PART 1: ALZHEIMER'S DISEASE- A GLOBAL EPIDEMIC

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Age-related dysfunction of the brain can escalate in aggressiveness and complexity over time as the victim progresses toward the end of life. **ALZHEIMER'S DISEASE** (AD) is currently viewed as a progressive neurodegenerative disease that is uniformly fatal. The most common form is termed Late-Onset Alzheimer's Disease (LOAD), which primarily impacts people over the age of 65 and is the focus of this article. In addition to its devasting impact on individuals with AD, it has a wide-reaching impact that touches every aspect of our society. But there is hope. In the following pages, we'll review the current state of the science and clinical approaches to AD, and introduce promising new ways to approach prevention and treatment. Making these changes will require a fundamental shift in how we approach not only AD but our health and healthcare as a whole.

All stakeholders must work together to change the tide in this global epidemic. From individuals, families, and communities to healthcare, research, and private and government institutions, we all have the opportunity to be part of the solution. It won't be easy, but to keep going in the same direction is unthinkable.

ALZHEIMER'S DISEASE WILL BANKRUPT HEALTHCARE

Without a drastic – and rapid- change in our approach, caring for people with dementia, particularly Alzheimer's disease, is predicted to bankrupt this country's healthcare systems by the year 2050. Currently, we spend more than $321 billion in direct healthcare costs caring for the more than 6 million Americans living with Alzheimer's. In large part due to the increase in our aging population, that number is expected to increase to 13.8 million, with costs projected to be over $1 trillion by 2050. [1] Evidence shows that taking a more holistic approach can improve quality of life [2 but this requires a different mindset and strategy. In addition to the staggering cost of healthcare, there is a hidden cost that often fails to receive attention: unpaid caregiving.

More than 11 million unpaid caregivers spend an estimated 18.4 billion hours a year caring for family members with Alzheimer's or other dementias. The value of these unpaid services is estimated at $350

billion [2], exceeding the direct healthcare costs. However, this number is even greater in terms of total impact, as it does not account for the emotional, physical, and social toll, nor does it include lost wages and related benefits due to caregiving responsibilities.

A DISEASE OF AGING

Alzheimer's disease is fatal and is the fifth-leading cause of death among Americans aged 65 and older. [3] This number does not include those with Alzheimer's who die of other diseases first, but where Alzheimer's was likely a contributing factor. While people aged 65 and older only survive an average of four to eight years after diagnosis, some can live as long as 20 years. [3]

Twice as many women as men are diagnosed with Alzheimer's disease, and women account for almost 2/3 of the approximately 7 million Americans currently living with Alzheimer's. [3e] Ethnicity also plays a role. Black/African American individuals have twice the risk of Alzheimer's disease compared to Non-Hispanic white individuals, and Hispanic/Latino individuals are just slightly lower at 1.5x. [4]

When looking at people 65 and older, the highest prevalence of AD is among Black/African American individuals at 13.8%, with Hispanic/Latino individuals at 12.2%, non-Hispanic white individuals at 10.3%, American Indian and Alaska Native individuals at 9.1%, and the lowest group being Asian American and Pacific Islander individuals at 8.4%. [4] The U.S. Census Bureau has predicted that the U.S. minority population will increase from 20% to almost half by 2060. Despite these statistics, most research has been conducted with non-Hispanic white populations, hampering both understanding of underlying causes as well as treatments for an increasing demographic. There are currently no good treatments in the conventional medical model, and thus people with Alzheimer's are often led to believe that there is nothing they can do. Ending up in a nursing home often seems inevitable.

NURSING HOME VS HOME CARE

According to the CDC, as of 2020 there were more than 15,000 nursing homes serving more than 1 million residents, and for-profit companies owned 70%. [6] One of the top three reasons older people are placed in assisted living facilities and nursing homes is dementia, with Alzheimer's being the most common type and accounting for almost half of all nursing home residents; this rate is even higher for Medicare beneficiaries. As people with Alzheimer's disease age, they are often found to have other forms of dementia as well. [3]

Research shows that those who are in nursing homes do better when provided with more specialized services. However, less than 5% of nursing home "beds" are in facilities that provide these. [6] But nursing home care is not inevitable. More than 60% of people with Alzheimer's disease and related dementias live at home, half of them living alone. [6] This concept of "aging in place" may help alleviate the burden of nursing home care. It also can help slow the progression of the disease, as people are kept in familiar environments that provide a sense of belonging and purpose. This continued connection to their community also provides better opportunities for social and cognitive engagement.

Living at home requires aids and adaptations, as well as caregiver support. This brings up another challenge: "Who provides the support?" How we treat the elderly reflects our societal values. With an overemphasis on achievement and productivity, those unable to meet this standard are seen

as “less important” and thus less valuable. Often, this intersects with traditionally female roles, including caretaking for the elderly, children, and those who are sick, infirm, or disabled.

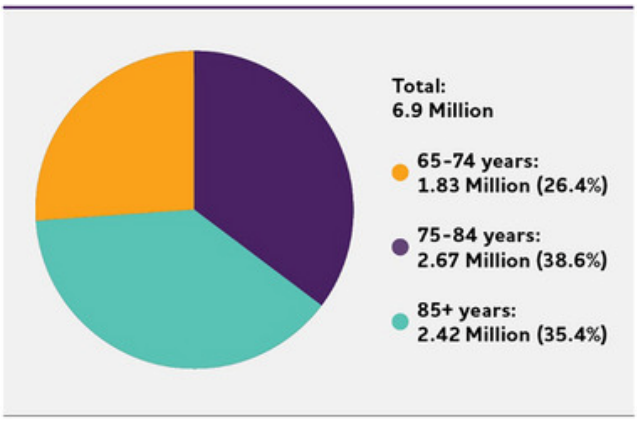
As women are often the primary caregivers, they are much more likely to disproportionately suffer additional consequences. Women from historically minority and marginalized groups with fewer resources and access to services are even more impacted. [3]

LEADING CAUSES OF ALZHEIMER’S DISEASE

Alzheimer’s disease is a complex interplay of genetic and environmental factors.

1. AGE

Age is the single largest risk factor for AD. The vast majority (90-95%) of people with AD are over age 65, with risk increasing with age.



Age distribution of AD in 2023. [3]

2. GENETICS

Specific forms of the APOE gene are associated with late onset Alzheimer’s disease (LOAD), the most common type that typically affects individuals after age 60. People carrying the E4 variant of the APOE gene have the largest genetic risk, based on research involving individuals primarily of European descent. Those with two copies of the APOE4 gene are estimated to have about a 60% risk of developing AD by age 85, and recent research suggests that the form of disease may be different than AD in those with normal APOE genes. [7]

Interestingly, this study also found that almost everyone with two copies of APOE4 developed brain changes in beta-amyloid and tau consistent with Alzheimer’s Disease by age 55. But previous studies have estimated that almost half—40%—of people with two copies of APOE4 don’t develop Alzheimer’s disease, so it’s not necessarily inevitable. [8]

Variants in genes regulating the inflammatory response have been implicated in AD. In 2013, a variant in the TREM2 gene was found to account for the next highest risk after APOE4. [9] Recently, a variant in the FMNL2 gene appears to link the connection between vascular disease in the brain with Alzheimer’s disease by reducing the clearance of amyloid in the brain. [10]

Research has revealed a number of other gene variants that are associated with AD more specifically in individuals with African heritage. Variants in genes linked to the immune response, and vascular systems were found to account for up to 30% of the heritability of AD in Black Americans. [11] A different APOE variant on APOE3, normally thought to be protective, was associated with an increased risk for African Americans if they also carried APOE4. New gene variants in ABCA7 have an even greater impact on AD risk for individuals with African ancestry vs European ancestry. [12] It is likely that ongoing research will continue to refine the genetic contributors for various populations, increasing our understanding of the disease and potential treatments.

We can’t change our genes, but they are not the only cause. While approximately 60% of patients with AD have APOE4 or other identifiable genetic risk factors, 40% don’t. [13] This is likely due to a combination of other genes that have recently been identified, along with dietary, lifestyle, and environmental factors. [8]
As with many other chronic diseases, this illustrates the importance of understanding how the interactions between our genes and environment can increase or decrease genetic predisposition for disease. These insights are crucial to finding clues that may help

accelerate better options for treatment and even prevention.

3. EPIGENETICS

Epigenetics involves changes that affect gene expression without changing the DNA sequence. It is the body's ability to quickly respond to environmental factors, and has been identified as a significant contributing factor to many health issues including Alzheimer's Disease. [14] It is one of the mechanisms by which diet and lifestyle factors impact genetics and contribute to AD – and how we can also leverage them to potentially reverse these processes.

4. ACCUMULATION OF BETA-AMYLOID AND TAU

The prevailing theory of why people develop Alzheimer's Disease has been focused on the role of specific protein alterations in the brain called beta-amyloid plaques and, more recently, tau neurofibrillary tangles. While these changes are thought to be the hallmark of AD in the brain, the limited focus on this "amyloid hypothesis" ignores scientific research into other biological mechanisms that contribute to the disease process.

Scientific research is shedding light on the complexity of Alzheimer's disease that goes far beyond beta-amyloid plaques and tau protein tangles. In fact, these changes are now thought to be a *result* of the underlying biological mechanisms that can lead to AD - which likely explains why pharmaceutical companies have pursued treatment without much success. [9]

This single-minded focus on the amyloid hypothesis, excluding other theories that challenged this accepted dogma, has significantly contributed to the lack of progress in finding treatments. [9] As a result of this and other biases, Alzheimer's Disease research has been grossly underfunded compared to other chronic diseases such as heart disease and HIV.

But even the funds invested have failed to deliver significant progress. Despite spending over $40 billion on drug development over the last 25 years, the FDA has approved only a handful of medications that are woefully inadequate in improving symptoms and disease progression. [15] None address the underlying causes and we have no cure.

Clearly, we need a different approach. Fortunately, dedicated scientific researchers have been making significant headway in understanding the underlying causes and exploring innovative approaches to treatment. With appropriate funding, these lay the foundation for more fruitful results that also address inequities in research and treatment access.

5. NEUROINFLAMMATION

Inflammation in the brain has been associated with several neurodegenerative diseases, of which Alzheimer's Disease is the most common. [16] In AD, this involves specialized cells in the brain called microglia. Damage to these microglia leads to dysfunction and degeneration of neurons, which then creates a circular cascade of more inflammation and more damage to mitochondria and neurons. [17]

Cytokines and the inflammasome are a central part of the neuroinflammatory process, activating numerous cascades that increase the pro-inflammatory response and deposition of beta-amyloid plaques that damage neurons.. [9]

Various toxins as well as microbiological agents including viruses, prions, parasites, and bacteria have

also been associated with triggering an inflammatory response and the development of AD. [18]

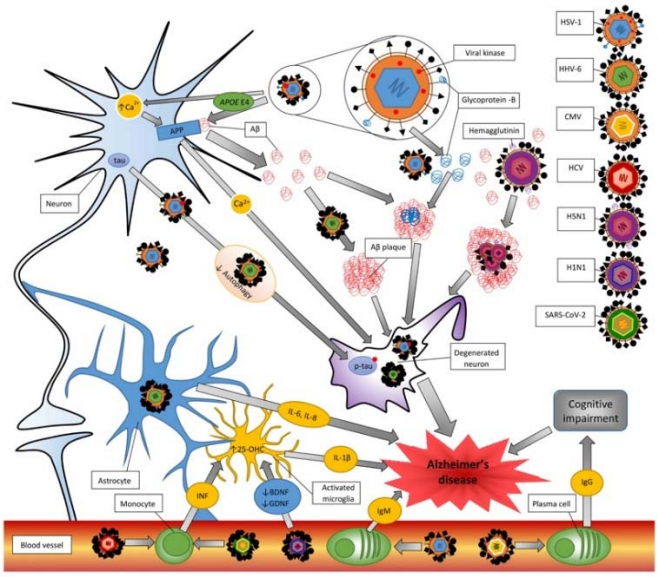


Image: Piekut et al. Fig. 1. The pathomechanism of virus-associated neurodegeneration. Herpes simplex virus 1.

6. MITOCHONDRIAL DYSFUNCTION

Maintaining healthy mitochondria is essential for biological functions, including in the brain. Mitochondria have been implicated in the development of many age-related diseases, including Alzheimer's disease (AD). [19] Mitochondria are considered the powerhouses of our cells, producing the energy we need to live in the form of ATP. Due to lack of energy stores in the brain for fat and glucose, which typically fuel cells, the mitochondria must produce the energy needed. Dysfunction of mitochondria has an outsized impact on the brain due to the high energy requirements of the neurons and glia. [19]

One of the mechanisms by which mitochondrial function is affected is through the connection of inflammation and oxidative stress – two biological responses that go hand in hand. The mitochondria create oxidative stress as part of the normal process of ATP production. In the face of excess energy demand, including inflammation, the level of oxidative stress can exceed the normal antioxidant mechanisms and lead to damaged mitochondria.

Another consequence of inflammation and oxidative stress is the disruption of normal maintenance that includes the ability to destroy old or damaged mitochondria, as well as generate new ones. This process of mitochondrial autophagy and biogenesis has been found to be related to aging and the progression of Alzheimer's Disease. [16]

7. VASCULAR DISEASE

Alzheimer's disease is associated with cardiovascular and cerebrovascular disease, associated with beta amyloid plaques and neurofibrillary tau tangles in up to 70% of people with Alzheimer's disease. [10] When blood vessels become diseased, blood flow to the brain is restricted, causing neuronal cell death. This leads to a circular cascade of inflammation and oxidative stress, and further damage to neurons in the brain.

Many diseases are associated with increased cardiovascular risk, including obesity, hypertension, hypercholesterolemia, diabetes, and metabolic syndrome. Each of these is also associated with inflammation and oxidative stress as well as mitochondrial dysfunction. It is likely a combination of the various factors, in addition to vascular dysfunction, that connect them with Alzheimer's disease risk.

MODIFIABLE RISK FACTORS

With all of these significant contributors to Alzheimer's disease, it's important to remember that we have some control over many risk factors - and they are thus potentially modifiable. The brain is an incredibly complex organ, and we need to reframe our reductionist thinking to approach the brain as an evolving, complex network that adapts to biological, social, and environmental influences to create a better approach to diseases such as Alzheimer's disease.

It is estimated that 40% of AD is related to modifiable risk factors [3], including:

- insulin resistance
- glucose dysregulation
- hypertension
- dyslipidemia
- obesity
- physical inactivity
- hearing loss
- smoking

- alcohol
- traumatic brain injury
- low levels of socialization and cognitive stimulation
- air pollution

These are all potential areas where we can improve both prevention and treatment and understand the protective mechanisms that may explain why some people don't get Alzheimer's disease despite multiple risk factors – including genetics.

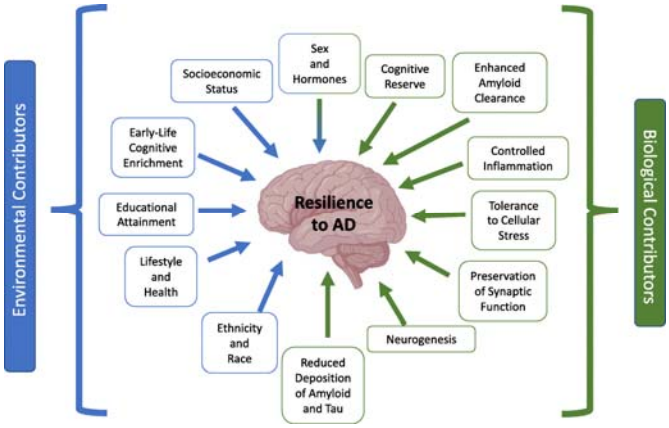


Image: Nday, CM et al Understanding the biological and neurological mechanisms behind resilience.

EARLY DETECTION

Currently, there is no treatment to effectively cure Alzheimer's, and the more the disease has progressed, the more difficult it is to slow progression or even reverse course.

Early detection is a crucial component to reducing morbidity and mortality from many diseases, and this needs to be extended to Alzheimer's Disease. It is evident that metabolic and brain changes can start 20 years or more before symptoms appear. New blood tests are emerging that may help us identify people with very early changes in brain biology – long before symptoms appear. [19] Having this information early may help to develop strategies to slow or even reverse them before a person ever develops symptoms of Alzheimer's Disease.

Diabetes, high cholesterol, and high blood pressure are some of the most common diseases that predispose to Alzheimer's Disease [19], and these also have altered metabolic and cellular changes that can be seen years or even decades before diagnosis. Here, too, early detection enables addressing these earlier in the disease process and can contribute to improving our approach to Alzheimer's Disease as well. [20] While conventional medicine does not effectively address the root causes of these diseases, Personalized Genomic & Functional Medicine has been shown to do just that – especially if addressed early.

In Part 2 of this series, we'll look at ways in which we already have many of the tools we need to make a difference in the treatment and potential prevention of Alzheimer's disease today. ■

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