

Maladaptive aging trajectory in late-onset Alzheimer's disease

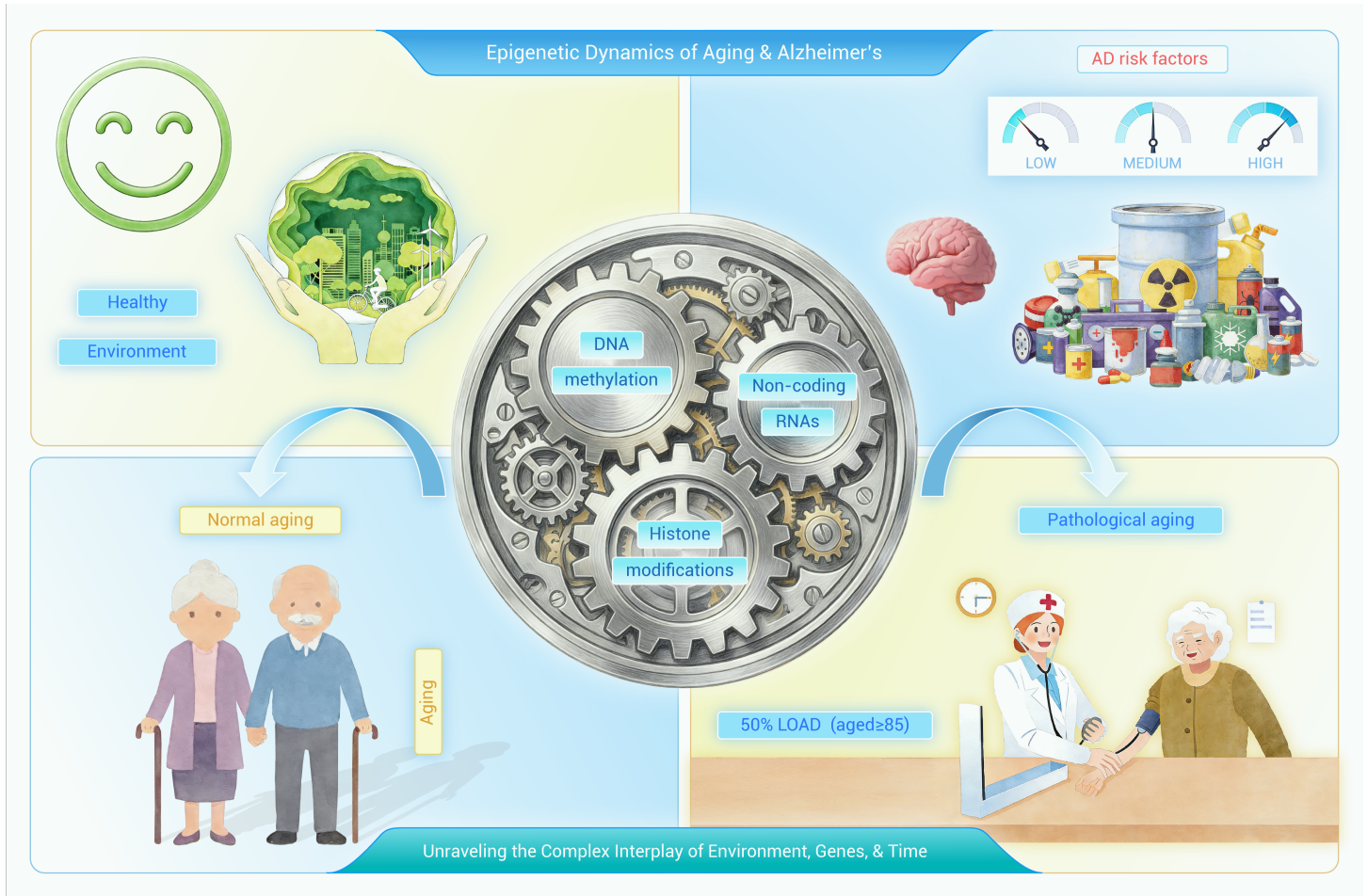
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Received: September 2, 2025; Accepted: February 11, 2026; Published Online: February 27, 2026; <https://doi.org/10.59717/j.xinn-life.2026.100206>

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GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- LOAD is fundamentally characterized as a pathological deviation from the trajectory of normal brain aging.
- LOAD is underpinned by integrated genetic, epigenetic, and environmental influences.
- Fostering healthy brain aging constitutes a central paradigm in the strategic shift toward preventing LOAD.

Maladaptive aging trajectory in late-onset Alzheimer's disease

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Received: September 2, 2025; Accepted: February 11, 2026; Published Online: February 27, 2026; <https://doi.org/10.59717/j.xinn-life.2026.100206>

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Citation: Lv T., Sun H., Xia T., et al. (2026). Maladaptive aging trajectory in late-onset Alzheimer's disease. *The Innovation Life* 4:100206.

Dementia constitutes a significant public health crisis, accounting for one-third of deaths among the elderly and exceeding the combined mortality of breast and prostate cancers. Alzheimer's disease (AD), the predominant form of dementia (60–70%), primarily manifests as late-onset AD (LOAD), which constitutes over 95% of all AD cases. The risk of developing LOAD escalates dramatically with age, affecting approximately half of individuals over 85 years of age, thus positioning LOAD as a critical age-related medical challenge. The present study proposes a novel conceptual framework for understanding LOAD, positing it not merely as a discrete disease but rather as a maladaptive trajectory of brain aging, in which physiological aging processes progressively evolve into pathological states. This transition is driven by synergistic interactions between genetic susceptibility, environmental exposures, and aging-related mechanisms, with epigenetic alterations serving as a central dynamic mediator. This analysis demonstrates that genetic factors, aging, and environmental influences collectively regulate LOAD susceptibility through a multidimensional interplay: while genes directly drive pathological pathways, their expression is dynamically modulated by age and environmental context via epigenetic mechanisms. Deciphering these complex interactions provides crucial insights into LOAD pathogenesis. This reconceptualisation necessitates a paradigm shift in therapeutic strategy. Rather than focusing exclusively on amyloid-centric approaches, we advocate targeting core aging mechanisms to enhance brain resilience. The most promising interventions aim to counteract maladaptive cognitive decline by improving proteostasis, modulating epigenetic drivers, and suppressing chronic neuroinflammation. This would reposition healthy brain aging as the cornerstone of LOAD prevention and treatment.

INTRODUCTION

Alzheimer's Disease (AD) is a growing global health crisis, currently affecting 40–50 million individuals. As the most prevalent neurodegenerative disorder and the sixth leading cause of mortality, its impact is profound and expanding. Estimates project that the number of people living with AD will rise to 131.5 million by 2050.^{1,2} The disease is pathologically characterized by progressive cognitive decline, neuronal loss, and the accumulation of amyloid plaques and neurofibrillary tangles.³ Clinically, it manifests as memory loss, speech impairments, behavioral and psychological symptoms of dementia (BPSD), and a terminal decline in executive function, often necessitating full-time care.⁴

The overwhelming majority of AD cases are LOAD, representing over 95% of all cases and primarily affecting individuals aged 65 and older.^{5–8} Its prevalence escalates dramatically with age, affecting an estimated 5–17% of people aged 65–74, 13.1–20% of those aged 75–84, and 33.3–50% of individuals aged 85 or older.^{9–14,289,290} This makes LOAD one of the most significant age-related diseases. In the face of a rapidly aging global population—where one in six people will be 60 or older by 2030—understanding and combating LOAD is an urgent public health priority.

For decades, the dominant paradigm in AD research and drug development has been the "amyloid hypothesis," which posits the accumulation of amyloid-beta as the central causative event. This focus is reflected in the current pharmacological arsenal, which consists largely of acetylcholinesterase inhibitors, NMDA receptor antagonists, and, more recently, therapies aimed at reducing amyloid beta aggregation.¹⁵ The FDA approval of anti-amyloid monoclonal antibodies like aducanumab, lecanemab, and donanemab represents the culmination of this approach.¹⁶ However, the clinical benefits of these agents have been modest at best. For instance, while

lecanemab demonstrably reduces amyloid plaques and shows a statistically significant slowing of cognitive decline, the clinical meaningfulness of this effect remains a subject of intense debate.¹⁷ As of 2025, over 3,300,000 studies on AD have been published, reflecting the vast and sustained research effort in this field, existing FDA-approved drugs offer only limited efficacy. The complex etiology of LOAD cannot be fully explained or effectively treated by targeting amyloid pathology alone.

The limitations of the amyloid-centric view necessitate a broader conceptual framework. The etiology of LOAD is now understood to arise from a complex interplay of three principal categories: genetics, aging, and environmental factors. While specific genetic variants influence risk, the expression of these genes is powerfully modulated by age and environmental exposures. This interplay suggests that LOAD is not merely a consequence of aging but rather a manifestation of maladaptive aging—a dysregulated epigenetic process accelerated by genetic risk and environmental stressors.

This "maladaptive aging" thesis posits that the molecular and cellular hallmarks of aging itself are the primary drivers of LOAD pathology. Therefore, a promising and potentially more effective avenue for future research and therapeutic development lies in combining anti-aging strategies with anti-LOAD interventions. Viewing LOAD through this lens acknowledges its complexity and demands a holistic approach. Each contributing factor—genetic, age-related, or environmental—represents a potential entry point for unraveling the pathogenesis of LOAD and for developing novel, multi-targeted therapeutic strategies aimed at promoting resilient brain aging.

THE RISKS OF LOAD

AD is a progressive neurological disorder, characterised by memory, cognitive, and behavioural impairments in older individuals. Typically manifesting in individuals aged 65 years and older, AD is characterised by the progressive loss of neurons in the cerebral cortex and hippocampus, abnormal accumulation of amyloid β -protein (A β), and the development of senile plaques. Moreover, hyperphosphorylation of tau proteins contributes to the formation of neurofibrillary tangles, resulting in impaired memory and cognitive decline. Tau proteins can aggregate and form neurofibrillary tangles, which progressively accumulate in the brain and are closely associated with the incidence and severity of AD. Additionally, dominant tau mutations result in elevated tau aggregation, neuroinflammation, and neurodegeneration. These abnormal tau conformations can recruit normal tau proteins, trigger the formation of additional misfolded tau proteins, and further enhance pathological fibrillar aggregation. The pathogenesis of AD is multifaceted, with recent research broadly categorizing it into three main factors: genetics, aging, and environmental influences. These factors interact and mutually influence each other, revealing risk factors associated with AD. Genes directly contribute to the development of AD; while aging and environmental factors influence gene expression levels.

Genetics of EOAD and LOAD

The well-defined genetic pathways of EOAD provide a foundational framework for deciphering the more complex and multifactorial regulatory mechanisms of LOAD. Genes play a significant role in the development of EOAD, with a heritability rate exceeding 90%.^{18,181–183} Researchers have discovered numerous genes associated with an increased risk of EOAD, including those illustrated in Figure 1.

(1) The amyloid precursor protein (APP) is cleaved by beta- and gamma-secretases to generate the A β , which is the principal component of the amyloid plaques found extracellularly in AD. Genetically, aside from familial AD mutations in genes such as APP, PSEN1, and PSEN2, individuals with

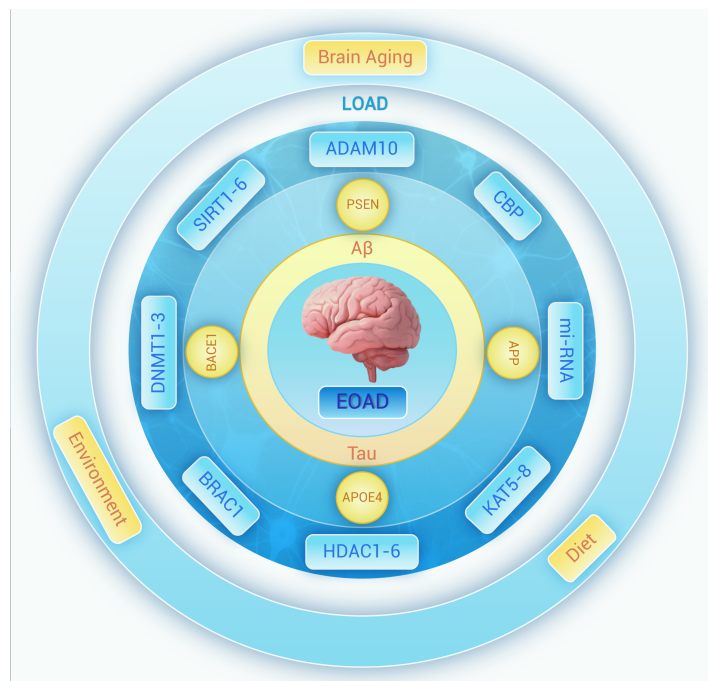


Figure 1. Direct and indirect links between AD and genes A β and tau protein tangles cause AD. APP, PSEN, BACE1 and ApoE4 are the highest AD risk genes. These are all linked to the production of A β . SIRT1-6, ADAM10 and CBP et al. have been identified as factors associated with the activity of the highest AD risk genes.

Down syndrome (Trisomy 21) provide compelling evidence for the central role of A β . These individuals possess an extra copy of chromosome 21, which harbors the APP gene, resulting in a lifelong gene dosage effect and overproduction of A β .¹⁸ This leads to an extremely high penetrance of AD pathology by middle age, underscoring the critical role of APP and A β homeostasis in disease initiation. It is important to note that significant A β plaque pathology can be found in the brains of cognitively normal older adults.¹⁸ This suggests that the mere presence of A β is insufficient to cause LOAD, and that factors such as the specific A β species (e.g., oligomers vs. plaques), the rate of accumulation, the brain's resilience mechanisms, and the co-occurrence of other pathologies like tau tangles, collectively determine the progression to clinical dementia.

(2) Presenilin 1 (PSEN1) is a component of the gamma-secretase complex, and is closely related to PSEN2. Together, PSEN1 and PSEN2 proteins form the γ -secretase complex, collaborating with Nicastrin (NCT), Presenilin enhancer 2 (Pen-2), and anterior pharynx 1 (Aph1) to sequentially cleave the APP C-terminal fragment β (CTF β), thereby leading to the release of A β peptides.¹⁹

(3) Additionally, the amyloid precursor protein cleaving enzyme-1 (BACE1, also referred to as β -secretase 1) functions as the key enzyme regulating the production of A β peptides in the brain.²⁰⁻²²

(4) Moreover, apolipoprotein E (APOE4) exerts the most substantial impact on the risk of LOAD.²³ Extensive and dependable clinical and fundamental research strongly indicates that APOE4 significantly increases the risk of LOAD by promoting amyloid pathology at earlier and more frequent rates in the brains of APOE4 carriers.²⁴⁻²⁶ While the discovery of highly penetrant mutations in APP, PSEN1, and PSEN2 was foundational in understanding amyloid pathology in early-onset AD, the genetic architecture of LOAD is fundamentally different and revolves around the APOE- ϵ 4 allele as the strongest genetic risk factor. Beyond this major locus, LOAD risk is predominantly shaped by polygenic risk, involving the aggregate effect of countless common variants, each with a small individual effect, that are being identified through large-scale genome-wide association studies. This polygenic background interacts with APOE status and environmental factors over a lifetime to ultimately determine an individual's susceptibility, underscoring that LOAD is not driven by a single genetic defect but by a complex risk threshold.

However, it is important to note that mutations in APP, PSEN1, and PSEN2 only represent 1% of AD cases.²⁷ Broadly speaking, the disease is multifactorial,

arising from the interaction of numerous genetic and non-genetic factors. The neurotoxicity linked to A β /tau,²⁸ ApoE4,²⁹ PSEN1/2,³⁰ and BACE1 is associated with brain aging.^{31,32}

Brain aging

While numerous genetic alterations have been linked to LOAD, most cases of LOAD lack strong genetic implications and are therefore attributed to non-genetic factors. Experts posit that LOAD, akin to other prevalent chronic illnesses, emerges from a combination of factors rather than a singular cause. It is noteworthy that EOAD accounts for a mere 5% of all AD cases, with the majority of AD patients (90-95%) falling under the category of LOAD, typically manifesting after the age of 65.³³⁻³⁶ Therefore, advancing age stands as the primary risk factor for LOAD.³⁷ Age represents the paramount risk factor for LOAD, with prevalence notably rising between the ages of 65 and 85.³⁸ The incidence of LOAD escalates significantly with aging.² The disease's incidence doubles every five years following the age of 65, leading to 1275 new cases diagnosed annually per 100,000 individuals aged over 65; thus, by the age of 85, 30-50% of individuals will be impacted by AD.³⁹

Brain aging is characterized by neurodegeneration.^{40,41} Key factors contributing to brain aging include the generation and buildup of free radicals (reactive oxygen species), gene regulation, mitochondrial dysfunction, apoptosis, and telomere shortening, all of which align with general aging markers. Elevated plasma levels of both p-tau and total tau (t-tau) have been observed to rise with age, correlating with decreased cognitive function and hastened cognitive deterioration, with tau serving as a predictor for LOAD development.^{42,43,184-186} Multiple studies have validated the significant associations of plasma follicle-stimulating hormone (FSH), insulin-like growth factor 1 (IGF-1), nicotinamide adenine dinucleotide (NAD⁺), or the ratio of NAD⁺/nicotinamide adenine dinucleotide reduced (NADH), Growth differentiation factor 11 (GDF11), Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) mRNA, and DNA methylation levels with both general aging and LOAD.⁴⁴⁻⁴⁸

Given the association between aging and LOAD, it is pertinent to inquire whether it is feasible to undergo the aging process without LOAD inevitably manifesting at any point, contingent upon the stage of life.⁴⁹ The study demonstrates that LOAD is directly associated with aging, but not necessarily with general aging theories. Therefore, it is plausible to link both LOAD and aging to aging theories and certain morphological, genetic, and biochemical aspects outlined in these theories. Nonetheless, distinguishing between normal aging and dementia like LOAD proves challenging due to aging being a primary risk factor for developing LOAD.⁵⁰⁻⁵² The senescence hypothesis of LOAD progression suggests that genotypic factors associated with LOAD act as stressors and that, in combination, they interfere with signaling pathways of cell survival and maintenance, such as the senescence pathway. When the damage is chronic and is greater than the homeostatic capacity of the cell, the accumulation of senescent cells would itself be toxic in LOAD.⁵²⁻⁵⁹

From a biological perspective, LOAD results from the gradual accumulation of molecular and cellular damage over time. Typical morphological changes associated with aging include brain volume loss, gray and white matter atrophy, cortical thinning, decreased gyrification, and ventricular enlargement.^{60,61} These age-related changes significantly affect individuals' daily activities and play a role in geriatric syndromes like LOAD.⁶²

The global population is aging, with a noticeable rise in the proportion of older individuals across nearly all countries. Population aging is emerging as a key social transformation of the twenty-first century.⁶³ How will the impending global population aging unfold? LOAD is not merely an advanced or intensified form of normal aging. Age is the primary risk factor for LOAD, yet the underlying reason for this association remains unknown.⁶⁴

Environment

While EOAD has a strong genetic component, a small fraction of cases (< 2%) are familial and can be linked to causative mutations in the APP and PSEN1/PSEN2 genes. Most cases of AD are LOAD, with genome-wide association studies (GWAS) uncovering more than 25 genetic factors associated with LOAD. However, these identified risk variants for AD explain only explain 24-33% of the variability in LOAD risk, indicating a considerable portion of "missing heritability" yet to be elucidated. Gene-environment interactions

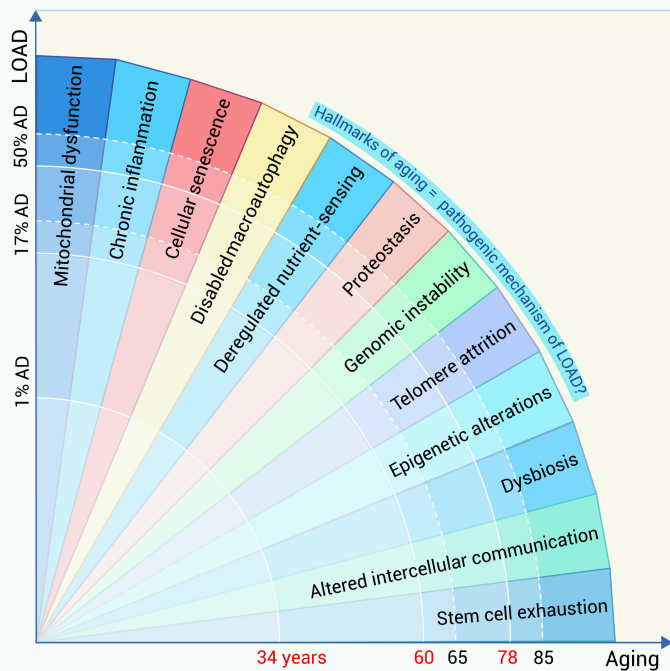


Figure 2. The prevalence of LOAD rises with hallmarks of aging The process of aging does not occur in a linear fashion, but rather in three distinct stages: 34, 60, and 78 years of age. This is in contrast to the period following the onset of aging, which spans from 65 to 85 years of age and is also associated with a high prevalence of AD.

represent a possible source of this unexplained heritability, where particular environmental factors could enhance the impact of modest genetic predisposition to LOAD. Meta-analyses indicate that LOAD cases may be linked to adjustable environmental factors throughout an individual's lifespan.⁷³

The research revealed that maintaining a healthy lifestyle was linked to a deceleration in memory decline, even when the APOE4 allele was present. Therefore, it can be concluded that lifestyle and environment can offer crucial insights for mitigating memory loss in older adults.⁷⁴ Additionally, findings from structural modeling and significant variations in age of onset within pairs indicate that environmental factors play a crucial role in the onset and progression of LOAD.⁷⁵

Diet

The pathogenesis of AD is complex, and diet has been identified as a key modifiable risk factor. Substantial evidence indicates that long-term dietary habits directly influence the progression of neurodegenerative pathology. For instance, the consumption of Western diets, which are abundant in saturated fats and refined sugars, has been demonstrated to promote inflammation and oxidative stress within the brain, thereby accelerating the process of brain damage. Conversely, dietary patterns such as the Mediterranean and MIND diets have been demonstrated to exert potent protective effects. These diets emphasise the consumption of vegetables, berries, nuts, whole grains, and omega-3-rich fish, with the benefits arising from the synergistic effects of polyphenols, antioxidants, and healthy fats. The aforementioned substances have been demonstrated to exert a mitigating effect on cerebral inflammation, thus enhancing cerebrovascular health and concomitantly reducing β -amyloid deposition. In summary, while genetic factors remain uncontrollable, the adoption of a brain-healthy diet is considered to be one of the most effective preventative strategies available to the public, offering significant hope for reducing the global burden of AD.^{132,213}

Notably, dietary patterns influence the gut microbiome, which can produce metabolites like short-chain fatty acids (e.g., butyrate) that function as endogenous histone deacetylase (HDAC) inhibitors, providing a direct mechanistic link between diet, epigenetic regulation, and brain health.²¹⁴

Do the hallmarks of aging underlie the pathogenesis of LOAD?

As demonstrated in the preceding discussion, it is evident that the inter-

play of environment, epigenetics, and aging significantly influences LOAD. Thus, is LOAD intrinsically linked to the aging process? A study conducted by Stanford University and published in Nature analyzed plasma data from 4,263 participants, quantifying protein levels to identify distinct biological aging stages occurring at 34, 60, and 78 years of age.⁸² Aging does not progress as a continuous process but rather occurs in three distinct stages. Notably, the incidence of LOAD increases sharply after the ages of 60 and 78, with approximately 17% of individuals aged 65 to 74 and 50% of those aged 85 or older developing AD. Therefore, it may be hypothesized that aging directly contributes to the development of LOAD (Figure 2). To explore this relationship, an investigation was conducted to examine the correlation between aging markers and LOAD.

Mitochondrial dysfunction in LOAD

During normal aging, mitochondrial size decreases, and the quality and activity of mitochondria decline. These changes are associated with neuronal mitochondrial dysfunction in LOAD, contributing to energy deficits that drive LOAD progression and promote pathological alterations in A β and tau proteins.⁸³ Studies suggest that the autophagy pathway, which is responsible for eliminating damaged mitochondria, is impaired in both LOAD and aging. This impairment leads to the accumulation of dysfunctional mitochondria.⁸⁴ Furthermore, neurons demand elevated ATP levels for their physiological activities, underscoring the role of mitochondrial dysfunction in the pathogenesis of LOAD. Mitochondrial dysfunction stimulates tau phosphorylation via AMPK activation and excessive mitochondrial fission, leading to compromised ATP synthesis.⁸⁵ Thus, the age-related decline in mitochondrial quality control escalates into a maladaptive, self-reinforcing cycle of energy failure and proteopathy, directly linking this hallmark of aging to LOAD pathogenesis.

Chronic inflammation in LOAD

The majority of older people experience inflammation, characterised by elevated levels of inflammatory markers in the bloodstream, leading to an increased risk of chronic disease, disability, frailty and premature mortality. Inflammation plays a dual role for neurons, providing neuroprotection during the acute phase response but becoming detrimental during the chronic phase response.^{86,193} Increased levels of the pro-inflammatory cytokine interleukin 1 (IL-1) have been linked to APP production and increased A β accumulation.^{87,88} Furthermore, elevated levels of IL-1 β levels have been demonstrated to enhance the synthesis of additional cytokines, such as IL-6, which further triggers the activation of Cyclin-dependent kinase 5 (Cdk5), a kinase associated with tau hyperphosphorylation.⁸⁹ Neuroinflammation seems to significantly contribute to the worsening of A β accumulation and tau hyperphosphorylation. This shift from the protective, acute inflammatory responses of a younger brain to a persistent, low-grade chronic inflammation in aging represents a maladaptive transition, where the immune system itself becomes a primary driver of LOAD pathology.

Cellular senescence in LOAD

LOAD is characterized by a significant senescence-associated secretory phenotype (SASP), which involves the abnormal secretion of growth factors, cytokines, reactive oxygen species (ROS), and metalloproteinases.⁹⁰ Astrocytes, the predominant glial cell population in the brain, play essential roles in various physiological functions of the central nervous system. Senescent astrocytes experience a reduction in normal physiological function and an upregulation in the secretion of SASP factors, which play a role in the accumulation of A β in LOAD, tau hyperphosphorylation, neurofibrillary tangle formation, and neurological impairments.⁹¹

Oligodendrocytes have been shown to play a role in immune modulation, stress responses, and cellular survival. Emerging evidence suggests their active involvement in and response to amyloid and tau pathology. Rather than being passive bystanders, oligodendrocytes appear to play a dual role in AD pathogenesis, potentially providing protective mechanisms against pathology while simultaneously contributing to disease progression.²² Additionally, senescent astrocytes have been shown to induce oligodendrocyte senescence, impairing myelination. Furthermore, the process of oligodendrocyte senescence is exacerbated by the presence of senescent microglia, which release components of the SASP, overexpress SA- β -gal, p16, and p21,

and promote A β accumulation.^{24,25} The accumulation of senescent glial cells creates a maladaptive feedback loop; rather than being cleared, these cells persist and poison the cerebral microenvironment, actively promoting the very pathologies they initially formed to contain.

Autophagy abnormalities in LOAD

The development of LOAD is also associated with an increase in misfolded proteins and the aggregation of A β /tau proteins.⁹² A β oligomers have the potential to hinder synaptic plasticity and signal transduction processes. Additionally, A β can encircle mitochondria, impair their function, resulting in the release of reactive oxygen species (ROS), hyperactivation of microglia, and the production of pro-inflammatory factors. Another significant alteration is the self-aggregation and accumulation of A β on neuronal membranes, leading to the generation of ROS, membrane lipid peroxidation, and the production of 4-hydroxy-2-nonenal. Consequently, this impairs the function of membrane dynamic ATPases, glucose and glutamate transporters, and disrupts neuronal Ca²⁺ homeostasis.⁹³ These effects result in neuronal hyperexcitability, increased susceptibility to excitotoxicity, metabolic failure, and ultimately A β neurotoxicity. Recent studies have revealed that cellular damage characteristic of LOAD manifests in neurons before the accumulation of amyloid fragments and the formation of amyloid plaques. Subsequent research has indicated that these neuronal cells exhibit impaired autophagy and are unable to effectively degrade A β , resulting in the associated phenotype.⁹⁴ The age-related slowing of autophagy, an otherwise manageable decline, becomes maladaptive in the context of LOAD, transforming a vital clearance mechanism into a bottleneck that allows toxic proteins to accumulate and drive disease.

Nutritional imbalances in LOAD

Nutrition plays a crucial role in influencing the health of older individuals, particularly those with LOAD. Logistic regression analysis has revealed that malnutrition poses a significant risk factor for the onset of LOAD. Alterations in dietary habits and nutrient intake play roles in the development, protection, and damage of the nervous system.⁹⁵ Dietary patterns offer a more comprehensive reflection of dietary complexity, and recent studies have delved into exploring the correlation between diet and LOAD. Following the Mediterranean diet, the Japanese diet, and a healthy diet has been linked to a decreased risk of developing LOAD. In general, limited studies indicate that increased consumption of fruits, vegetables, fish, nuts, legumes, and whole grains, along with reduced intake of meat, high-fat foods, sodium, sweets, and refined cereals, are linked to a lower risk of LOAD. Large randomized trials with sufficient power and detailed descriptions of patient populations and interventions are required to ascertain the causal role of specific nutrients, foods, and dietary patterns in the pathogenesis of LOAD. Due to the scarcity of studies on dietary patterns and LOAD, additional research is warranted. Therefore, poor nutrition in aging is not merely a correlate of ill health but a maladaptive factor that can accelerate the underlying biological processes of aging, thereby increasing the risk and progression of LOAD.

Imbalance of protein metabolism in LOAD

One of the characteristic events in LOAD is the misfolding, aggregation, and buildup of A β , resulting in cellular dysfunction, synaptic connection loss, and brain damage. The amyloid in LOAD can be broadly defined as an insoluble protein aggregate with a characteristic highly ordered, β -sheet-rich structural pattern. These structures can be histologically identified using dyes such as Congo red and thioflavin. While some amyloid proteins may have adaptive physiological functions, the majority are regarded as abnormal and linked to various clinical conditions, such as systemic amyloidosis and certain neurodegenerative diseases.⁹⁶ Improved clearance of monomeric A β and A β aggregates through A β immunotherapy has been effectively employed to decrease brain A β levels and enhance cognitive function in mouse models of amyloid. Early efforts to actively immunize against human A β were halted due to adverse immune reactions in certain patients. Nevertheless, passive immunotherapeutic strategies have progressed to clinical trials, and intravenous immunoglobulin may also prove effective in lowering A β levels in the brain.^{96,97} The age-related decline in protein homeostasis, or proteostasis, becomes maladaptive when the balance tips from controlled protein regulation

to the uncontrolled aggregation of A β , effectively overwhelming the brain's natural clearance systems.

Genomic instability in LOAD

Genome instability, characterized by alterations in DNA information content through mutations, is widely recognized as a hallmark of aging.⁹⁸ The pathogenesis of LOAD is intricate, with various gene variants linked to an elevated lifetime risk of the disease. Maintaining the integrity of nuclear and mitochondrial DNA is crucial for neuronal development, maintenance, and function. DNA damage and changes in cellular DNA repair capacity are implicated in the aging process and age-related neurodegenerative diseases, such as LOAD.⁹⁹ These findings are supported by studies using animal models of LOAD and animals with deficiencies in DNA repair mechanisms. Recently, new mechanisms linking DNA damage to neuronal dysfunction have been discovered, paving the way for the development of noninvasive treatment approaches. Additional research into the molecular pathways linking DNA damage to LOAD pathology could facilitate the development of innovative treatment strategies for this disabling condition.¹⁰⁰ As aging diminishes DNA repair capability, DNA damage escalates and accumulates within neurons. This results in heightened cellular oxidative stress and an augmented inflammatory response, initiating the onset of age-related neurodegenerative diseases and accelerating neuronal aging and the development of LOAD.^{99,101,102} The cumulative failure of DNA repair mechanisms with age is a quintessential maladaptive process, as the post-mitotic neuron becomes a reservoir for damage, leading to functional decay and the activation of pathogenic pathways central to LOAD.

Shortened telomeres in LOAD

Telomeres, which are located at the tips of chromosomes, undergo a process of shortening with each cell division. This process, known as "replicative senescence," plays a crucial role in regulating the proliferation of human cells, thereby limiting their division potential to a finite number of times. Increasing evidence suggests that telomere shortening not only affects stem cell function but also contributes to the process of aging by hindering regeneration and organ maintenance. Furthermore, studies have demonstrated a correlation between telomere shortening and an increased risk of developing LOAD.¹⁰³ Telomere shortening has been associated with cognitive impairment, amyloid pathology, and hyperphosphorylation of tau in LOAD, and it plays a crucial role in LOAD pathogenesis via oxidative stress and inflammation mechanisms.¹⁰⁴ In LOAD, telomere shortening transcends its role as a mere marker of cellular age and becomes a maladaptive driver of pathology, promoting the disease state through stress and inflammatory signaling that disrupts the neuronal environment.

Epigenetic alterations in LOAD

Epigenetic mechanisms facilitate the integration of long-term non-genetic influences within specific genetic backgrounds. A growing body of evidence has documented numerous epigenetic modifications associated with LOAD.⁷² For example, the accumulation of dysregulated epigenetic mechanisms during aging, the primary risk factor for LOAD, could contribute to the disease's onset. Similarly, mutations in various enzymes involved in the epigenetic machinery have been linked to neurodegenerative processes affected in LOAD, such as impaired learning and memory formation. Both genome-wide and locus-specific epigenetic modifications have been documented, with multiple epigenetically dysregulated genes validated by independent research groups.⁷² These studies paint a picture of LOAD being linked to DNA hypermethylation and histone deacetylation, indicating an overall repressed chromatin state and reduced epigenetic plasticity in LOAD.¹⁰⁵ The aging-associated drift in the epigenetic landscape becomes maladaptive in LOAD, leading to a loss of transcriptional resilience and the silencing of genes critical for neuronal plasticity and stress response, thereby locking cells into a pathological state.

Dysbiosis of intestinal flora in LOAD

The dysbiosis of gut microbiota, recently identified as a risk factor for LOAD, can trigger an inflammatory response in the brain. It is widely believed that the pathogenesis of LOAD is multifactorial.¹⁰⁶ The gut microbiota repre-

Table 1. Environmental-epigenetic links to aging and AD.

Number	Environmental factors	Epigenetic factor	AD	Aging	Else with aging	Reference to aging	Reference to AD
1	Cadmium	Histone acetylation, DNA methylation and damage.	Increased risk of AD.	Increased in aged-cognitive decline.	Oxidative stress.	[206]	[204], [205]
2	Arsenic	DNA methylation, histone posttranslational modifications, and microRNAs.	Developments of AD.	Neurological and cognitive dysfunction.	Neuronal death, oxidative stress, inflammation, mitochondrial dysfunctions, ER stress, apoptosis, impaired protein homeostasis, and abnormal calcium signaling.	[209]	[207], [208]
3	Obesity	DNA methylation, and miRNAs modifications.	Increased risk of AD.	Neurodegeneration.	Gut microbiota modifications and unbalanced food intake.	[212]	[210], [211]
4	Diet	DNA methylation, histone modifications, and miRNA.	Remains uncertain.	Impairs hippocampal synaptic plasticity and cognition in middle - aged.	Gut microbiome.	[216]	[213], [214], [215]
5	Light	DNA methylation.	Neurodegeneration.	UV-induced oxidative DNA damage.	ROS	[219]	[217], [218]
6	Heavy metals	Hypermethylation of CpG and specific genes.	Induced AD.	Aging brain.	Toxicity, neurotoxicity.	[222]	[220], [221]
7	Infectious agents	DNA methylation, histone modification, and miRNA.	Accumulation of A β , promote tau hyperphosphorylation.	Neurodegeneration.	Infectious disease.	[225]	[223], [224]
8	Formaldehyde	DNA global methylation, Histone alterations, and microRNA.	Induced early AD.	Toxicity in age-related Neural.	Age-Related Cognitive Impairment.	[228]	[226], [227]
9	Immune	Histone acetylation, methylation, SUMOylation, ubiquitination, citrullination, lactylation, and DNA methylation.	Neuroinflammation.	Aging is associated with maladaptive immune response.	Immune system.	[230]	[229], [285]
10	Psychiatric factors	DNA methylation.	Risk factors for AD.	Accelerated aging.	Cognitive deficits.	[233]	[231], [232]
11	Smoking	DNA methylation, histone modifications, and miRNA.	Increased AD risk.	Accelerated vascular aging.	Cardiovascular disease.	[236]	[234], [235]
12	Olfactory	DNA methylation.	Cognitive decline and AD.	Longevity.	Olfactory loss in aging.	[239]	[237], [238]
13	Education	Epigenetic in aging.	Risk factors for AD.	Epigenetic Clocks.		[242]	[240], [241]
14	Malnutrition	Histone modifications, DNA methylation, and microRNA.	Decreased mental function of AD patients.	Risk of aging.	Nutrieipigenomics, immune system.	[245]	[243], [244]
15	Virus	DNA methylation.	Risk of AD.	Neuronal dysfunction.	Cancers.	[248]	[246], [247]
16	Physical activity	DNA methylation and microRNA.	Risk of AD.	Physical activity to ease aging.	Cardiovascular health.	[250]	[249]
17	Alcohol Consumption	DNA and histone methylation and acetylation.	Risk of AD.	Oxidative stress and DNA damage.	Nicotinamide adenine dinucleotide, adenosine triphosphate.	[252]	[251]
18	Pesticide Exposure	DNA methylation, histone modifications, and microRNA expression.	Risk of AD.	Neurodegeneration.	DNA damage.	[255]	[253], [254]
19	Vascular	HDAC9, H3K4me3, histone modification, DNA methylation, and noncoding RNA.	Improve vascular function attenuate AD pathology.	—	—	[257]	[256]
20	Traumatic brain injury	Histone modifications, DNA methylation, and noncoding RNAs; Chromatin remodeling.	Risk of AD	Accelerated cognitive aging.	Mitochondria.	[260]	[258], [259]

Table 1. (Continued)

Number	Environmental factors	Epigenetic factor	AD	Aging	Else with aging	Reference to aging	Reference to AD
21	Cardiovascular	DNA methylation, histone modification, and non-coding RNA.	Risk of AD.	Neural decline in aging.	Cellular reprogramming.	[263]	[261], [262]
22	Air pollution	Histone, microRNA, and DNA methylation.	Cognitive decline and AD.	Cognitive impairment and neurodegeneration.	Oxidative stress, aging phenotype.	[266]	[264], [265]
23	Noise	DNA methylation.	Accelerates the risk of cognitive impairment and AD.	Short-term memory.		[269]	[267], [268]
24	Social and cognitive engagement	DNA methylation and histone modifications, small non-coding RNA, microRNA.	Cognitive impairment represents early-stage AD.	Cognitive decline.	Cellular damage.	[272]	[270], [271]
25	Health factors and behaviors	DNA methylation, histone modifications, and miRNAs.	Risk of AD.	Behavioral determinants of healthy aging.		[275]	[273], [274]
26	Mercury	DNA hypomethylation.	Apolipoprotein E as a moderator.	Neuronal damage and neurodegenerative.	Toxicity.	[278]	[276], [277]
27	Bilirubin	DNA methylation.	Antioxidant and neuroprotectant.	Antioxidative.	Toxicity in the brain, kidney, and erythrocytes. Membrane and mitochondrial dysfunction, oxidative stress, apoptosis, necrosis, endoplasmic reticulum stress, excitotoxicity, inflammation.	[281]	[279], [280]
28	Metal	DNA methylation, chromatin modification, small non-coding RNAs.	A β amyloid pathogenesis argues.	Neurodegenerative disorders.	Neurotoxicity, oxidative stress.	[284]	[282], [283]

sents the most intricate micro-ecosystem in mammals, suggesting a crucial symbiotic relationship with the human body. The diversity of gut microbiota can be significantly affected by various diets, chemical agents, and stress. Research has shown that disruptions in the gut microbiota composition may contribute to LOAD. Emerging evidence from recent studies indicates a direct association between LOAD and gut microbiota impairment. Hence, fecal microbiota therapy (FMT) could offer a promising strategy to alleviate neurodegenerative disorders, specifically LOAD.^{107,108} The age-related shift in gut microbiota composition, or dysbiosis, is a maladaptive process occurring outside the brain that nonetheless directly influences neuroinflammation and pathology within it, exemplifying a systemic failure of aging that contributes to LOAD.

Altered cellular communications in LOAD

LOAD has been extensively researched, and while a complete comprehension of its pathogenesis is still lacking, mounting evidence suggests that non-cell-autonomous mechanisms are crucial in initiating and temporally progressing or spreading the primary pathology.¹⁰⁹ Understanding the intricate intercellular disruptions associated with LOAD will advance endeavors to create effective interventions for preventing or reversing symptom progression in LOAD.¹¹⁰ Astrocytes seem to play a central role in the pathological intercellular communication that is increasingly recognized as a defining characteristic of numerous neurodegenerative conditions. In a murine model of LOAD, the deletion of C-X3-C motif receptor 1 (CX3CR1) gene disrupted this communication, leading to a reduction in A β plaque pathology.¹¹¹ The finely tuned intercellular dialogue of a healthy brain deteriorates with age into a maladaptive cacophony, where distorted signals from glial cells actively contribute to neurodegeneration instead of supporting neuronal function.

Stem cell exhaustion in LOAD

Recent findings indicate that APP may have a significant impact on stem

cell generation and adult neuronal regeneration, among other functions.¹¹² Additionally, studies have demonstrated that APP can elevate chemokine levels to modulate cell migration.¹¹³ This raises the question of how to regenerate neurons by expanding neural stem cells (NSCs) in the presence of elevated APP levels. Conversely, the heightened levels of APP observed in Down syndrome patients who later develop LOAD may diminish the native NSCs pool through the promotion of premature glial differentiation.¹¹⁴ In the pathological context of APP in the LOAD brain, the role of APP may necessitate the exploration of neurodegenerative treatment strategies. NSCs can also be utilized to enhance the production of growth factors. NSCs have the potential to enhance neurogenesis and improve cognitive function by secreting neurotrophic factors such as brain-derived neurotrophic factor (BDNF), as evidenced in transgenic models of AD.¹¹⁵ The age-related exhaustion of neural stem cells represents a maladaptive failure of the brain's innate regenerative capacity, leaving it unable to repair damage or maintain plasticity in the face of accumulating LOAD pathology.¹⁹⁴⁻²⁰³

While we present these aging hallmarks as contributors to LOAD pathogenesis, it is critical to acknowledge the complex, bidirectional nature of these relationships. For instance, A β and tau pathology can, in turn, exacerbate mitochondrial dysfunction and neuroinflammation, creating a vicious cycle. Therefore, many of these hallmarks are likely both drivers and consequences of the disease process. Therapeutic strategies targeting them may still be beneficial by breaking this cycle and ameliorating symptoms, even if they do not address a single 'root cause'.

Epigenetics establishes a connection between the environment and genes in the processes of aging/LOAD

Given the close connection between LOAD and aging, do the signs of aging correlate with LOAD? The present study hypothesises that epigenetic modifications influenced by the environment play a role in this regard. It is postulated that environmental factors can trigger alterations in epigenetic mecha-

Table 2. Epigenetic and neurodegeneration.

Number	Epigenetics	Neurodegeneration	Reference
1	5-mC	5mC Regulation of nerve gene expression.	[291]
2	5-hmC	5hmC increases brain aging.	[292]
3	H2A	H2A acts as a negative regulator of learning.	[293]
4	H2B	H2B acetylation in cognitive dysfunction.	[294]
5	H3	Brains with AD show increased H3 phosphorylation.	[295]
6	H4	H4 in the hippocampus was significantly reduced in AD.	[296]
7	MacroH2A	MacroH2A regulates neuronal pluripotency.	[297]
8	HP1α	Loss of HP1α in neurodegeneration.	[298]
9	H3K27me3	H3K27me3 downregulates brain-derived neurotrophic factor.	[299]
10	H4K20me3	H4K20me3 enriched in neural stem cells.	[300-303]
11	miR-29	miR-29 is associated with neurodegenerative diseases.	
12	H3K4me3	H3K4me3 is altered in the AD brain.	[303],[304]
13	H4K16ac	H4K16ac play a role in age-related neurodegeneration.	[305]
14	H4K12ac	H4K12ac plays a role in learning and memory.	[306]

nisms, which may contribute to the development of both aging and LOAD. The present study thus establishes a connection between aging and LOAD through the medium of epigenetics.

Environment and epigenetic

Environmental toxicants can alter epigenetic regulatory elements such as DNA methylation and microRNA expression. Indeed, depending on the context and exposure, various mechanisms may contribute to changes in epigenetics. Contextual factors may encompass genomic features like relative location (repeat, promoter, etc.), current methylation status, nucleosome positioning, local and regional CpG density, and binding sites for transcription factors. For instance, the chromatin structure, including the distinction between heterochromatin and euchromatin, can influence the capacity of exposures directly interacting with DNA or transcription factors and different binding elements to induce epigenetic modifications. Several studies have associated reactive oxygen species and oxidative stress, whether from exposure or as a consequence of inflammatory responses, as crucial factors in the process leading to epigenetic changes.⁷⁶ In humans, environmental factors that could influence the epigenetic status in adulthood can be categorized into four groups: diet, living or working environment, medications, and unhealthy behaviors. An excellent illustration of how environmental factors can change the epigenetic profile of an organism is the hypermethylation of tumor-suppressor gene promoters observed in non-tumor lung tissues of smokers but not in those of nonsmokers. Numerous studies have reported that chronic alcohol consumption in rats leads to multiple epigenetic changes. For example, chronic ethanol intake inhibits the ubiquitin-proteasome pathway in the nucleus, affecting the turnover of transcription factors and histone-modifying enzymes, thereby modifying epigenetic processes (Table 1).⁷⁷

Epigenetics and aging

Various types of epigenetic information are encoded within the epigenome, such as heterochromatin, histone acetyltransferases (HATs), histone deacetylases (HDACs), histone methylation with age, histone ubiquitination, nucleosome remodeling, DNA methylation, and non-coding RNAs (ncRNAs). Collectively, these diverse forms of epigenetic information from our epigenome and play crucial roles in governing the function and destiny of cells and tissues in unicellular and multicellular organisms. Each of these distinct types of epigenetic information is crucial for the aging process. The packaging of genomic DNA into the intricately organized chromatin structure governs all nuclear genomic processes, such as DNA replication, transcription, recombination, and DNA repair, by regulating DNA accessibility. Increasing

evidence in recent years strongly suggests that chromatin structure, which harbors a significant portion of epigenetic information, plays a pivotal role in the aging process. Research in humans and robust aging models indicates that, akin to other cellular biological structures, the epigenome undergoes a gradual loss of its configuration with age (Table 1).⁷⁸

Modifications at the epigenetic level in AD

Given that APOE4 explains only a small percentage (approximately 4%) of heritability, it has been proposed that the remaining risk could be attributed to changes in epigenetic mechanisms.^{65,187} For example, the accumulation of dysregulated epigenetic mechanisms in aging, the primary risk factor for LOAD, could contribute to the onset of the disease. Age is influenced by a combination of genetic and non-genetic factors, including epigenetic processes such as methylation, histone modifications, chromatin structure, and non-coding RNAs.^{66,67} LOAD is not just an advanced or worsened form of normal aging; epigenetics connects aging to LOAD.^{64,188-191} Changes in histone acetylation, deacetylation, DNA methylation, and expression of non-coding ribonucleic acids (ncRNAs) have been observed in LOAD.⁶⁸

The brain is mainly composed of neurons, astrocytes, microglia and oligodendrocytes. Neurons are postmitotic and susceptible to age-related epigenetic changes. Phosphorylation or hyperphosphorylation of histone H3 and deacetylation of histone H4 have been observed in the hippocampus of early LOAD patients.⁶⁹ These findings imply a significant role of age-related epigenetic factors in the pathogenesis of LOAD. Astrocytic APOE4 enhances acetyl-CoA levels, histone acetylation, and neuronal transcription, while APOE4 exhibits reduced capacity for metabolic and epigenetic regulation in neurons compared to APOE3.⁷⁰ This study demonstrates, for the first time, that APOE4 enhances nuclear translocation of histone deacetylases (HDACs) in human neurons, leading to decreased Brain-derived neurotrophic factor (BDNF) expression, while APOE3 boosts histone 3 acetylation and elevates BDNF expression.^{71,192} Furthermore, mutations in various enzymes of the epigenetic machinery have been linked to neurodegenerative processes affected in LOAD, including impaired learning and memory formation. Both genome-wide and locus-specific epigenetic changes have been documented, with multiple genes showing epigenetic dysregulation confirmed by independent research teams. These findings paint a picture of LOAD linked to DNA hypermethylation and histone deacetylation, indicating an overall repressive chromatin environment and reduced epigenetic plasticity in LOAD.⁷² The question that arises is what causes epigenetic changes?

Environment-epigenetics- aging axis in LOAD

LOAD is a complex condition influenced by both genetic and environmen-

Table 3. Epigenetic and AD.

Number	Genes	Epigenetics	Epigenetics to AD	References
1	ApoE4	HDAC4	ApoE4 promotes the association of HDAC4 with BDNF.	[32],[70]
2	ApoE4	HDAC6	ApoE4 promotes the association of HDAC6 with BDNF.	
3	ApoE4	DNMT1	Increased in AD.	
4	ApoE4	DNMT3a	Downregulated in AD.	[310]
5	ApoE4	DNMT3b	DNMT3B interaction with the APOE4.	[311],[312]
6	ApoE4	m6A methyltransferase	Ameliorates AD pathology.	[313]
7	ApoE4	Catechol-O-methyltransferase	Increased risk for AD.	[314]
8	APOE4	5hmC	Lower expression in AD.	[315]
9	ApoE4	N-Methyltransferase	Increased in the brains of AD.	[316]
10	ApoE4	5hmC	Increase 5hmC in AD.	[317]
11	ApoE4 CpG	DNA methylation	Neural cell dysfunction in AD brain.	[318]
12	PSEN1	DNMT hypomethylation	Leading to A β overproduction.	[319]
13	PSEN1	H3 hyperacetylation	Leading to A β overproduction.	
14	PSEN1/2	CBP/p300	Increased PSEN transcription activity.	[320]
15	PSEN1/2	Methylation of histone H3K9/14	Enhances PS1 and BACE expression.	[321]
16	PSEN1/2	5hmC	Lower expression in AD.	[315]
17	BACE1	H3 hyperacetylation	Leading to A β overproduction.	[319]
18	BACE1	DNMT hypomethylation	Leading to A β overproduction.	
19	BACE1	miR-29c	miR-29c regulates BACE1 protein expression.	[322],[323],[324]
20	BACE1	miR-106b	MiR-106b increases A β levels by repressing ABCA1 expression.	[325] [326]
21	BACE1	miR-124	miR-124 is a potent negative regulator of BACE1.	[327]
22	APP	miR-124	miR-124 could target the BACE1.	[328]
23	APP	miR-106b	MiR-106b increases A β levels.	[329]
24	APP	miR-101	miR-101 regulates APP.	[329]
25	APP	miR-132	MiR-132-3p is downregulated in AD.	[317]
26	APP	Tip60	APP interaction with Tip60.	[288]
27	APP	HDAC4/6	HDAC mediates the damage of A β .	[192]
28	APP	BRCA1	A β itself was sufficient to up-regulate BRCA1,	[179]
29	APP	H3 hyperacetylation	Leading to A β overproduction.	[319]
30	APP	DNMT hypomethylation	Leading to A β overproduction.	
31	Ace-tau	SIRT1	Ace-tau was significantly reduced by SIRT1 overexpression.	[169]
32	Ace-tau	BRCA1	Colocalization of BRCA1 with Tau.	[167]
33	Ace-tau	p300	p300-induced tau acetylation.	[140]
34	P-tau	HDAC4/6	Pan-HDAC inhibitors promote tau aggregation by increasing the level of acetylated tau.	[52]
35	P-tau	DUSP22	DUSP22 mediates PKA - dependent TAU phosphorylation.	[147]

tal factors. The findings indicate that genetic factors explain approximately 30% of the observed phenotypic variance, leaving more than 70% of this variance unexplained by the known LOAD genes.⁷⁹ Gene-environment interactions have been identified for a variety of lifestyle factors in LOAD. The majority of LOAD cases exhibit a complex etiology that likely includes multiple susceptibility genes and environmental factors. Research in animal models and humans has demonstrated that environmental risk factors for LOAD, including diet, lifestyle, alcohol, smoking, and pollutants, can lead to epigenetic alterations in crucial LOAD-related genes and pathways. The interplay between the environment and genetics influences the aging process, as

proposed by non-stochastic theories, including subgroups such as the theory of cellular aging or programmed senescence, theory of telomeres, theory of intrinsic mutagenesis, neuroendocrine theory, and immunological theory.⁸⁰ Various natural antioxidants, along with caloric restriction and physical activity, have the potential to mitigate oxidation and hinder cognitive decline associated with brain aging and LOAD. Numerous antioxidants have been shown to exert their effects through epigenetic mechanisms (Tables 2-3).⁸¹

When evaluating gene-environment interactions in LOAD, it is crucial to take into account epigenetic modifications. Environmental factors can modify epigenetic factors that have a direct impact on both LOAD and the aging

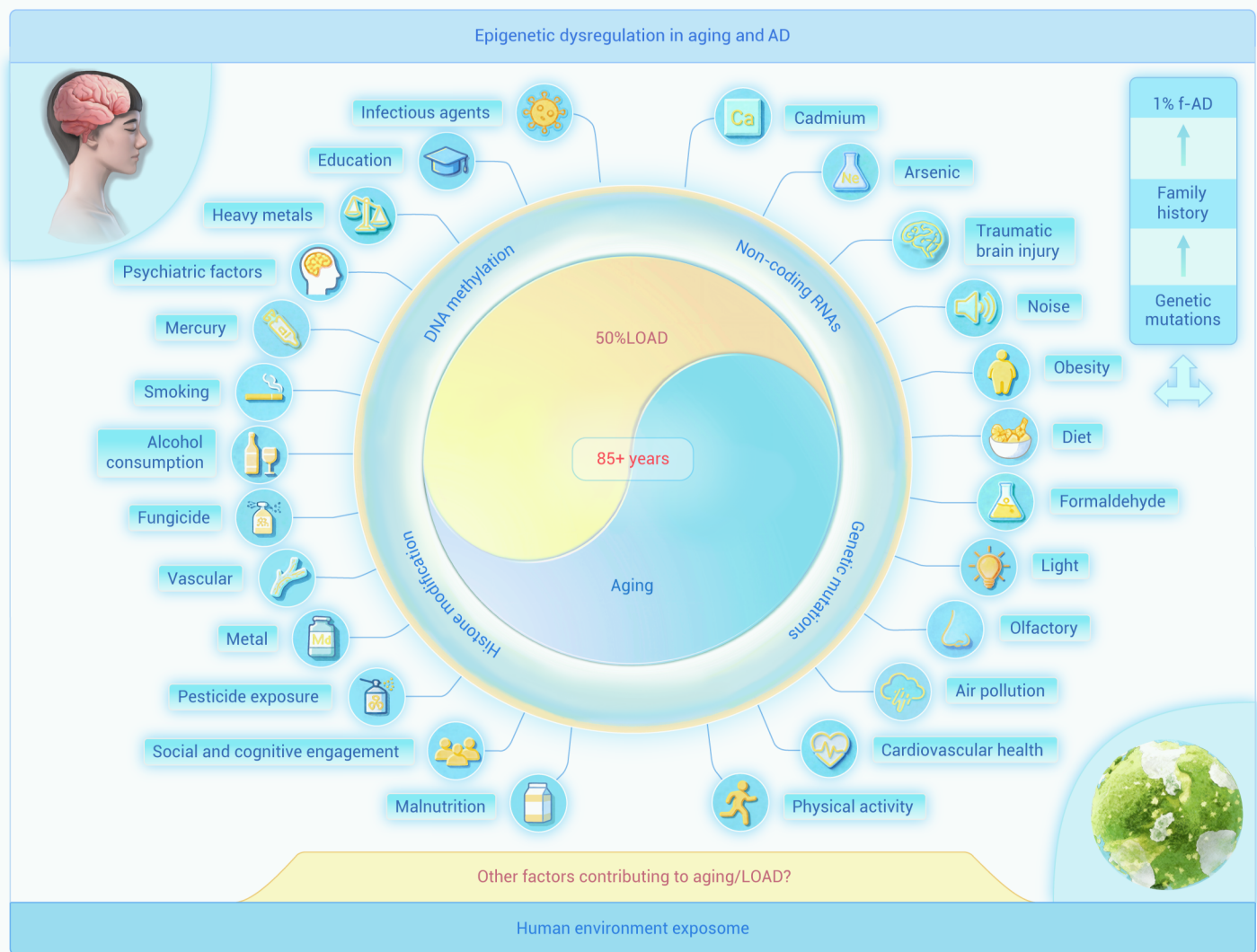


Figure 3. Epigenetics links environment with aging or LOAD One percent of f-AD is attributable to genetic mutations; environmental factors can precipitate the aging process through epigenetic mechanisms; nevertheless, certain deleterious environmental factors have the potential to induce epigenetic abnormalities, which may subsequently contribute to the development of AD.

process (Figure 3, Tables 1-3).

Can anti-aging interventions combat LOAD?

The substantial pathophysiological overlap between biological aging and LOAD has established the targeting of shared aging hallmarks as a compelling therapeutic paradigm (Table 4). However, translating this conceptual framework into viable clinical strategies necessitates a critical evolution from descriptive catalogues of targets to a rigorous analytical review. This section evaluates the principal anti-aging avenues for LOAD, interrogating the supporting evidence, acknowledging contradictory findings, and delineating the significant translational barriers that must be overcome.

Targeting mitochondrial dysfunction: Beyond energetic rescue

Mitochondrial dysfunction, a cornerstone of both aging and LOAD, contributes to bioenergetic deficit, oxidative stress, and neuronal apoptosis. The therapeutic hypothesis is bolstered by evidence that mitochondrial impairment often precedes A β deposition, suggesting its role as an upstream driver. Preclinical investigations have identified promising candidates, including the mitochondrial-targeted peptide SS-31 (Elamipretide), which restores axonal transport and mitigates A β cytotoxicity; compounds such as Hemiramycin-TEMPO conjugates and the Drp1 inhibitor Mdivi-1, which aim to scavenge reactive oxygen species or curb pathological fission; and PPAR agonists like bezafibrate and thiazolidinediones (e.g., pioglitazone) that

enhance mitochondrial biogenesis via PGC-1 α modulation, with the latter showing modest cognitive benefits in clinical trials.^{116,117}

Despite compelling preclinical data, translating mitochondrial therapies faces considerable challenges. Many findings derive from transgenic models with aggressive pathology, which may not accurately mirror the insidious mitochondrial decline in human LOAD. The clinical failure of several antioxidant strategies, despite strong preclinical rationale, underscores the complexity of redox biology and highlights conflicting data. A primary obstacle is the development of agents capable of targeted mitochondrial delivery within the human brain while minimizing off-target effects. Furthermore, mitochondrial dysfunction in LOAD exists in a reciprocal relationship with other pathological processes, complicating the isolation of a specific therapeutic window.

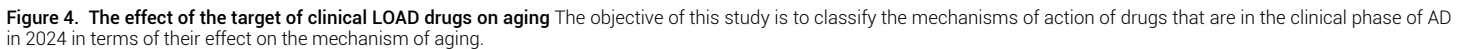
Targeting chronic inflammation: A double-edged sword

Sustained neuroinflammation, mediated by activated microglia and astrocytes, is a hallmark of LOAD. Immunotherapeutic approaches represent the most clinically advanced application of this target. Anti-A β monoclonal antibodies (e.g., Lecanemab, Donanemab) have demonstrated efficacy in plaque removal and slowing cognitive decline, achieving regulatory approval.^{93,120} Anti-tau antibodies (e.g., Semorinemab) seek to inhibit pathological spread and are in earlier clinical development.¹²⁰ Additionally, strategies to modulate microglial function, such as TREM2 agonistic antibodies, aim to promote a

Table 4. Anti-aging therapeutic strategies for LOAD.

Hallmark of Aging	Treatment Strategy / Category	Specific Examples	Proposed Mechanism of Action	Key References
Mitochondrial Dysfunction	Mitochondria-Targeting Peptides	SS-31 (Elamipretide)	Targets inner mitochondrial membrane; prevents oxidative damage, restores transport.	[116, 117]
	ROS Scavengers	Hemigranicidin-TEMPO	Combines mitochondrial targeting with a ROS scavenger.	[116, 117]
	Fission Inhibitors	Mdivi-1	Inhibits Drp1 to suppress excessive mitochondrial fission.	[116, 117]
	Metabolic Modulators & Enhancers	Bezafibrate, Pioglitazone; Nicotinamide Riboside, Serine, Resveratrol	Modulate function via PPAR/PGC-1 α pathway; boost NAD ⁺ ; enhance proteostasis.	[116, 117]
Chronic Inflammation	Immunotherapy (A β & Tau)	Aducanumab, Lecanemab, Donanemab; Semorinemab	Monoclonal antibodies to clear amyloid plaques or tau pathology.	[118, 119]
	Microglial Modulators	TREM2 Agonistic Antibodies	Enhance microglial phagocytosis of A β and dampen harmful inflammation.	[120]
	Cytokine & Signaling Inhibition	Anti-IL-1, Anti-IL-6, NLRP3 Knockdown, Salsalate	Reduce pro-inflammatory cytokines and inflammasome activity.	[121-123]
Cellular Senescence	Senolytics	Dasatinib + Quercetin	Selectively clear senescent cells (e.g., astrocytes, microglia).	[124, 127]
	Metabolic Boosters	Nicotinamide Mononucleotide (NMN)	Increases NAD ⁺ levels; reduces A β toxicity, improves cognition.	[126]
	Other Interventions	Metformin, Hyperbaric Oxygen Therapy (HBOT)	May reduce senescence; improves pathology in models.	[125, 126]
Impaired Autophagy	mTOR Inhibition & Inducers	Rapamycin, Lithium salts, Carbamazepine, Trehalose	Enhance autophagy clearance via mTOR-dependent and independent pathways.	[128, 129]
	Sirtuin Activators & Natural Compounds	Resveratrol, SRT1460, SRT1720; Ginsenoside-Rg2, Curcumin	Activate Sirt1 and other pathways to promote autophagy and clear A β .	[128, 129]
Deregulated Nutrient Sensing	Neurotrophic Factor Support	BDNF, NT-3, FGF, IGF	Support neuronal survival, plasticity, and metabolic function.	[70, 130, 131]
	Dietary Regimens	Caloric Restriction (CR), Mediterranean Diet	Anti-aging effects; modulate nutrient-sensing pathways (e.g., IGF-1, mTOR).	[130, 131]
Loss of Proteostasis	Proteopathy & Aggregation Inhibitors	Iridubin-3'-monoxime (I3M)	Inhibits GSK3 β (reducing tau tangles) and A β aggregation.	[134, 137]
	Clearance Enhancers	IRL-1620, Glucagon-like peptide-1 agonists	Improves cerebral blood flow and A β clearance.	[137]
	Immunotherapy	Passive Immunization (Anti-A β antibodies)	Promotes microglial clearance of amyloid plaques via Fc receptors.	[129, 137]
Genomic Instability	DNA Protectants & Repair	Grape Seed Polyphenols, Curcumin	Reduce genomic instability events; support DNA repair processes.	[138, 139]
Telomere Attrition	Telomerase Activation	Telomerase Gene Therapy	Counteracts telomere shortening's role in neurodegeneration in models.	[140, 141]
Epigenetic Alterations	HDAC Inhibitors	Valproic Acid, SAHA, Nicotinamide	Reverse repressive chromatin state; may reduce A β /tau pathology.	[143]
	Natural Epigenetic Modulators	Curcumin, Resveratrol, Catechins	DNMT and HDAC inhibitory activity; restore epigenetic flexibility.	[143]
Gut Dysbiosis	Microbiome-Targeted Drugs	GV-971 (Sodium Oligomannate), Baicalin	Alters gut microbiota; reduces neuroinflammation via gut-brain axis.	[59, 144]
	Microbiome Transplantation	Fecal Microbiota Transplantation (FMT)	Restores healthy gut flora; reduces pathology and cognitive deficits.	[145, 146]
	Dietary Intervention	Mediterranean Diet, Prebiotics	Shapes gut bacterial community to support brain health.	[77, 11]
Altered Intercellular Communication	Neurotransmitter Targeting	Lecozotan (5-HT1A), Donepezil (AChEI), SB-742457 (5-HT6)	Modulates serotonin, acetylcholine systems to improve cognition and behavior.	[148]
	Gut-Brain Axis Modulation	Probiotics, Specific Diets	Influences production of neurotransmitters (ACh, GABA, serotonin) by gut microbiota.	[148-156, 307, 308]
Stem Cell Exhaustion	Stem Cell Therapy	Neural Stem Cell (NSC) Transplantation, hUC-MSCs	Replenishes cell pool; secretes trophic factors; reduces A β /tau.	[157-162]
	Endogenous NSC Boost	Peripheral administration of factors	Aims to augment the body's own neural stem cells for regeneration.	[157]

Note: Many of these treatments are in preclinical or early clinical trial stages. The table summarizes proposed mechanisms based on the provided text and is not an exhaustive list of all research or clinical status.



The success of anti-A β immunotherapies validates neuroinflammation as a druggable target. However, limitations persist, including modest effect sizes, high treatment costs, and significant risks such as amyloid-related imaging abnormalities (ARIA). A critical conceptual challenge is the dual role of inflammation: while chronic neuroinflammation is deleterious, acute inflammatory responses are essential for plaque clearance. Consequently, therapeutic timing is paramount, as interventions may prove ineffective or harmful following extensive neurodegeneration. The precision offered by targeting specific pathways (e.g., TREM2) may also be undermined by the

The accumulation of senescent cells, which secrete a pro-inflammatory and tissue-destructive SASP, is a fundamental aging process. Preclinical studies in tauopathy models demonstrate that genetically or pharmacologically eliminating senescent glial cells (e.g., with the senolytic combination dasatinib and quercetin) reduces tau pathology, neuroinflammation, and cognitive deficits,^{124,206} prompting an ongoing Phase II trial in LOAD.¹²⁷ Adjuvant strategies such as NAD⁺ boosters (e.g., NMN) and hyperbaric oxygen therapy have also shown potential in models to ameliorate A β toxicity and improve cognition.^{125,126}

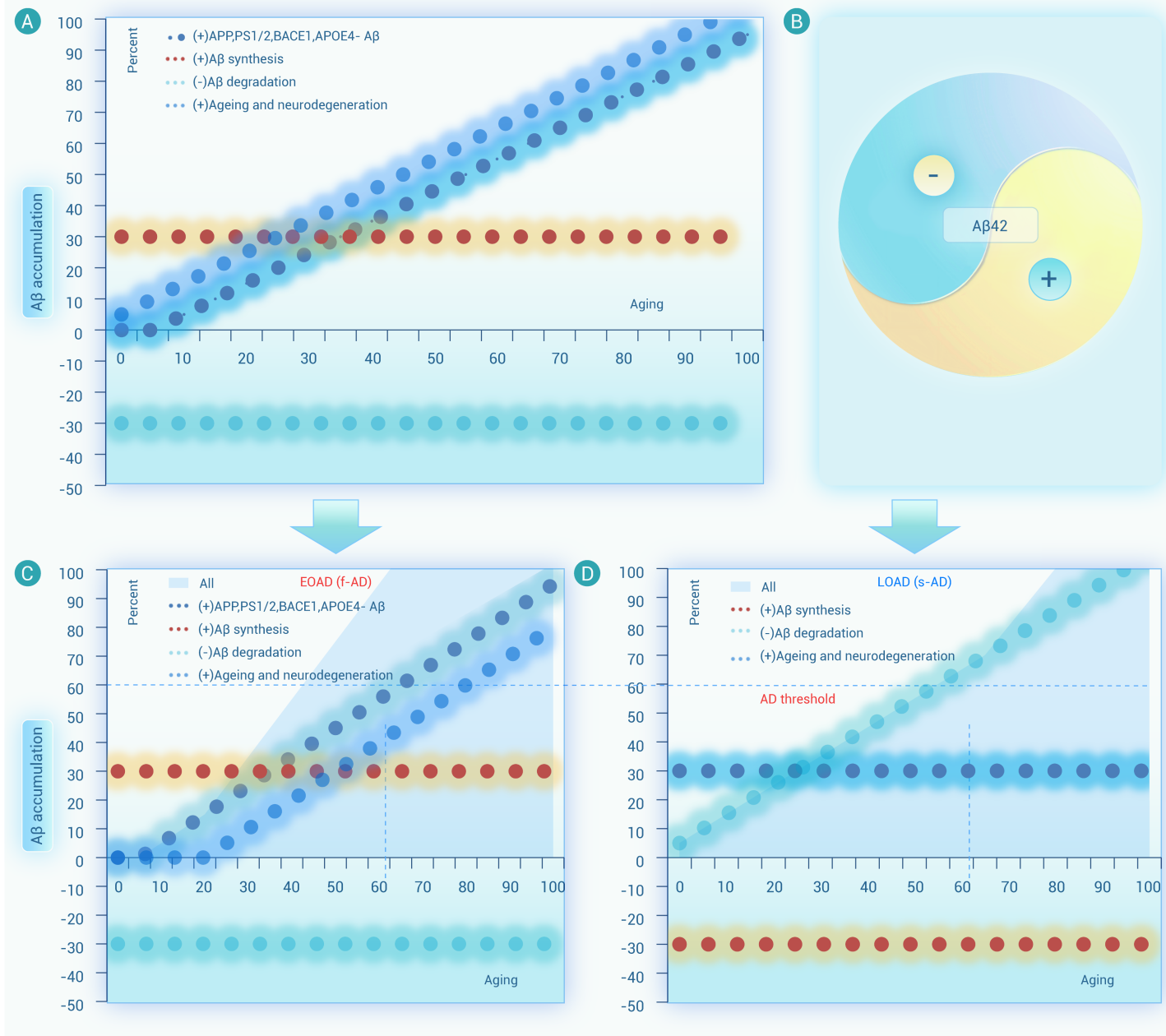


Figure 5. A dynamic equilibrium model for EOAD and LOAD This model proposes that A β levels are governed by a balance between synthesis and degradation (A) Key factors influencing A β dynamics: Synthesis is driven by APP and PS1/2, while degradation is a clearance capacity that declines with age. (B) Under normal conditions, a dynamic equilibrium is maintained between A β synthesis and degradation. (C) In EOAD, mutations in core genes (e.g., APP, PS1, PS2) lead to increased A β synthesis, disrupting the equilibrium and causing pathology. (D) In LOAD, normal A β synthesis is coupled with an age-related decrease in degradation capacity, which is exacerbated by neurodegenerative processes. This imbalance also disrupts the equilibrium, leading to the accumulation of A β .

The senolytic approach, while promising, is in its infancy for LOAD. Fundamental questions remain unanswered: which senescent cell types (e.g., astrocytes, microglia, neurons) are most pathogenic in the human brain? Can systemically administered senolytics cross the blood-brain barrier sufficiently to clear central nervous system senescent cells without causing unacceptable off-target effects?¹³³ The pleiotropic mechanisms of NAD⁺ boosters complicate the attribution of benefits solely to senescence reduction.²⁸⁶ Crucially, long-term safety data for the chronic senolytic regimens required in LOAD are currently absent.

Other mechanistic avenues: Shared promises and challenges

A concise analysis of additional interconnected targets reveals shared promises and challenges. Enhancing autophagy (via Sirt1 activators, mTOR inhibition) promotes toxic protein clearance in models,^{128,129} but achieving brain-specific modulation without disrupting basal homeostasis and over-

coming poor bioavailability (e.g., of resveratrol) are major barriers. Nutritional and gut microbiome interventions, including the Mediterranean diet, polyphenols, and the oligomannate GV-971—which showed cognitive benefit in a Phase 3 trial¹¹⁴—hold epidemiological and preclinical promise.^{130,131} However, human studies often yield weak or inconsistent results, complicated by compliance issues and high interpersonal variability in microbiome composition and response. Strategies to bolster proteostasis or modulate epigenetic marks can reduce protein aggregates in models,^{134-137,142,143} but these pathways are ubiquitously essential, raising serious toxicity concerns from systemic inhibition, alongside challenges of blood-brain barrier penetration and selectivity. Finally, approaches addressing genomic instability, telomere attrition, or stem cell depletion are supported by animal data but are among the most challenging to translate,^{138-141,157} due to unclear telomere dynamics in neurons, and the formidable delivery, integration, and safety hurdles associated with stem cell or genetic therapies for a sporadic disease.

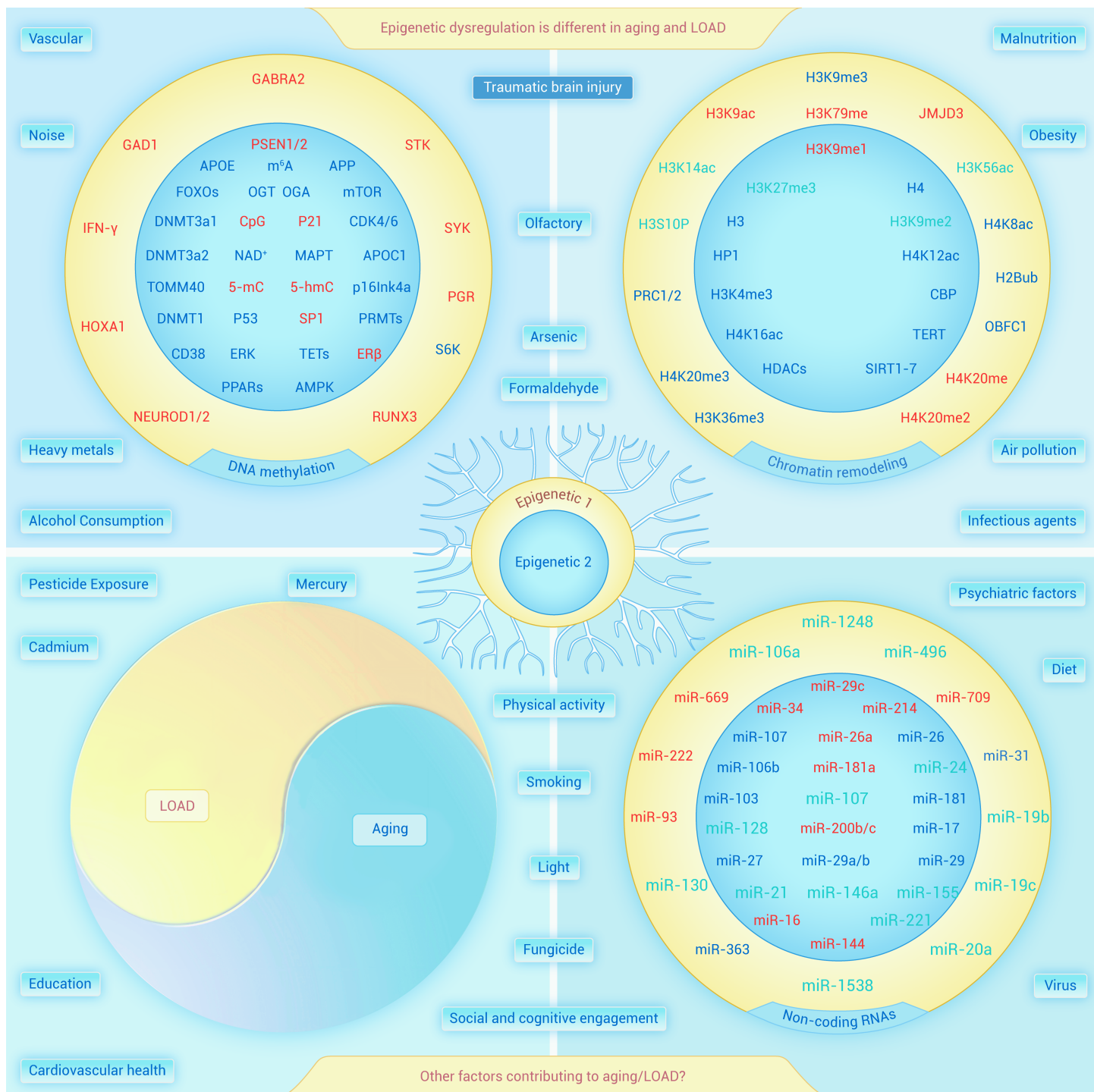


Figure 6. Epigenetic dysregulation in LOAD The epigenetic1 ensemble contains epigenetic2, a factor that is significantly altered during aging, However, only the epigenetic2 portion is altered in LOAD.

Synthesis and future perspectives

Transitioning the anti-aging paradigm for LOAD from a list of targets to an effective treatment strategy requires confronting several overarching barriers:

Translational Gaps: The most significant challenge is the disconnect between robust effects in accelerated animal models and the modest outcomes in human trials, which often fail to recapitulate the decades-long prodromal phase of LOAD.

Biomarker and Patient Stratification: A critical limitation is the lack of mechanism-specific biomarkers to identify patient subpopulations most likely to respond to a given therapy (e.g., those with a high burden of senescent cells).

Combination Therapy Imperative: Given the multifactorial pathology of

LOAD, monotherapies targeting single aging hallmarks are likely inadequate. Rational combination strategies, informed by systems biology, are essential but introduce immense logistical and regulatory complexity.

Timing of Intervention: Preclinical success is typically achieved with early intervention, underscoring the necessity for preventive or early prodromal treatment in humans and demanding a paradigm shift in clinical trial design towards secondary prevention.

In conclusion, while the targeting of fundamental aging processes provides a fertile conceptual framework for LOAD therapeutics, its ultimate success is contingent upon a rigorous critical approach that fully acknowledges biological complexity, pathway interdependencies, and substantial translational obstacles. Future research must prioritize the development of more human-relevant

models, precise biomarkers for patient stratification, and innovative clinical trial designs capable of evaluating rational combination therapies at the earliest stages of disease.

From anti-aging to anti-LOAD

As demonstrated by the previous research, there is a notable correlation between the aging process and the development of LOAD. This prompts the question of whether the pharmacological agents employed in the treatment of AD may also exert an influence on the aging process. Treatment of LOAD includes drug treatments and non-drug treatments.

(1) The FDA has approved seven drugs for the treatment of LOAD: donepezil, aducanumab, rivastigmine, galantamine, brexpiprazole, memantine and lecanemab. In the 2024 LOAD drug studies, 127 drugs are in clinical trials. Of these, 32 drugs are in Phase 3; 81 drugs are in Phase 2; and 25 drugs are in Phase 1 (Table S1). As illustrated in the Figure 4, the clinical trials of drugs for LOAD have been conducted in a sequential manner, with each subsequent trial aiming to address a specific aspect of the disease. These aspects include improving severity, accelerating protein degradation, improving mitochondrial function, enhancing cellular connectivity, and slowing down cellular senescence (Figure 4).¹⁶³⁻¹⁶⁸

(2) Non-drug Treatments: physical activity, memory and orientation exercises, and music- and art-based therapies. Furthermore, nutritional therapy (nutrient-sensing) represents the primary non-pharmacological treatment modality.^{167,287}

A synthesized framework of AD

The prevailing amyloid-centric model has provided valuable, yet incomplete, insights into LOAD. A more holistic framework positions LOAD not as an inevitable consequence of time, but as a pathological acceleration of the aging process within the brain—a maladaptive aging phenotype.¹⁶⁹

Central to this view is the interplay between core proteinopathies and aging. The levels of insoluble A β 42 and tau in the brain increase with advancing age even in neurologically normal individuals, suggesting that the processes underlying protein aggregation are intrinsically linked to aging itself.^{170,171} LOAD represents a severe escalation of this continuum, with A β levels highest in LOAD, lowest in normal aging, and intermediate in a transitional state of "pathologic aging" (Figure 5).^{172,173} This progression prompts a critical question: is the transition from aging to LOAD a deterministic or stochastic process?

Evidence suggests it is not inevitable. The lower prevalence of LOAD among centenarians indicates that advanced age alone is insufficient to cause the disease.^{174,175} Instead, we propose that epigenetic dysregulation acts as the critical catalyst that decouples brain aging from chronological aging.^{36,176} Epigenetic mechanisms form a bridge between genetic risk, environmental exposures, and the aging-LOAD process. While many age-related epigenetic changes are universal, only a specific subset appears to be implicated in LOAD.¹⁷⁷⁻¹⁸⁰ This divergence positions LOAD not merely as "more aging," but as an epigenetic anomaly of aging—a state where the brain's adaptive capacity to manage age-related stressors becomes fundamentally compromised.

This synthesized framework, illustrated in the figure below, redefines LOAD as a disease of dysregulated resilience. It posits that the convergence of genetic susceptibility and environmental factors drives an aberrant epigenetic program, which in turn accelerates the hallmarks of brain aging, leading to the protein aggregation, synaptic failure, and neuronal loss characteristic of LOAD. LOAD as a manifestation of maladaptive aging (Figure 6 & Tables 2-3)?

CONCLUSION AND FUTURE DIRECTIONS

The evidence synthesized in this review compellingly argues that LOAD is not a distinct disease separate from aging, but rather a manifestation of maladaptive aging in the brain. The hallmarks of aging—mitochondrial dysfunction, chronic inflammation, cellular senescence, and genomic instability, among others—do not merely coincide with LOAD; they are its primary drivers. In this model, age-related physiological declines escalate into self-perpetuating, pathological cycles that drive A β and tau pathology, disrupt synaptic function, and exhaust the brain's regenerative capacity.

This leads us to propose the "Environment-Epigenetics-Aging-LOAD" axis

as a central framework for understanding the disease. In this paradigm:

(1) aging is the foundational process, gradually increasing systemic vulnerability;

(2) environment (encompassing diet, toxins, lifestyle, and gut microbiota) acts as a constant modulator;

(3) epigenetics serves as the critical interface, translating the cumulative burden of aging and environmental exposures into stable, maladaptive gene expression profiles that define the LOAD brain.

This framework explains why LOAD is so challenging to treat: it is a multi-system failure rooted in the core processes of aging itself. Consequently, the most promising therapeutic strategies are those that target these foundational drivers. "Anti-aging" approaches are not merely adjacent to LOAD treatment; they are central to it. This includes senolytics to clear senescent glial cells, interventions to enhance mitophagy and protein clearance, and strategies to counteract epigenetic silencing.

Looking forward, the field must prioritize several critical directions. First, research must move beyond single-pathway interventions and embrace combination therapies that target multiple hallmarks of aging simultaneously. Second, we must refine our clinical trial paradigms by moving away from poorly defined "healthy" elderly cohorts and instead develop richer, multi-dimensional biomarkers of biological—rather than just chronological—age. Finally, a greater emphasis on large-scale, longitudinal studies that integrate genetic, epigenetic, environmental, and lifestyle data is essential to fully elucidate the complex interactions within the "Environment-Epigenetics-Aging-LOAD" axis.

In conclusion, while the physiological process of aging is inevitable, its maladaptive expression as LOAD is not. By redefining LOAD as a disorder of accelerated brain aging, we shift the therapeutic paradigm from a singular pursuit of amyloid clearance to targeting the core mechanisms of aging itself. This opens the door to a new class of interventions—such as senolytics to clear dysfunctional cells, epigenetic therapies to reverse repressive chromatin states, and strategies to enhance mitochondrial resilience—aimed not just at symptoms, but at the root causes of the disease. The ultimate goal is to intervene in these maladaptive trajectories, thereby preserving cognitive function and achieving a longer healthspan.

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FUNDING AND ACKNOWLEDGMENTS

This work was supported by the Yunnan Fundamental Research Projects (grant NO. 202501AT070400 and 202501AT070397). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

All authors have read and reviewed the original draft and agreed to the published the present version of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

No new data were created or analyzed in this study.

SUPPLEMENTAL INFORMATION

It can be found online at <https://doi.org/10.59717/j.xinn-life.2026.100206>