 1 trillion supporting cells such as glial cells, and more than 1 quadrillion connections. Therein lies the potential protection against the trauma and wear and tear that accumulate with aging. These connections can confer tremendous cognitive resilience that could enable the brain to withstand much of a lifetime's trauma. In the 20th century, we have seen a sharp rise in life expectancy that came about with

There has been cumulative evidence that aging does not have to lead to cognitive decline.

history. For the last few centuries, we knew about the importance of this incredible organ, but we did not know much about its physiology or pathology, and we knew even less about how to improve its function and avoid disease.

It was only at the turn of the 20th century that we acquired novel tools in our armamentarium to better understand the brain. Initially, it was tissue stains that gave us a better delineation of structure, and later, amazing imaging techniques allowed us not only to understand the structure, but also the function of the brain.

In fact, it was not until 2009, through the work of Herculano-Houzel,¹ that we

life-saving discoveries such as antibiotics and heroic public health measures. But with the success came a prolonged, sustained challenge to this overworked organ. As society ages, we will face the challenges that come with cognitive aging. Given that the fastest growing population in the United States and most of the developed world is individuals 65 years and older, there is an urgent need to address the problem of cognitive aging.

The challenge ahead of us is expected to overwhelm the Western world—the epidemiological "tsunami" of dementia. Briefly, dementia is a neurological

condition where cognitive deficits progress to the point where a person can no longer take care of some of their daily activities. Dementia is an umbrella category that includes Alzheimer's disease (AD), Lewy Body disease, frontotemporal dementia, Parkinson's dementia, vascular dementia, and many more. AD constitutes 60% to 70% of all dementias and is the most feared disease among those 55 years and older.² AD is the fastest growing epidemic in the Western world.³ In the United States, it is the leading cause of morbidity. It is currently listed as the fourth leading cause of mortality and morbidity.⁴ Every 65 s, a person is diagnosed with this dreaded disease.⁵ This number is an underestimate of the true prevalence because a great proportion of the population never receives a formal diagnosis, instead enduring solitude and simply perishing because many families consider it just part of normal aging. Today, we have 5.8 million individuals with the diagnosis, and this number is expected to grow to 16 million by 2050.⁶

What appears to be an even greater public health dilemma is that while we have been succeeding at reducing mortality from many chronic diseases such as diabetes, HIV, heart disease, and most cancers in the past 15 years, mortality from AD has grown by more than 123%.⁷ In fact, today, 1 in 10 individuals older than 65 years is diagnosed with AD.⁶ This number doubles every 10 years until at age 85 years, nearly 50% will have developed the disease.⁶ The cost of AD has already surpassed all other diseases: AD is now the most expensive disease in the United States and most of the developed world. In the United States, the direct cost of AD has been estimated at around \$277 billion in combined spending, \$60 billion of which comprises out-of-pocket expenses. Compare this to the second and third most expensive diseases, heart disease and all cancers, at a cost of \$120 billion and \$57 billion, respectively.⁵ More disturbing is the fact that certain populations are suffering disproportionately because AD does not affect all communities equally.

Women,^{6,8,9} African Americans, and Hispanics appear to be at much greater risk. One of 6 women are diagnosed with dementia in their lifetime as compared with 1 in 11 men.⁶ Compared with Caucasians, African Americans have a 4-time greater risk of developing AD, and Hispanics have a 2.7 times greater risk.¹⁰⁻¹⁴ These numbers appear to be increasing exponentially. By 2050, the number of individuals suffering from this horrific disease is expected to climb to nearly 140 million worldwide,¹⁵ and the cost of AD is expected to climb to more than 1.1 trillion in the United States and nearly \$20 trillion worldwide.⁵ These numbers are alarming, and they should be, because they are not only going to collapse the health care system but the entire social structure of developed countries as we know it.

In the past few decades, we have become aware of the concept of successful cognitive aging. There has been cumulative evidence that aging does not have to lead to cognitive decline. We have many examples of "successful cognitive agers"—those who have lived physically and cognitively vibrant lives well into their 80s, 90s, and beyond. These "successful cognitive agers" are not exceptions, but rather a product of a healthy lifestyle.¹⁶

Reversing the Tide of Misinformation

The path to reversing the alarming trends outlined above starts by challenging some myths that have taken us down a myopic laboratory and clinical research path that has failed us repeatedly.

The first myth is that there is nothing we can do to prevent AD. This assumption is so pervasive and accepted that most institutions that deal with the disease at the clinical, community, or national levels consistently promulgate this idea. Remarkably, this categorical claim is made in the face of tremendous data that powerfully contradicts it.

Why is there such resistance to a counter-narrative? Why are most academic institutions and communities consistently

negating or disparaging the idea that we may have some measure of control over our cognitive fate? The reason appears to lie in a deep-seated and systematic bias in the world of research and grantsmanship against complexity. Research funding and grants are set up mostly in a way to fund projects that are manageable, financially and logistically, within a finite time horizon. Looking at diseases in their complex interactions is almost unmanageable within the budgets and timelines of funding agencies such as the National Institutes of Health. Thus, the reductionist approach to AD research is not appropriate, and there is an urgent need to move away from the linear, single-molecule approach to more complex models of explaining diseases such as AD. It is in this environment that we have been chasing amyloid plaques and neurofibrillary tangles for the past 30 years. In fact, simply searching for the term β -amyloid in PubMed reveals 52 480 articles, which disproportionately outweighs the relationship of any other molecule or intervention with AD. There is no denying the fact that these 2 molecules are involved, at some level, in this disease. The question is whether they are the main driving force behind the majority of cases of AD or whether they are consequent to what occurs upstream in the life cycle of the disease.¹⁷

To that end, researchers have created many cellular and animal models of the disease on which they have tested thousands of molecules. They create the proverbial "lesion" and find a molecular "plug" to fix it. In this way, they have been able to cure or at least curtail the disease in dozens of scenarios. But when translated to human trials, these methods have failed to provide the desired outcome in every instance.¹⁸

The second myth is that AD is an exclusively genetic disease. This statement on its face is not a myth because all diseases have a genetic aspect. After all, every cell—except for mature red blood cells—has DNA, and all our cellular processes, be they normal function, degeneration, or proliferation, are driven by genetic processes. But different diseases are influenced

uniquely by genes. Certain diseases are strongly driven by a single gene mutation, which can power the disease course. One example of a point mutation or single gene degenerative disease is Huntington's disease, which results from a single point mutation on chromosome 4. The clinical manifestation of this disease is consequent to this point mutation that produces a triplet codon (CAG). In these patients, the CAG segment is repeated many times. If the repeat number is more than 40, the disease is destined to manifest. The greater the number of CAG repeats, the more likely a patient will develop the disease at an earlier age and with greater intensity.¹⁹ Other examples of neurological diseases that are heavily driven by genetic or chromosomal flaws are muscular dystrophy and Down syndrome (DS). In these diseases, the genetic anomaly drives the manifestation of the symptoms, and the course is fairly predictable.

Other genetic diseases have a multifactorial inheritance pattern and are caused by a combination of small, inherited variations in genes, often strongly influenced by environmental factors. Most chronic diseases such as heart disease, diabetes, and most cancers fall into this category.

When looking at AD from a genetic prism, except for 3 genes—*Presenilin-1*, *Presenilin-2*, and amyloid precursor protein (*APP*)—which appear to be responsible for only 3% of AD cases—a great majority of patients appear to have a multifactorial origin to their disease. We have learned that for this larger segment of those at risk, the disease is related to the body's ability to respond to various life stressors. To date, more than 25 genetic loci have been implicated in AD by a combination of linkage, genome-wide association, and whole genome/exome sequencing.^{20,21} The most common gene associated with AD is the *APOE* gene. It has 3 common forms, *ApoE2*, *ApoE3*, and *ApoE4*, and they are considered risk genes. Whereas *ApoE2* appears to significantly reduce the risk of developing AD, *ApoE3* is neutral, and *ApoE4* is associated with

increased risk. If one inherits an *ApoE4* gene from 1 parent, their risk is increased 4-fold. If, on the other hand, an allele is inherited from each parent, the risk goes up by as much as 12 times.²² In the United States, only 2% of the population has 2 *ApoE4* alleles. Interestingly, those who have 2 alleles do not necessarily develop AD. In fact, 50% do not develop dementia at all.²² Another perspective into the *ApoE4* gene comes to us from a 2001 study from Nigeria, where a much greater proportion of the population was found to be *ApoE4* positive. Yet the proportion of the population, despite the *ApoE4* positive alleles, who developed AD was much smaller compared with the rest of the world. There is evidence that in this population, lifestyle had a much stronger effect on the development of the disease. There is a plethora of evidence implicating the influence of lifestyle on these genes.²³⁻²⁸

Other genes that have been attributed to AD include those that deal with the body's immune response, the ability to efficiently metabolize lipids, energy metabolism, and the brain's waste degradation process—to be more precise, the cell's lysosomal disposal system and autophagy, and its ability to get rid of waste.^{29,30}

These genes simply represent a range of responses to a lifetime of cumulative assault through our lifestyle choices. The outcome, dementia versus healthy cognitive aging, speaks to a life of excess lipids, inefficient energy use from simple sugars, long-term inflammation, oxidative stress, and the cell's inability to effectively eliminate waste during a lifespan of 70 to 80 years or more. With poor genes for any or all of these responses, in the context of unhealthy lifestyle choices, the brain gets overwhelmed earlier and more extensively in life.

The 3 genes that have a very strong penetrance and will invariably express AD in their carriers, usually before the age of 65 years, are the *Presenilin-1*, *Presenilin-2*, and *APP* genes. These genes undoubtedly have a strong association with amyloid production and

have been the main drivers behind the amyloid hypothesis.³¹

The *APP* gene encodes a very important transmembrane protein that has been found to be involved in many growth and immunological processes. To date, 32 types of mutations in the *APP* gene have been identified that are known to increase the risk of developing AD. Individuals with DS have 3 copies of chromosome 21, which is where the *APP* gene resides. This redundancy of the *APP* gene leads to amplification of the gene and the gene product, which is usually β -amyloid, resulting in a much greater and earlier prevalence of AD in this population.³² Research reveals that almost all individuals with DS have amyloid plaques by age 40 years, but not every person with DS eventually develops AD. In fact, 50% never develop AD. There is a strong correlation between better management of proxies of vascular health (hypertension, hyperlipidemia, and diabetes) and delay and avoidance of AD.³³⁻³⁵

Therefore, in almost all cases of AD, genes provide a risk range, but it is lifestyle that ultimately determines at which point in that range disease manifests. Our own work and a comprehensive review of the literature has demonstrated that the central drivers of late onset AD, which constitute more than 90% of all cases, are 4-fold: (1) glucose or energy dysregulation, (2) lipid dysregulation, (3) inflammation, and (4) oxidation.

These pathways coexist and contribute to various aspects of the disease. Lately, AD has been described, by some, as type 3 diabetes³⁶; others have described it as a garbage disposal disease and yet others as an inflammatory/immune regulation disease. The reality is that one can approach the disease from different paths. There are patients who have a history of chronic insulin resistance or diabetes, and in these cases, insulin resistance primarily drives the disease, and yet chronic inflammation may be the main driving force behind the inception and propagation of the disease in other cases such as chronic traumatic encephalitis. Lipid dysregulation, as

driven by *Apo e4* or other pathways, can serve as a driver of neurovascular and neurodegenerative disease as well. And finally, oxidative stress can be a major driver of neurodegeneration as a result of free radical formation, damaging neural architecture and vasculature.³⁷ We also know that chronic, low-grade systemic inflammation is common in insulin-resistant states, which are seen consistently in many of the pathways toward the disease.³⁸ These 4 processes are involved in the neurovascular and neurodegenerative processes. The only factor that changes is the dominant driver of the underlying pathology.

Given that these pathways are the drivers of brain pathology in AD, we searched the literature for the most prevalent sources of these pathological pathways and evidence of ways to ameliorate them early in the process. One factor that appears to have a central role in inflammation and oxidation is nutrition.

“NEURO”: The Components of Lifestyle Change

The authors have created an acronym—“NEURO”—to help lifestyle practitioners and the public remember the most important lifestyle elements in the treatment and prevention of AD based on the evidence. “N” is for Nutrition, “E” Exercise, “U” for Unwind (stress management), “R” for Restorative Sleep, and “O” for Optimize. The following subsections will expand on the evidence base for each of these components.

Nutrition

Of course, nutrition is important. After all, we consume food 3 to 6 times per day, 7 days a week, 52 weeks per year, often over an 80-year lifespan. Everything we eat can either help sustain and build our brains or break down and damage our brains.

Everything we consume has an energy coefficient because it produces a certain amount of energy in our body. The quality of food based on its nutrient

density can profoundly affect the brain at the cellular and genetic levels. Below, we list some of the seminal articles that point to the effect of food on the brain and ultimate development of AD.

Kivipelto et al³⁹ demonstrated, in 2002, in a large prospective population-based study in eastern Finland, that the risk for AD from treatable factors such as elevated total cholesterol and blood pressure appeared to be greater than that from the *Apo e4* allele and genetic risk. Although the *Apo e4* allele was an independent risk factor for AD, even after adjustment for midlife vascular risk factors and other confounders (OR = 2.1 [95% CI = 1.1 to 4.1]), the risk for AD was higher for those with elevated midlife values for serum total cholesterol (OR = 2.8 [CI = 1.2 to 6.7]) and systolic blood pressure (OR = 2.6 [CI = 1.1 to 6.6]), and these factors remained significant even after adjustment for *Apo e* genotype and other confounding factors.³⁹

In the Chicago Health and Aging Study conducted by Morris et al,⁴⁰ high intake of saturated and trans-unsaturated (hydrogenated) fats increased the risk of AD by 2.2 times and 2.4 times, respectively, compared with those with the lowest level of consumption. In contrast, intake of omega-3 polyunsaturated fat and monounsaturated fat were inversely associated with AD. Researchers examined the association between fat consumption and AD in a stratified random sample of 815 community residents aged 65 years and older who were unaffected by AD at baseline and who completed a food-frequency questionnaire. After a mean follow-up of 3.9 years, 131 persons developed AD. Intakes of saturated fat and trans-unsaturated fat were positively associated with risk of AD, whereas intakes of polyunsaturated fat and monounsaturated fat were inversely associated.⁴⁰

In 1993, Giem et al⁴¹ at Loma Linda University Health investigated the relationship between meat consumption and dementia among the Seventh Day Adventists. The first cohort included

272 California residents matched for age, sex, and zip code (1 vegan, 1 lacto-ovo-vegetarian, and 2 “heavy” meat eaters in each of 68 quartiles). The second cohort included 2984 unmatched participants who resided within the Loma Linda, California, area. All individuals were enrolled in the Adventist Health Study. Those who consumed meat, including poultry and fish, had twice the risk of developing dementia compared with vegetarians (relative risk = 2.18; *P* = 0.065), and the discrepancy was further widened (relative risk = 2.99; *P* = 0.048) when past meat consumption was taken into account.

In the Kaiser Permanente Northern California Group of 9900 patients, individuals with high cholesterol during midlife had a 57% higher risk of developing AD later in life. Even borderline high cholesterol increased the risk of AD by 23%.⁴²

In the Women’s Health Study, nearly 6000 women were followed over 4 years. Higher saturated fat intake was associated with a poor trajectory of cognition, specifically a faster decline in memory (by 70%). Women with the lowest saturated fat intake had the neuropsychological test scores of women 6 years younger.⁴³

In the Rush University Memory and Aging Project, Morris et al⁴⁴ examined the adherence to the MIND diet on 1000 patients, 58 to 98 years old. Strict adherence to the MIND diet (promotes plant-based diet, limits meat, salt, and dairy) resulted in a 53% reduction in risk for AD. In fact, even moderate adherence to the diet was associated with a 35% risk reduction. Participants who showed high adherence to the diet had cognitive functioning equivalent to a person who was 7.5 years younger.⁴⁴

Given that brain health is one of the fastest growing markets in the nutraceuticals and vitamin world, we thought it important to provide a quick review. Various antioxidants are often consumed in pill form for AD prevention, but the clinical value of antioxidants for this application is often ambiguous. Likewise, most randomized controlled

trials on nutritional supplements for the prevention of AD have remained inconclusive so far. However, replacement of B vitamins and DHA have been associated with lower rates of AD and cognitive decline. Low B vitamin levels, particularly vitamin B12, and a consequent increase in homocysteine are associated with cognitive impairment, and its replacement results in improved outcomes.⁴⁵ B12 vitamin supplementation can slow atrophy of specific brain regions that are a key component of the AD process and that are associated with cognitive decline. In a randomized controlled study on elderly individuals with mild cognitive impairment (MCI; VITACOG), high-dose B vitamin treatment (folic acid 0.8 mg, vitamin B6 20 mg, vitamin B12 0.5 mg) slowed shrinkage of the whole brain volume over 2 years.⁴⁶ In another study, B vitamin treatment reduced cerebral atrophy in regions specifically susceptible to AD pathology, such as the medial temporal lobe, by as much as 7-fold. Low DHA (omega-3 fatty acids) levels have also been associated with lower cognitive status, and its replacement has been linked to improved cognitive outcomes among adults.⁴⁷

Lifestyle, not genetics, has been shown to be a strong determinant of dementia in a community setting. There are many examples of ecological studies indicating how diet and lifestyle in general can increase the incidence of dementia when a population adopts a “Western” diet high in processed foods and sources of saturated fats. For example, the incidence of AD was found to be up to 5 times lower for Africans in Nigeria than for Nigerians in Indianapolis, despite the higher prevalence of *Apo e4* carriers in both populations.⁴⁸ This indicates that environmental factors such as lifestyle have a stronger effect on the development of disease than genes. Other proxies of poor lifestyle such as prediabetes and diabetes have also been implicated in AD. Growing evidence supports the concept that AD is a metabolic disease mediated by impairments in the brain’s responsiveness

and sensitivity to insulin, glucose utilization, and energy metabolism, which lead to increased oxidative stress, inflammation, and worsening of brain insulin resistance. In a nationwide study, we were able to demonstrate that insulin resistance is inversely associated with cognitive status among the elderly, even after adjusting for diabetes, stroke, and heart disease.⁴⁹

The articles we cited here represent only a small fraction of all the research publications that speak to the benefits of a comprehensive, unprocessed, plant-based diet for preserving brain health and potentially avoiding AD. At the core, the key takeaways are the following:

1. Reduce processed sugars
2. Reduce fats, especially saturated fat
3. Reduce animal products (meat, dairy, cheese)
4. Reduce processed foods
5. Consume more plants of all varieties, especially greens and beans
6. Increase fruit consumption, especially berries
7. Reduce salt consumption

Exercise

The second factor that has been found to have a significant influence on brain health and resilience is exercise. When it comes to exercise, the science has been even more remarkable, not because it is that much more significant than nutrition, but rather because until recently, we did not have as much data on the relationship between exercise, cognition, and brain aging. Human and nonhuman animal studies have shown that aerobic exercise can improve a number of aspects of cognition and performance.⁵⁰⁻⁵⁵ The data have been fast and furious, and they have revealed the amazing curative and regenerative effect of exercise with regard to the brain. But at the same time, we have been forced to look at exercise in a different way. As preventive neurologists, we always bring up the importance of exercise in brain health, and almost every elderly patient tells us that exercise is not an area of concern for them. But on further investigation, their exercise program

turns out to be a slow walk around the neighborhood, working around the house, or working in their garden. As beneficial as these leisure time physical activities are, they are more aligned with meditation and relaxation and not necessarily consistent with the kind of exercise necessary for brain health. Reviewing the literature, the type of exercise that is truly beneficial for the brain is much more strenuous and specialized.

In the Framingham Longitudinal Study, daily brisk walks resulted in a 40% lower risk of developing AD later in life.⁵⁶ In a 2010 meta-analysis of 15 studies and nearly 34 000 people, the authors found that a high level of physical activity could lower the risk of cognitive decline by 38%.⁵⁷ Those participants who engaged in a less-intensive, more moderate form of exercise still had a 35% lower risk of cognitive impairment. The LADIS (Leukoraiosis and DISability) study was a European multicenter collaboration that began in 2001 with the aim of assessing the independent role of cerebral white matter disease in predicting disability in individuals aged 65 to 84 years. In one of the secondary analyses of the data set, researchers investigated the effects of exercise on 639 elderly individuals whose cognition and vascular health were tested every 3 years. Those who exercised had a 40% lower risk of cognitive impairment and dementia as well as a 60% lower risk of vascular dementia.⁵⁸ At Wake Forest University, a group of researchers led by Baker⁵⁹ studied the effects of stretching and intensive exercise in individuals with MCI. Participants were placed in an exercise program for 45 minutes a day, 4 days a week, over a 6-month period. The intensive exercise group (n = 37) had increased blood flow to the frontal lobe, increased brain size, improved executive function, and protection against cognitive decline despite these individuals’ strong genetic risk for AD. The stretching group (n = 34) had brain shrinkage and decreased executive function as a result of the normal course of dementia.⁵⁹

In contrast, sedentary behavior has been associated with cognitive decline, in addition to many other chronic diseases of aging, such as diabetes, hypertension, cardiovascular disease, and all-cause mortality.⁶⁰ This has been attributed to poor vascular health as well as oxidation and inflammation in the brain. Indeed, inflammation is significantly lower among individuals who exercise on a regular basis. In a systematic review and meta-analysis of 43 studies published between 1995 and 2012 (3575 participants), a structured exercise program significantly lowered inflammatory markers in the blood. These dramatic results were seen after only 4 weeks of exercise.⁶¹

Strength or resistance training is as important for brain health as aerobic activity, if not more. Studies have suggested a direct link between resistance training and improved cognitive outcome. Mavros et al⁶² measured the effects of a resistance training program (2-3 times a week for 6 months) on a group of 100 older adults age >55 years with MCI. Nearly 47% of the participants achieved normal cognitive scores after the intervention, and these results were maintained over a period of 18 months. Greater lower body strength was especially effective at improving cognitive performance.⁶²

In summary, the type of activities that has been found to be most beneficial for brain health and potentially contribute to the reversal of cognitive impairment include the following:

1. a regimented exercise program that involves regular, fairly extensive aerobic exercise;
2. leg strengthening exercises; and
3. regular movement throughout the day

Unwind: Stress Management

Stress can negatively affect the brain and secondarily the rest of the body through its effects on the endocrine, autonomic, and immune cascades. Critical areas such as the prefrontal cortex and the limbic system, which are responsible for physiological and behavioral stress, can be damaged at the

cellular level as a result of continued stress load.⁶³ Such stress can be adaptive and protective in a short, controlled, and goal-oriented form. However, it can become destructive, causing significant disarray in the neurochemical, hormonal, and immunological systems through its effect on the limbic system, hypothalamus, and pituitary axis during chronic, purposeless, and uncontrolled stress.^{63,64}

When stress is perceived as “bad,” meaning the stress caused by activities (jobs, projects, life events) not driven by one’s own purpose or on one’s own timeline and with no control over its outcome, the result is chaos in one’s health through the limbic, hypothalamic, and pituitary axes. The latter cascade has been consistently shown to release cortisol and adrenaline and cause an imbalance in the homeostasis of thyroid, insulin, and growth hormones as well as increased levels of cortisol and adrenaline.^{65,66} Yet the same pathway can release an entirely different cascade of hormones and chemicals that create harmony and physiological stability in one’s body when the stress (job, education, work, project) is perceived as challenging yet purposeful and under one’s control.⁶⁶

In one study by McLaughlin et al,⁶⁷ elderly individuals with increased cortisol levels had on average a 14% reduction in hippocampal volume and impaired hippocampus-dependent memory. When the hippocampus is damaged by cortisol, it struggles to regulate the body’s stress system and results in the secretion of even more cortisol, a vicious cycle that in turn damages more cells.⁶⁷

Stress decreases the level of BDNF (brain-derived neurotrophic factor), thereby inhibiting the growth of new neurons and connections, whereas exercise, a stress-reducing activity, appeared to increase levels of BDNF.⁶⁸ In contrast, techniques to allay bad stress and build focus and attention have been associated with reduced cerebral inflammation and atrophy.

Meditation has been associated with reduced atrophy, greater neuroplasticity, and improved cognition.⁶⁹ In a study by

researchers at Harvard University, functional magnetic resonance imaging (MRI) was used to measure cortical thickness in 20 individuals who were experienced in meditation. Brain regions associated with attention and sensory processing were thicker in meditators than in matched controls. These differences were most pronounced in older participants, suggesting that meditation might offset age-related changes in brain volume.⁷⁰

In a study conducted at UCLA, meditation increased hippocampal volume in a sample of elderly individuals.⁷¹ Given the role of the hippocampus in memory encoding processes and its susceptibility to stress and other pathophysiological pathways of neurodegeneration, stress management and meditation/mindfulness seem to have a potential role in an armamentarium of preventive strategies. The research to date points to several important takeaways to stress management:

1. identifying one’s good and bad stress;
2. working toward increasing good (purpose driven, success oriented) stress and reducing bad stress; and
3. including meditation and mindfulness techniques throughout the day.

Restore: Restorative Sleep

Sleep has a critical role in promoting brain health. Research over the past decade has documented that sleep disturbances have a powerful influence on the risk for developing neurodegenerative disease. One of the biggest enigmas in evolution has been sleep. What evolutionary forces would have warranted the need for sleep? What evolutionary advantage could have been gained in being unconscious and paralyzed for nearly 8 hours, or one-third of our day? It is only in the past decade that we have begun to understand what happens to our bodies during sleep and that sleep is especially central to the health of the most active organ, the brain. We have realized that sleep serves 2 extremely important functions: (1) to help organize and consolidate memories

and thoughts and (2) to detox the brain from all the day's cumulative inflammatory, oxidative, and waste by-products.

A study by Rouch et al⁷² demonstrated that long-term night-shift workers experience suppressed melatonin production at night because of continuous light exposure and are at an increased risk for cognitive impairment. In the VISAT (Aging, Health, and Work) cross-sectional study, the long-term influence of shift work on verbal memory and cognitive speed was investigated. The study consisted of 3237 participants, who were workers across the age spectrum, of various occupational statuses. Data collected by questionnaires included items on working hours, shift work, and sleep disorders. Cognitive abilities were assessed using neuropsychological tests. The authors found that male shift workers had lower cognitive performance than never exposed workers. In the same population, memory performance tended to decrease with increasing shift work duration. Former shift workers who stopped their shift work at least 4 years prior performed better on cognitive tests, suggesting a possible reversibility of effect. This study demonstrated that cognitive functioning tends to be impaired by a long-term exposure to shift work, and neuropsychological performance tends to decrease with increases in the duration of exposure to shift work.⁷²

Another study on sleep deprivation demonstrated that microglia destroy healthy neurons and their connections. Microglia, which are the "janitor cells" that serve to detox the brain (essential for clearing harmful by-products), go awry during periods of sleep deprivation. It has been shown that chronic sleep deprivation activates microglia, promotes their phagocytic activity, and does so in the absence of overt signs of neuroinflammation, suggesting that like many other stressors, extended sleep disruption may lead to a state of sustained microglia activation. The damage sustained by this abnormal state

appears to be cumulative over the long term and may explain the brain shrinkage found in individuals who consistently fail to get enough sleep.⁷³

In a review and meta-analysis of 7 studies, which included more than 13 000 participants, scientists at the University of South Florida reported that sleep apnea increased the risk of AD by 70%.⁷⁴ It is critical that those who suffer from sleep disturbance identify the source of the problem and do not automatically resort to sleep medications because some forms of sleep aids may be somewhat benign in the short term but are often harmful in the long term.^{75,76} It has been demonstrated that with the right sleep hygiene program and cognitive behavioral therapy, a significant number of sleep problems can be resolved over time.⁷⁷

What we know to date about sleep and its effect on the brain include the following:

1. restorative sleep that is around 7 to 8 hours a night involves going through deep sleep through the different phases of sleep several times per night;
2. this process leads to memory and cognitive consolidation and organization as well as detoxification;
3. almost everyone can achieve ultimate restorative sleep, over time, through consistent sleep hygiene implementation as well as cognitive behavioral techniques;
4. if one suspects the possibility of sleep apnea, he or she should immediately get tested for it because untreated sleep apnea and other sleep disorders can significantly increase one's risk for dementia and AD in particular.

Optimize

We have now learned that the first 4 lifestyle factors (nutrition, exercise, stress, and sleep) have an immense influence on inflammation, oxidation, energy metabolism, and lipid dysregulation and, thus, have a tremendous effect on cognitive aging and ultimate propagation of diseases such as AD. Optimizing these 4 lifestyle factors can reduce one's risk

for developing dementia significantly, especially if started earlier in life.

The last element in our acronym has no direct effect on the 4 pathological processes but greatly influences the connections between neurons. As one can imagine, anything that influences this aspect of the brain, which amounts to each cell making thousands of connections as opposed to a few connections, would give the brain tremendous redundancy and resilience. This last element of our plan is the "O," which stands for optimizing mental and social activities.

The most important factor of all for brain health and resilience as we age appears to be cognitive reserve. Cognitive reserve represents the redundancy of neuronal connections achieved through cognitively challenging activities that force the neurons to make significantly more axonal connections than when not challenged.⁷⁸ The idea of cognitive reserve against damage to the brain originates from the repeated observation that there does not seem to be a direct relationship between the degree of brain pathology or brain damage and the clinical manifestation of that damage. That is, research has shown that some patients with significant β -amyloid accumulation or vascular disease show no symptoms of AD, despite their advanced pathology. The hypothesis suggests that there are individual differences in the ability to cope with AD pathology because these neural reserves are invoked when one is coping with increased task demands. More connections means more redundancy, therefore more resilience.⁷⁹ These connections between individual neurons can be a few or as many as thousands, which can give profound protection against toxic, metabolic, and physical challenges.⁷⁹

We now know that complex real-life activities around one's passion and purpose, such as challenging jobs, learning musical instruments, and speaking multiple languages, are most effective in optimizing mental processes and building cognitive reserve and brain

capacity. Outlined below are a number of studies that support this conclusion.

The Nun's study was one of the studies that provided us great insight into the protection that this redundancy could incur. Katzman et al⁸⁰ described cases of cognitively normal, elderly women who were discovered to have advanced AD pathology in their brains at death. They speculated that these women did not express the clinical features of AD because their brains were larger than average. Factors other than IQ and education might also provide reserve and influence the incidence of AD.⁸¹ It has been seen that a decline in everyday cognitive experiences and activity patterns may result in disuse and consequent atrophy of cognitive processes and skills. On the other hand, stimulating brain activities significantly increase neuronal connectivity and, consequently, not only stop cognitive decline, but increase brain size and cognitive capacity.⁸²⁻⁸⁵

Over the years, because of the terrifying nature of dementia and the advent of technology in the realm of health, multiple digital brain game platforms have become available. The pattern of cognition in dementia is almost always a combination of declines, of varying degrees, in multiple domains, and most current games do not cater to the complexity of the brain. Despite this limitation, some brain games have shown promising results. A study published in 2014 by researchers at the University of Florida known as ACTIVE (Advanced Cognitive Training In Vital Elderly), examined the effects of cognitive training programs on 2785 healthy older adults.⁸⁶ Participants were divided into 3 groups. One got training for memory improvement, one for reasoning, and one with computerized training in speed-of-processing. Scientists measured cognitive and functional changes immediately and at 1, 2, 3, 5, and 10 years after the training to see if they affected how participants performed daily tasks. Results of that study, published in 2014, found modest benefits in the reasoning and speed-of-processing groups, but not memory.⁸⁶

Other complex activities seem to have more benefits to cognition. The London Taxi Drivers study identified differences in hippocampal gray matter volume in London taxi drivers.⁸⁷ Structural MRIs of the brains of humans with extensive navigation experience, licensed London taxi drivers, were analyzed and compared with those of controls who did not drive taxis. The hippocampi of taxi drivers were significantly larger relative to those of controls, which translated to complex spatial knowledge and cognitive reserve as a consequence. The hippocampal volume correlated with the amount of time spent as a taxi driver.⁸⁷

The Wisconsin Registry for AD Prevention examined the effect of job complexity on cognitive reserve and white matter disease. Boots et al⁸⁸ investigated this query in 284 cognitively healthy participants (average age = 60 years). Participants with complex jobs had better cognitive performance despite the presence of white matter lesions in their brains. They concluded that a complex, mentally stimulating lifestyle can lessen the effects of the harmful structural changes associated with AD.⁸⁸

We conducted a meta-analytic review to examine the efficacy of cognitive intervention in individuals diagnosed with MCI. Individuals with MCI who received multicomponent training or interventions targeting multiple domains (including lifestyle changes) were apt to display improvement on outcome measures of cognition postintervention. We also found that interventions around a person's weakness (particular cognitive domain) were most effective.⁸⁹

In summary, cognitive optimizing appears to be most effectively achieved when

1. individuals are involved in complex tasks (involving multiple cognitive domains of the brain), such as learning musical instruments, learning languages, and leading projects; especially job complexity has greater effect on building cognitive reserve;
2. activities are challenging, thus continually pushing the brain to adapt; and

3. activities are purpose driven—this creates positive stress for the brain.

Additional Risk Factors

Although these 5 lifestyle factors are central to protecting the brain, there are many others that have been shown to influence our risk for developing AD. One major factor is smoking. In one study by Ott et al,⁹⁰ smoking increased the risk of developing dementia by 2-fold, and those who do not smoke or stop smoking significantly reduce their risk for developing dementia. Another risk factor is the effect of alcohol on the nervous system. The topic is quite complicated and is based on definitions such as alcohol use disorder, alcoholism, and binge drinking, versus moderate alcohol use, which is defined as 2 drinks per night for men and 1 for women. There is evidence of general neuronal loss and specific regional damage to the brain secondary to alcohol consumption. Also, dendritic and synaptic changes have been documented in uncomplicated alcoholics, and these, together with receptor and transmitter changes, may explain functional changes and cognitive deficits that precede the more severe structural neuronal changes. Indeed, alcohol-related neuronal loss has been documented in specific regions of the frontal cortex, hypothalamus, and the cerebellum. A recent study by Schwarzwinger et al⁹¹ showed an association between alcohol use disorders in French hospitalized patients and dementia. Alcohol use disorders were a major risk factor for onset of all types of dementia and especially early-onset dementia.⁹¹ Yet another study by Topiwala and Ebmeier⁹² questioned the benefits of any amount of alcohol for the brain and attributed many of the results from previous studies showing possible benefit to socioeconomic and educational confound, concluding that if there were any benefit, it was probably limited to 1 drink per day.

A meta-analysis by Loughrey et al⁹³ in 2018 found hearing loss to be a biomarker or potential modifiable risk

factor for cognitive decline and dementia. Another major contributor to increased risk for dementia is history of traumatic brain injury. Over the past few years, many studies have demonstrated a relationship between traumatic brain injury and dementia. Although the intensity of the trauma was a major risk factor, a study by Nordström and Nordström⁹⁴ found that even brain trauma 30 years earlier increased one's risk for dementia.

Conclusion

The studies we have reviewed are just a few of many that have provided insight into the power of lifestyle on brain health and our ability to avoid diseases such as AD. Given the social and economic burden that AD will inflict on our society and the fact that we have absolutely no curative or disease-modifying treatment at this point or on the horizon, promulgation and implementation of lifestyle measures that have repeatedly been shown to be effective are an absolute public health necessity. There is evidence that lifestyle intervention for diseases such as obesity, diabetes, heart disease, stroke, and many other chronic diseases is more likely to be effective at the community level.⁹⁵ Given that the latter diseases share similar efforts with regard to prevention, a similar approach at the community level would most likely be effective for dementia, including AD. Thus, it is important that we start educating communities about how to implement the necessary environmental changes that would potentially combat this tsunami of mental health.

The only community brain health and AD prevention model in the country that has started implementing lifestyle changes at the community level to alter the risk prevalence of the disease is our program at the Beach Cities Health District in Southern California. We enthusiastically welcome collaborations with other communities throughout the country and the world to implement similar changes and reduce the prevalence of dementia worldwide.

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