Review Article

Neurodegeneration as Convergent Three-Pathway Failure: A Unified Framework for Alzheimer's & Related Dementias

Caroline C. Rodgers[1]

1. Independent researcher

Alzheimer's and related dementias are not inevitable consequences of aging. This manuscript proposes that they arise when cumulative stress exceeds the repair capacity of three biological systems critical for maintaining brain health: proteostatic capacity, mitochondrial function, and neuroimmune regulation. Key influences such as genetics, environmental exposures, and health history do not act as determinants; they modify the baseline load borne by these pathways, influencing not only whether it is approaching a threshold, but how quickly it reaches the tipping point. To illustrate how diverse influences accumulate, the analysis maps 18 modifiable lifestyle factors onto the three convergent pathways. This approach reframes neurodegenerative risk as a dynamic, cumulative process and highlights opportunities for individualized assessment and targeted mitigation strategies long before symptoms emerge.

Corresponding author: Caroline C. Rodgers, caroline.rodgers@rocketmail.com

Introduction

Alzheimer's disease is defined biologically by the presence of amyloid-beta plaques and pathologic tau deposits, as detected by biomarkers or confirmed at autopsy. The clinical syndrome most commonly associated with Alzheimer's disease typically begins with early memory impairment and progresses to affect language, spatial navigation, executive function, and daily living, although presentations can vary. Historically, because these symptoms often unfold in a predictable sequence, Alzheimer's disease has been treated as a single, unified disorder [1]. Lewy body dementia, a synucleinopathy that often overlaps with Parkinson's disease, is marked by fluctuating cognition, visual hallucinations, REM sleep behavior

 doi.org/10.32388/MRLNYS.3

disorder, and parkinsonism — a less orderly and more variable constellation of symptoms [2]. Frontotemporal dementia (FTD) presents in several distinct variants — behavioral, language, and motor — reflecting the selective vulnerability of different frontal and temporal networks [3]. This variability has long made FTD particularly challenging to understand and difficult to unify under a single mechanism. Vascular insufficiency frequently co-occurs with all of these conditions and can accelerate or shape disease progression [4].

Despite these differences, Alzheimer's disease and the related dementias may represent distinct manifestations of a convergence of stress across three interdependent systems that maintain brain health: proteostatic capacity, mitochondrial function, and neuroimmune regulation. Although all three pathways ultimately lose resilience in progressive disease, different disorders show different points of initial vulnerability. In Alzheimer's disease and related proteinopathies, proteostatic dysfunction often appears among the earliest detectable abnormalities [3][5][6]. Each system can absorb isolated insults, but chronic or repeated stress gradually erodes repair capacity, making the pathways increasingly vulnerable to failing together. In this framework, progressive neurodegeneration emerges only when all three pathways are compromised, explaining why individuals with similar exposures may experience different outcomes and why substantial neuropathology can exist without significant impairment.

The rising global prevalence of Alzheimer's disease suggests that modern exposures and habits may be imposing chronic, cumulative stress on these systems [7]. Large international studies have identified numerous modifiable lifestyle factors, reinforcing that dementia is not an inevitable consequence of aging. However, the diversity of identified risks — spanning vascular, metabolic, inflammatory, behavioral, and psychosocial domains — makes it difficult to design coherent strategies. Understanding neurodegeneration as the cumulative load on three interconnected pathways provides a unifying explanation for why such varied risk factors can produce similar clinical outcomes, and why no single biomarker or insult fully accounts for disease onset or progression. It also raises the possibility that identifying and treating the pathway under the greatest stress — rather than addressing symptoms alone — may offer a more effective approach to pausing or slowing disease progression.

Differences in pathway load and resilience are evident in populations at the extremes of lifelong protection and risk. Some members of the School Sisters of Notre Dame show unusually low rates of cognitive decline despite Alzheimer's-type neuropathology [8], reflecting a lifetime of stable routines and the absence of behaviors or exposures that would undermine these critical systems. In contrast, individuals with Down syndrome experience early and accelerated vulnerability due to trisomy 21, which

increases APP expression, metabolic strain, and chronic immune dysregulation — stressing all three systems and producing Alzheimer's neuropathology years earlier than in the general population [9]. These two populations demonstrate how lifelong variation in systems load shapes cognitive outcomes.

This paper argues that diverse modifiable lifestyle factors can be understood by their cumulative impact on three interconnected pathways.

Critical Pathways for Brain Health

The three major systems that sustain neurological function are:

1. **Proteostasis:** This system maintains healthy proteins by refolding those that are misfolded, tagging irreparable proteins for degradation, and clearing damaged or aggregated proteins through the ubiquitin–proteasome and autophagy–lysosomal systems. When refolding, degradation, or lysosomal clearance become overwhelmed, misfolded proteins accumulate — a process central to the pathophysiology of Alzheimer's disease (Aβ and tau), Lewy body dementia (α-synuclein), and frontotemporal dementia (tau or TDP-43). Across these disorders, proteostatic strain appears early in the disease process and contributes to downstream mitochondrial and neuroimmune dysfunction [10].
2. **Mitochondrial capacity:** Synaptic signaling is energy-intensive, which is why the brain — roughly two percent of body weight — consumes about 20 percent of the body's energy. Mitochondria supply this energy while also regulating calcium buffering, redox balance, and the initiation of repair processes. When mitochondrial output is chronically constrained — through impaired oxidative phosphorylation, reduced biogenesis, or increased reactive oxygen species (ROS) — neuronal resilience declines and vulnerability to downstream dysfunction increases. In Alzheimer's disease, mitochondrial efficiency is reduced early through Aβ-related membrane disruption and tau-related transport deficits; in Lewy body dementia, α-synuclein interferes with complex I and mitochondrial membrane integrity; and in frontotemporal dementia, TDP-43 and tau pathology disrupt mitochondrial dynamics and axonal transport. Across these conditions, mitochondrial impairment is not the sole initiating event, but a consistent and amplifying feature that lowers the threshold at which other system failures lead to progressive neurodegeneration [11].
3. **Neuroimmune regulation:** The brain's support cells — particularly microglia and astrocytes — coordinate immune surveillance and tissue repair. When chronically overtaxed as is found in

Alzheimer's, they can shift into a pro-inflammatory state, leading to immune dysregulation and disruption of the blood–brain barrier [12]. Similar patterns of chronic microglial activation and impaired immune resolution are implicated across neurodegenerative diseases, including Lewy body dementia and FTD.

Neurodegeneration emerges when these three pathways all experience sustained stress. The outcome depends less on any single insult than on the brain's ability to repair, compensate, and adapt over time. When resilience erodes across all three systems, they cross a threshold beyond which decline becomes progressive. The failure to identify a single cause for most neurodegenerative diseases — despite decades of effort — reflects this underlying architecture. These conditions arise not from one initiating insult but from the convergence of all three compromised pathways, with outcomes shaped by each individual's capacity to buffer stress over time.

Genetics do not equal destiny

There is little direct evidence that inheritance is a key factor in most cases of Alzheimer's disease and related dementias, apart from FTD, which is why most are designated sporadic. Even when genetic predispositions are present, the common or rare variants or loci involved do not introduce new disease mechanisms; instead, they weaken one or more of the same biological pathways that maintain brain health [13]. Some of the most commonly known genetic variants reveal the mechanisms at work:

Alzheimer's disease: Alzheimer's disease offers the clearest example of how genetic risk maps onto the three-pathway framework, with both common variants (APOE ε4) and rare familial mutations (APP, PSEN1, PSEN2) converging on lipid handling, proteostasis, and inflammatory regulation. Conversely, the rarer APOE ε2 variant is protective, improving lipid handling and dampening baseline neuroimmune activation [14] — further illustrating how genetic differences shift vulnerability by modulating the same three systems.

Lewy Body Dementia: Although most cases are sporadic, several genetic variants increase susceptibility by altering α-synuclein handling, mitochondrial stability, or lysosomal clearance. Mutations in *SNCA* (α-synuclein) can increase the tendency of the protein to misfold and aggregate, directly stressing proteostatic systems. Variants that impair lysosomal enzyme function, reduce the cell's ability to clear misfolded proteins and heighten neuroimmune activation. These mechanisms converge on the same pathways implicated in Parkinson's disease, but with a cortical-first pattern of vulnerability [6].

FTD: A larger proportion of FTD cases have identifiable genetic contributors, most commonly mutations in *MAPT*, *GRN*, or expansions in *C9orf72*. Each of these affects a different arm of the three-system framework: *MAPT* mutations disrupt microtubule stability and increase proteostatic burden; *GRN* haploinsufficiency impairs lysosomal function and heightens neuroimmune reactivity; and *C9orf72* expansions generate toxic RNA and dipeptide repeats that strain mitochondrial and proteostatic capacity simultaneously [15]. By weakening these pathways from the start, these mutations reduce resilience long before aging-related erosion occurs, resulting in earlier onset. Because these systems support distinct but interdependent frontotemporal networks, each clinical variant reflects the particular network under greatest strain — yet all impair insight early, as integrative hubs lose connective capacity first.

Together, these genetic examples illustrate that inherited risks do not create new disease pathways — they simply reduce the resilience of the existing ones, lowering the threshold at which lifelong stressors can tip the system into failure. Seen this way, genetics helps explain why people respond differently to similar exposures or age-related changes: some individuals begin life with less resilient protective systems, leaving them more vulnerable as stressors accumulate across decades. Genetic risk, then, does not contradict a convergence model of neurodegeneration — it reinforces it, showing how pathways that are weakened from the start can push the brain past a threshold from system compensation to progressive disease.

Vascular Insufficiency as an Upstream Systems Stressor

Vascular dysfunction provides one of the clearest bridges between lifestyle risk factors and neurodegeneration because even mild impairments in cerebral blood flow directly stress all three pathways required for brain maintenance. Impaired perivascular and glymphatic clearance slows the removal of misfolded proteins and metabolic waste, increasing proteostatic burden from the outset. Chronic hypoperfusion limits mitochondrial energy availability, reducing the metabolic reserve needed for synaptic upkeep. Disruption of the blood–brain barrier (BBB) exposes neural tissue to circulating inflammatory mediators and primes microglia toward a heightened immune tone, reducing their capacity for normal synaptic and neuronal support [16]. Together, these vascular changes act as upstream amplifiers that push vulnerable systems toward failure, regardless of the specific neurodegenerative diagnosis.

Mechanistic Mapping of Health & Lifestyle Factors to the Three Pathways

The 2024 Lancet Commission on dementia prevention, intervention, and care identified 14 modifiable dementia risk factors, representing an extraordinary synthesis of epidemiological evidence and making clear how many aspects of daily life influence long-term brain health [7]. In the following analysis, these 14 factors are presented first. The subsequent four factors — healthy diet, sleep quality, cognitive engagement, and chronic stress — were discussed in the 2024 report as emerging or promising contributors but were not elevated to the formal list of modifiable risk factors due to insufficient epidemiologic evidence. Each of the four, however, is supported by mechanistic or epidemiologic findings linking it to dementia risk, as highlighted in a 2025 international consensus statement on nutrition, metabolic health, and brain aging [17]. Please note that the factors are not weighted, and their order does not imply relative impact.

1) PHYSICAL ACTIVITY

Supports:

- *Proteostasis*: enhances autophagy and lysosomal clearance, preventing backlog of damaged proteins.
- *Mitochondria*: increases biogenesis and ATP (adenosine triphosphate) availability, expanding energetic reserve and reducing ROS load.
- *Neuroimmune*: reduces inflammatory tone, allowing microglia to shift to balanced surveillance states.

When absent:

- *Proteostasis*: impaired clearance of damaged proteins, increasing proteostatic strain.
- *Mitochondria*: allows dysfunctional mitochondria to persist, reducing available energy.
- *Neuroimmune*: inactivity causes immune cells to drift toward pro-inflammatory states.

2) SMOKING

Supports (when stopped):

- *Proteostasis*: lower toxin-induced misfolding and reduced burden on repair and clearance pathways.
- *Mitochondria*: reduced oxidative injury allows more efficient ATP production and less ROS spillover.
- *Neuroimmune*: decreased toxin exposure reduces chronic immune priming.

When ongoing:

- *Proteostasis*: toxin exposure drives misfolding, overwhelms repair systems, and increases proteostatic strain.
- *Mitochondria*: chronic oxidative stress damages mitochondrial membranes and impairs energy production.
- *Neuroimmune*: persistent endothelial and tissue injury heightens inflammation.

3) HARMFUL ALCOHOL USE

Supports (when treated):

- *Proteostasis*: less ER stress and reduced accumulation of misfolded or damaged proteins.
- *Mitochondria*: lower toxic metabolite load allows more stable ATP production and less oxidative strain.
- *Neuroimmune*: reduced glial signaling and lower baseline inflammatory signaling.

When untreated:

- *Proteostasis*: impaired clearance and increased burden of damaged or misfolded proteins.
- *Mitochondria*: direct toxicity disrupts membranes, increases ROS, and impairs energy production.
- *Neuroimmune*: heightened glial activation and sustained inflammatory tone.

4) OBESITY

Supports (when reduced):

- *Proteostasis*: reduced ER stress improves folding capacity and lowers baseline clearance burden.
- *Mitochondria*: lower metabolic overload decreases substrate pressure and reduces ROS generation.
- *Neuroimmune*: less adipose-driven cytokine release reduces systemic and central inflammatory tone.

When present:

- *Proteostasis*: ER stress and misfolding increaseas metabolic load rises.
- *Mitochondria*: excess substrate supply strains mitochondrial function and elevates oxidative stress.
- *Neuroimmune*: adipose-derived inflammatory signals drive persistent systemic inflammation.

5) HYPERTENSION

Supports (when controlled):

- *Proteostasis*: controlled blood pressure maintains steady perfusion, reducing ischemic stress.

- *Mitochondria*: protects microvasculature, stabilizing oxygen supply and preserving ATP production.
- *Neuroimmune*: stable pressure prevents BBB leakage and downstream immune activation.

When uncontrolled:

- *Proteostasis*: ischemic injury due to elevated pressure, damaging microvessels.
- *Mitochondria*: disrupted oxygen delivery increases ROS, impairing ATP production.
- *Neuroimmune*: endothelial injury triggers chronic vascular inflammation.

6) DIABETES (Including insulin resistance/impaired glucose metabolism)

Supports (when controlled):

- *Proteostasis*: stable glucose levels limit glycation stress, supporting proper folding and clearance.
- *Mitochondria*: controlled insulin signaling allows efficient fuel use, sustaining ATP production.
- *Neuroimmune*: balanced metabolic signaling reduces inflammation.

When uncontrolled:

- *Proteostasis*: increased glycation, misfolding and strained clearance pathways.
- *Mitochondria*: excess glucose impairs function, increasing oxidative stress and reducing energy.
- *Neuroimmune*: metabolic dysregulation induces chronic inflammation.

7) EDUCATION LEVEL

Supports (when high):

- *Proteostasis*: enriched synaptic remodeling may support proteostatic health by increasing opportunities for clearance and reducing aggregation risk.
- *Mitochondria*: lifelong cognitive load is associated with energetic resilience, potentially improving ATP efficiency and metabolic flexibility.
- *Neuroimmune*: sustained cognitive engagement is linked to lower allostatic load, which may buffer against stress-induced immune activation.

When low:

- *Proteostasis*: reduced remodeling, with fewer opportunities to clear damaged proteins, greater risk of accumulation.
- *Mitochondria*: lower reserve, decreasing metabolic “cushion” during systemic strain or aging stressors.

- *Neuroimmune*: lower cognitive engagement increases vulnerability to stressors.

8) SOCIAL ENGAGEMENT

Supports:

- *Proteostasis*: social engagement is associated with healthier synaptic turnover and may help maintain adaptive remodeling.
- *Mitochondria*: ongoing social interaction is linked to sustained synaptic activity and energetic demand, which may help keep complex neural circuits resilient.
- *Neuroimmune*: reduces stress-related inflammation and lowers baseline inflammatory tone.

When absent:

- *Proteostasis*: reduced synaptic remodeling and lower turnover.
- *Mitochondria*: reduced synaptic activity and diminished energetic engagement.
- *Neuroimmune*: social isolation is strongly linked to heightened stress signaling and increased inflammatory activation.

9) DEPRESSION

Supports (when treated):

- *Proteostasis*: treatment improves sleep quality, supporting glymphatic clearance of misfolded proteins.
- *Mitochondria*: lowers cortisol, improving energy metabolism and ATP efficiency.
- *Neuroimmune*: reduced inflammatory tone, stabilizing microglial activity.

When untreated:

- *Proteostasis*: impaired repair, leading to protein aggregation.
- *Mitochondria*: cortisol-driven exposure impairs mitochondrial efficiency.
- *Neuroimmune*: immune activation, with heightened inflammatory signaling.

10) AIR POLLUTION (including second-hand smoke)

Supports (when reduced):

- *Proteostasis*: reduced protein oxidation and misfolding, lowering aggregation risk.
- *Mitochondria*: less oxidative stress from particulate exposure, preserving ATP production.

- *Neuroimmune*: lower systemic and central nervous system (CNS) inflammation, helping preserve BBB integrity.

When high:

- *Proteostasis*: protein oxidation leads to misfolding and aggregation, overwhelming clearance systems.
- *Mitochondria*: particulate-induced oxidative injury, reducing energy production and mitochondrial resistance.
- *Neuroimmune*: chronic inflammatory activation, disrupting the BBB, increasing vulnerability to neurotoxic exposures.

11,12) SENSORY IMPAIRMENT (hearing and/or vision loss)

Supports (when corrected):

- *Proteostasis*: reduced chronic compensatory synaptic stress from degraded sensory input, reducing misfolding pressure.
- *Mitochondria*: reduced compensatory cortical energy demand, preserving metabolic reserve.
- *Neuroimmune*: reduced isolation-driven inflammation and stress-related microglial activation, stabilizing immune tone.

When uncorrected:

- *Proteostasis*: sustained strain leads to misfolding, impaired turnover and aggregation.
- *Mitochondria*: increased energetic load from compensatory processing, driving inefficiency and oxidative stress.
- *Neuroimmune*: social withdrawal and chronic stress sustain inflammatory activation, eroding resilience.

13) CHOLESTEROL (dyslipidemia/high LDL)

Supports:

- *Proteostasis*: balanced lipid transport supports membrane integrity and synaptic vesicle dynamics, reducing misfolding pressure on protein-handling systems.
- *Mitochondria*: healthy lipid profiles maintain mitochondrial membrane composition and reduce oxidized-lipid–driven energetic stress.

- *Neuroimmune*: stable lipid metabolism limits endothelial inflammation and helps preserve blood–brain barrier function, keeping microglial activation low and regulated.

When poor:

- *Proteostasis*: oxidized LDL and disrupted lipid transport (including ApoE-related pathways) impair membrane stability and increase proteostatic burden.
- *Mitochondria*: excess or oxidized lipids damage mitochondrial membranes, reduce ATP efficiency, and increase ROS production.
- *Neuroimmune*: dyslipidemia promotes endothelial inflammation, microvascular injury, and BBB permeability, sustaining chronic neuroimmune activation.

14) TRAUMATIC BRAIN INJURY (TBI)

Supports (when preventable or mitigated):

- *Proteostasis*: prevents tau hyperphosphorylation and misfolding cascades, maintaining clearance capacity.
- *Mitochondria*: avoids acute energetic collapse and chronic fragmentation, preserving ATP production.
- *Neuroimmune*: avoids microglial priming and chronic neuroinflammation, stabilizing immune tone.

When present:

- *Proteostasis*: tauopathy-like misfolding, impaired clearance, and aggregation.
- *Mitochondria*: acute dysfunction and oxidative stress, contributing to long-term instability.
- *Neuroimmune*: chronic microglial activation, sustaining persistent inflammatory signaling and BBB disruption.

15) HEALTHY DIET

Supports:

- *Proteostasis*: lowers misfolded-protein burden via reduced glycation (sugar-induced protein damage) and oxidative injury, both of which promote misfolding and overwhelm clearance systems.
- *Mitochondria*: stabilizes glucose supply, reduces oxidative load, improves cellular energy efficiency.
- *Neuroimmune*: reduces chronic inflammation through polyphenols and omega-3 fatty acids, supporting microglial stability and lowering baseline immune activation.

When poor:

- *Proteostasis*: increased glycation and impaired clearance, driving protein aggregation.
- *Mitochondria*: increased ROS, damaging membranes and impairing energy production.
- *Neuroimmune*: chronic low-grade inflammation, destabilizing baseline immune tone.

16) SLEEP QUALITY

Supports:

- *Proteostasis*: glymphatic clearance of misfolded proteins and nightly reduction of proteostatic load.
- *Mitochondria*: nightly repair, redox restoration, and metabolic reset.
- *Neuroimmune*: circadian regulation of immune tone and microglial activity.

When poor:

- *Proteostasis*: backlog of misfolded proteins and reduced clearance capacity.
- *Mitochondria*: impaired repair and disrupted metabolic recovery.
- *Neuroimmune*: circadian disruption elevates inflammatory signaling.

17) COGNITIVE ENGAGEMENT

Supports:

- *Proteostasis*: promotes synaptic remodeling – constant turnover stimulates clearance machinery, reducing misfolded protein accumulation.
- *Mitochondria*: sustained energetic demand builds resilience – frequent firing trains mitochondria for efficient ATP production and metabolic flexibility.
- *Neuroimmune*: reduces stress-related activation by lowering allostatic load, dampening cortisol and microglial priming.

When low:

- *Proteostasis*: impaired synaptic turnover, providing fewer opportunities to clear damaged proteins.
- *Mitochondria*: reduced reserve, as lowered demand signals lead to smaller, less efficient mitochondrial populations.
- *Neuroimmune*: vulnerability to stress, as reduced cognitive buffering increases susceptibility to inflammatory activation.

18) CHRONIC STRESS

Supports (when mitigated):

- *Proteostasis*: improved repair, facilitating clearance of misfolded proteins through enhanced autophagy and glymphatic flow.
- *Mitochondria*: reduced cortisol load, aiding energy production by lowering oxidative strain and preserving ATP efficiency.
- *Neuroimmune*: reduced microglial priming, stabilizing immune tone, preventing exaggerated inflammatory responses.

When persistent:

- *Proteostasis*: impaired repair, leading to protein aggregation and reduced clearance capacity.
- *Mitochondria*: dysfunction caused by oxidative damage, impairing ATP production and metabolic resilience.
- *Neuroimmune*: microglial priming leading to chronic inflammation, causing a chronically harmful state that maintains inflammatory signaling beyond adaptive needs.

These 18 factors suggest that a structured, clinically usable checklist could help quantify an individual's cumulative risk by mapping each factor onto the three convergent systems. Such a tool could help clinicians identify which pathways are most affected and why. Embedding targeted recommendations into the checklist would make the process actionable, transforming a broad set of lifestyle and medical variables into a coherent, system-level risk profile. Consistent with the Lancet Commission's emphasis that it is never too early or too late to modify these risk factors, this approach creates opportunities for proactive changes that could slow or even prevent cognitive decline [7].

How Environmental Exposures & Infections Fit the Convergence Model

It has long been known that many environmental and physiological stressors erode the same three pathways that sustain brain health. Chronic exposure to pollutants, heavy metals, and other toxins increases oxidative load, impairs mitochondrial efficiency, and disrupts proteostatic and immune regulation. Recurrent or untreated infections similarly impose repeated neuroimmune activation [18], whereas vaccines targeting shingles and respiratory syncytial virus (RSV) have been found to reduce dementia risk [19]. Chronic infections such as herpesviruses [20] or periodontal disease [21] can maintain a

low-grade activated immune state, incrementally taxing all three systems and gradually diminishing the repair capacity that keeps them stable.

Taken together, genetic predispositions, environmental exposures, and lifestyle-linked physiological stressors do not represent competing explanations for neurodegenerative disease. They are overlapping contributors to the same cumulative system load. Genetic variants determine baseline resilience, environmental exposures add intermittent or chronic demands on those systems, while health history and everyday behaviors — sleep, substance use, diet and physical activity — shape how effectively these systems recover between stressors. Because these influences accumulate slowly, the total burden placed on these systems over decades explains why neurodegeneration typically emerges later in life.

Mapping Related Dementias and Mixed Pathology

Understanding Alzheimer's disease within a three-system framework also clarifies why related dementias share overlapping features and why mixed pathology is so common in late life. Lewy body dementia, Parkinson's disease dementia, frontotemporal dementia, and vascular contributions each stress the same three systems, but in different sequences and with different dominant pressures. Variations in timing and degree produce distinct clinical presentations, yet the underlying vulnerabilities are shared.

Mixed dementia pathology, often treated as a diagnostic complication, is better understood as the predictable outcome of cumulative system erosion. When proteostasis, mitochondrial strain, impaired and chronic immune activation progress at different rates across brain regions, multiple pathological signatures can emerge simultaneously. Rather than representing separate diseases, these patterns reflect the brain's attempt to compensate as multiple protective systems weaken together. This perspective explains why neuropathological boundaries blur in older adults and why clinical symptoms often reflect contributions from more than one system.

Discussion

This manuscript reframes neurodegeneration as the cumulative failure of three maintenance systems — proteostatic capacity, mitochondrial function, and neuroimmune regulation — and situates a wide range of environmental, physiological, and behavioral stressors within this convergence framework. Although Alzheimer's and related dementias are not natural consequences of aging, lifetime habits and exposures, combined with a gradually declining repair capacity, can progressively weaken these systems. Within this

model, diverse influences on dementia risk can be understood as modifiers of system load, shaping how quickly or slowly these systems erode over the lifespan.

Alzheimer's disease now has the most sophisticated biomarker ecosystem in all of neurodegeneration — plasma assays, CSF signatures, PET tracers, and staging frameworks that are the envy of every adjacent field. Yet this success has revealed a structural limitation: these biomarkers track downstream artifacts of systems already under strain. They illuminate proteostatic overload, metabolic collapse, and neuroimmune drift with remarkable clarity, but they do not identify the upstream failure that made these cascades possible. As a result, even perfect detection of amyloid, tau, or other neurodegenerative signatures cannot yield a pharmaceutical "silver bullet" because no downstream therapy can substitute for repairing the mitochondrial, proteostatic, and neuroimmune systems whose erosion set the stage for pathology in the first place.

All of the stressors associated with dementia identified by the Lancet Commission exert their effects by impairing waste clearance, increasing energetic demand, or sustaining low-grade immune activation. However, the system stresses do not act in isolation — they may also interact. For example, sleep disruption becomes far more metabolically costly when it occurs against a backdrop of circadian misalignment, because the brain must maintain basic function while its time-sensitive repair programs are weakened. Aging amplifies the impact of all such stressors by narrowing the brain's remaining compensatory capacity.

Emerging clinical observations also fit this framework. Early data from cohorts of individuals with type 2 diabetes suggest that GLP-1 receptor agonists may reduce dementia risk by improving metabolic efficiency, lowering inflammatory tone, and possibly enhancing proteostatic clearance — three mechanisms that map directly onto the system pathways described here [22][23]. Although these findings remain preliminary, they illustrate how addressing a single high-impact risk factor can relieve stress across all three systems.

The decades-long nun study provides a compelling illustration of how strong compensatory systems can preserve cognitive function even in the presence of substantial neuropathology. Participants who remained cognitively healthy into advanced age often showed extensive amyloid plaques and neurofibrillary tangles at autopsy — levels typically associated with dementia. Their resilience has been attributed to factors such as cognitive reserve and stable routines. Yet equally important, their lives lacked many of the stressors that erode pathway resilience. In this light, the disconnect between neuropathology and cognitive outcomes is not paradoxical but predictable: when proteostatic,

mitochondrial, and neuroimmune systems remain stable, the brain can tolerate substantial pathological burden.

Down syndrome illustrates the opposite extreme. Triplication of chromosome 21 increases amyloid precursor protein expression, placing a constant burden on protein management and waste-clearance systems. Overexpression of genes involved in oxidative stress contributes to chronic mitochondrial strain, while neuroimmune regulation is altered from early life. Each of these factors alone might be manageable, but together they impose continuous stress across all three systems, leading to the near-universal early development of Alzheimer-type pathology. Down syndrome thus reinforces the central premise of this framework: neurodegeneration emerges not from a single cause, but from the convergence of multiple impaired systems.

Between these extremes lies the general population, where individuals differ widely in their baseline resilience and in the cumulative stress experienced over a lifetime. Early-life health, metabolic status, sleep quality, environmental exposures, infections, and lifestyle patterns — many of which have shifted dramatically in recent decades — all influence the compensatory capacity a person begins with and how quickly it erodes. Advancing age increases the likelihood that cumulative stress and declining repair capacity will intersect, not because age causes neurodegeneration, but because compensatory systems become harder to maintain.

Within this broader landscape, several nuances within the risk-factor literature are important for interpretation. The 2020 Lancet Commission found that the protective effect of education is concentrated in the years up to age 20, underscoring the critical importance of early education [24]. In contrast, the 2024 Lancet standing Commission reported that midlife cognitive stimulation from work or hobbies confers protection even in individuals with low formal education. The latest Lancet report found even stronger evidence that depression is strongly associated with dementia risk — although in some individuals it may be a prodromal symptom rather than an upstream causal factor. Whichever the case, it should always be treated. Excessive alcohol use in midlife, although strongly associated with dementia risk [7], is notably the only modifiable risk factor linked to early-onset dementia (prior to age 65) that does not have a genetic basis [24].

Genetic variation further shapes baseline system load by influencing proteostatic capacity, mitochondrial efficiency, and neuroimmune responsiveness from early life. Some individuals inherit variants that confer above-average resilience, while others begin life with reduced reserve in one or more systems. These inherited differences do not determine outcomes, but they influence how much compensatory

capacity a person starts with and how quickly it may erode under cumulative stress. In this framework, genetics functions as part of the initial conditions that interact with lifelong habits, exposures, and repair capacity.

Although longitudinal measures of cumulative system load remain limited, this framework provides a coherent structure for interpreting existing findings and identifying priorities for future research. It suggests that everyday clinical decisions may influence neurodegenerative vulnerability by altering cumulative stress on these systems. It also highlights the value of strengthening primary care capacity for routine screening of sleep disorders, sensory impairment, cardiometabolic and other modifiable risk factors in older adults, supported by clear referral pathways when indicated. Ongoing management of conditions such as obesity, hypertension and diabetes may be particularly important, given their well-established roles in accelerating vascular dysfunction, metabolic strain, and inflammatory activation.

Conclusion

This framework proposes that neurodegenerative diseases arise when the three core systems that sustain brain health can no longer compensate for cumulative stress. It raises the possibility that neurodegenerative risk could one day be estimated — and mitigated — by assessing the status of these systems on an individual basis and developing targeted interventions that restore resilience wherever possible. As tools for measuring proteostatic capacity, mitochondrial efficiency, and neuroimmune regulation continue to advance, a systems-level approach may allow pathway load to be quantified directly, creating opportunities for interventions that delay or prevent the emergence of dementia.

About the Author

Caroline C. Rodgers is an independent science theorist whose peer-reviewed work spans neurodegeneration, autism, and maternal and neonatal health. She explores the potential biological roots of public health issues that are incompletely explained by prevailing theories.

Statements and Declarations

Funding

The author received no external funding for this work.

Conflicts of Interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contribution

The author is solely responsible for the conception, development, and writing of this manuscript.

Acknowledgements

Bing Copilot was used as an editorial tool during manuscript preparation to check factual claims, refine phrasing, and locate supporting citations. The free version of ChatGPT was used for occasional manuscript reviews. Adobe Acrobat AI was employed to query documents and verify the precision of cited text.

References

1. ^*Jack CR Jr, Bennett DA, Blennow K, et al. (2018). "NIA-AA Research Framework: Toward a Biological Definition of Alzheimer's Disease." Alzheimers Dement. **14**(4):535–562. doi:10.1016/j.jalz.2018.02.018.*
2. ^*McKeith IG, Boeve BF, Dickson DW, et al. (2017). "Diagnosis and Management of Dementia with Lewy Bodies: Fourth Consensus Report of the DLB Consortium." Neurology. **89**(1):88–100. doi:10.1212/WNL.0000000000004058.*
3. a, b*Bang J, Spina S, Miller BL (2015). "Frontotemporal Dementia." Lancet. **386**(10004):1672–1682. doi:10.1016/S0140-6736(15)00461-4.*
4. ^*Jellinger KA (2013). "Pathology and Pathogenesis of Vascular Cognitive Impairment-A Critical Update." Front Aging Neurosci. **5**:17. doi:10.3389/fnagi.2013.00017.*
5. ^*De Strooper B, Karran E (2016). "The Cellular Phase of Alzheimer's Disease." Cell. **164**(4):603–615. doi:10.1016/j.cell.2015.12.056.*
6. a, b*Surguchov A (2022). "Synucleins: New Data on Misfolding, Aggregation and Role in Diseases." Biomedicines. **10**(12):3241. doi:10.3390/biomedicines10123241.*
7. a, b, c, d*Livingston G, Huntley J, Liu KY, et al. (2024). "Dementia Prevention, Intervention, and Care: 2024 Report of the Lancet Standing Commission." Lancet. **404**(10452):572–628. doi:10.1016/S0140-6736(24)01296-0.*

8. ^ Clarke KM, Etemadmoghadam S, Danner B, et al. (2025). "The Nun Study: Insights from 30 Years of Aging and Dementia Research." Alzheimers Dement. **21**:e14626. doi:10.1002/alz.14626.
9. ^ Garcia O, Dominguez de la Cruz E, Luna-Martínez IG, et al. (2025). "Development of Alzheimer's Disease i n Down Syndrome." Explor Neurosci. **4**:1006104. doi:10.37349/en.2025.1006104.
10. ^ Wilson DM 3rd, Cookson MR, Van Den Bosch L, et al. (2023). "Hallmarks of Neurodegenerative Diseases." C ell. **186**(4):693–714. doi:10.1016/j.cell.2022.12.032.
11. ^ Klemmensen MM, Borrowman SH, Pearce C, et al. (2024). "Mitochondrial Dysfunction in Neurodegenerati ve Disorders." Neurotherapeutics. **21**(1):e00292. doi:10.1016/j.neurot.2023.10.002.
12. ^ Heneka MT, Carson MJ, El Khoury J, et al. (2015). "Neuroinflammation in Alzheimer's Disease." Lancet Neu rol. **14**(4):388–405. doi:10.1016/S1474-4422(15)70016-5.
13. ^ Lambert JC, Ramirez A, Grenier-Boley B, Bellenguez C (2023). "Step by Step: Towards a Better Understandi ng of the Genetic Architecture of Alzheimer's Disease." Mol Psychiatry. **28**(7):2716–2727. doi:10.1038/s41380-023-02076-1.
14. ^ Holtzman DM, Morris JC, Goate AM (2011). "Alzheimer's Disease: The Challenge of the Second Century." Sc i Transl Med. **3**(77):77sr1. doi:10.1126/scitranslmed.3002369.
15. ^ Greaves CV, Rohrer JD (2019). "An Update on Genetic Frontotemporal Dementia." J Neurol. **266**(8):2075–20 86. doi:10.1007/s00415-019-09363-4.
16. ^ Iadecola C (2017). "The Neurovascular Unit Coming of Age: A Journey Through Neurovascular Coupling in Health and Disease." Neuron. **96**(1):17–42. doi:10.1016/j.neuron.2017.07.030.
17. ^ Johnstone AM, Albanese E, Crabtree DR, et al. (2025). "Consensus Statement on Exploring the Nexus Betw een Nutrition, Brain Health and Dementia Prevention." Nutr Metab (Lond). **22**(1):82. doi:10.1186/s12986-025-00981-6.
18. ^ Sipilä PN, Heikkilä N, Lindbohm JV, et al. (2021). "Hospital-Treated Infectious Diseases and the Risk of Dem entia: A Large, Multicohort, Observational Study with a Replication Cohort." Lancet Infect Dis. **21**(11):1557–1 567. doi:10.1016/S1473-3099(21)00144-4.
19. ^ Taquet M, Todd JA, Harrison PJ (2025). "Lower Risk of Dementia with AS01-Adjuvanted Vaccination Again st Shingles and Respiratory Syncytial Virus Infections." NPJ Vaccines. **10**(1):130. doi:10.1038/s41541-025-0117 2-3.
20. ^ Itzhaki RF (2014). "Herpes Simplex Virus Type 1 and Alzheimer's Disease: Increasing Evidence for a Major Role of the Virus." Front Aging Neurosci. **6**:202. doi:10.3389/fnagi.2014.00202.

21. ^Chen CK, Wu YT, Chang YC (2017). "Association Between Chronic Periodontitis and the Risk of Alzheimer's Disease: A Retrospective, Population-Based, Matched-Cohort Study." Alzheimers Res Ther. **9**(1):56. doi:10.1186/s13195-017-0282-6.

22. ^Kopp KO, Glotfelty EJ, Li Y, Greig NH (2022). "Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists and Neuroinflammation: Implications for Neurodegenerative Disease Treatment." Pharmacol Res. **186**:106550. doi:10.1016/j.phrs.2022.106550.

23. ^Nørgaard CH, Friedrich S, Hansen CT, et al. (2022). "Treatment with Glucagon-Like Peptide-1 Receptor Agonists and Incidence of Dementia: Data from Pooled Double-Blind Randomized Controlled Trials and Nationwide Disease and Prescription Registers." Alzheimers Dement (N Y). **8**(1):e12268. doi:10.1002/trc2.12268.

24. a, bLivingston G, Huntley J, Sommerlad A, et al. (2020). "Dementia Prevention, Intervention, and Care: 2020 Report of the Lancet Commission." Lancet. **396**(10248):413–446. doi:10.1016/S0140-6736(20)30367-6.

Declarations

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.