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**Systematic Review**

# Multimodal mechanistic pathways in Alzheimer's disease: toward an integrated model of pathogenesis

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## ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by β-amyloid plaques, tau tangles, synaptic dysfunction, and large-scale network failure. While the amyloid cascade hypothesis has dominated, emerging evidence suggests distinct yet interacting amyloid and tau trajectories influenced by genetic, vascular, metabolic, and inflammatory factors. Understanding this multimodal convergence is key to redefining AD pathogenesis. Following PRISMA 2020 guidelines, mechanistic studies published from January 2016 to August 2025 were reviewed from pubmed and the cochrane library. Eligible studies provided original data on molecular, cellular, or systems-level mechanisms of AD. Findings were synthesized across seven domains: amyloid, tau, neuroinflammation, synaptic dysfunction, mitochondrial stress, metabolic dysregulation, and genetics. Across 22 studies, evidence supports a shift from a linear amyloid model to a multidimensional framework. Amyloid and tau initiate independently but later interact to accelerate degeneration. APOE ε4 carriers show amyloid-driven disease, while non-carriers exhibit tau-dominant progression, with females showing higher vulnerability. fMRI and DTI reveal early Default Mode Network and white matter disruption. Biomarkers (Aβ42, tau, NfL, neurogranin, SNAP25) detect early changes, while mitochondrial and glial dysfunction and vascular-metabolic stress further modulate progression. AD emerges from converging genetic, molecular, and network-level abnormalities. A multimodal approach integrating imaging, fluid biomarkers, and genetics offers promise for early detection, risk stratification, and personalized multi-target therapies.

**Keywords:** Alzheimer's disease, Amyloid, Tau, Synaptic dysfunction, Neuroinflammation, Pathogenesis

## INTRODUCTION

Alzheimer's disease (AD) is the leading cause of dementia worldwide and remains one of the most extensively studied neurodegenerative disorders. Historically, the diagnosis of AD relied primarily on clinical manifestations such as progressive memory impairment and cognitive decline. However, advances in biomarker research have led to a significant shift in how the disease is defined. Rather than viewing AD solely as a clinical syndrome, it is now increasingly recognized as a biological process characterized by the accumulation of β-amyloid plaques and tau pathology, which can be detected years before symptoms become apparent.[1]

Reflecting this evolving understanding, the 2024 Alzheimer's Association (AA) criteria define AD based on the presence of AD neuropathologic changes, particularly amyloid pathology, irrespective of an individual's clinical status.[2]

The defining pathological features of AD are extracellular β-amyloid plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein. The presence of both lesions remains fundamental to the diagnosis of the disease and distinguishes AD from other neurodegenerative conditions.[3] Although these pathological hallmarks have been central to AD research for decades, they do not fully explain the wide variation observed in disease onset, progression, and clinical presentation.

Understanding how AD develops remains a major challenge. While amyloid and tau pathology occupy a central role in current disease models, growing evidence suggests that several other biological processes contribute to disease progression. Neuroinflammation, oxidative stress, mitochondrial dysfunction, synaptic loss, metabolic disturbances, and genetic susceptibility have all been implicated in AD pathogenesis.[3,4] These processes are closely interconnected, making it difficult to determine where the disease begins and how individual mechanisms influence one another over time.

The concept of a single linear pathway leading to AD has therefore become increasingly difficult to support. Studies have shown that pathological changes can emerge in different sequences and to varying degrees among individuals, contributing to the heterogeneity that characterizes the disease.[5]

This variability highlights the limitations of examining individual mechanisms in isolation and emphasizes the need for a broader understanding of how multiple pathological processes interact throughout the course of AD.

Recent advances in genomics, transcriptomics, proteomics, metabolomics, neuroimaging, and biomarker research have provided new opportunities to study AD from a more integrated perspective. By combining information across these domains, researchers can better understand how molecular and cellular changes relate to one another and how they collectively contribute to disease progression. Such approaches may help identify key biological pathways that are not apparent when individual mechanisms are studied separately.

Given the multifactorial nature of AD, an integrated view of disease pathogenesis is increasingly necessary.[5] While amyloid and tau remain central to current models, evidence supporting the roles of neuroinflammation, vascular dysfunction, synaptic and white matter changes, and genetic regulation continues to grow.

This review examines these major mechanistic pathways and brings together findings from neuropathology, genetics, biomarkers, and neuroimaging to provide a comprehensive overview of the processes involved in the development and progression of AD.

## METHODS

### *Protocol*

This review was conducted following the PRISMA 2020 guidelines to ensure clarity, transparency, and reproducibility and the flow diagram has been shown in Figure 1. The protocol was not registered with PROSPERO, as the platform primarily focuses on systematic reviews of interventional studies, whereas our review synthesizes mechanistic and multimodal pathways in AD rather than clinical interventions.

The diagram depicts the structured workflow of study identification, screening, eligibility assessment, and final inclusion, conducted in accordance with the PRISMA guidelines.

### *Study selection criteria*

We considered original research articles exploring molecular, cellular, or systems-level mechanisms of AD. We included peer-reviewed studies which included original research studies providing mechanistic data on AD with emphasis on amyloid-β pathway, tau pathology, neuroinflammation/microglia, synaptic dysfunction, mitochondrial dysfunction and oxidative stress, metabolic/growth factor dysregulation and genetic pathways, human studies or experimental models relevant to AD, peer-reviewed articles published in scientific journals, studies reporting molecular, cellular, genetic, or biochemical mechanisms related to AD, articles published in English, studies with full-text availability, studies published within the defined time frame of the review and studies with sufficient methodological detail to allow assessment of outcomes.

Exclusion criteria included review articles, meta-analyses, editorials, letters, and commentaries, case reports or studies without original mechanistic data, studies involving subjects with mixed or unspecified forms of dementia without separate analysis of AD, clinical trials focusing solely on treatment efficacy without exploring mechanisms, studies not available in full text, non-English language publications, studies with incomplete methodology or poor reproducibility, experimental studies not relevant to AD pathogenesis.

### *Information sources and search*

A structured search was carried out in PubMed (January 2016–August 2025) and the Cochrane library (January 2020–August 2025). Search terms combined AD with keywords related to biomarkers, imaging, neuroinflammation, amyloid, tau, genetics, and treatment approaches. Filters restricted results to human studies, English-language publications, and specific study designs such as clinical trials and observational studies. Duplicate entries were removed before screening.

### *Screening and extraction*

Titles and abstracts were first screened by two reviewers, followed by full-text assessment based on the inclusion criteria. Any disagreements were resolved through discussion. Data extraction used a standardized form capturing study details (e.g., DOI, authors, year, design, population/model, methods, biomarkers assessed, mechanistic category, and outcomes).

### *Quality and bias assessment*

Risk of bias was evaluated with tools matched to study type: Newcastle-Ottawa scale (NOS), ARRIVE 2.0, AXIS, JBI checklist, Q-Genie and GWAS risk of bias tools. Scores are reported in supplementary Table 1.

### *Data synthesis*

Due to heterogeneity across study designs and measures, findings were narratively synthesized and grouped by mechanistic category: amyloid, tau, neuroinflammation/ microglia, synaptic dysfunction, mitochondrial stress, metabolic/growth factor pathways, and genetic contributions.

Within each category, the direction and strength of evidence were summarized.

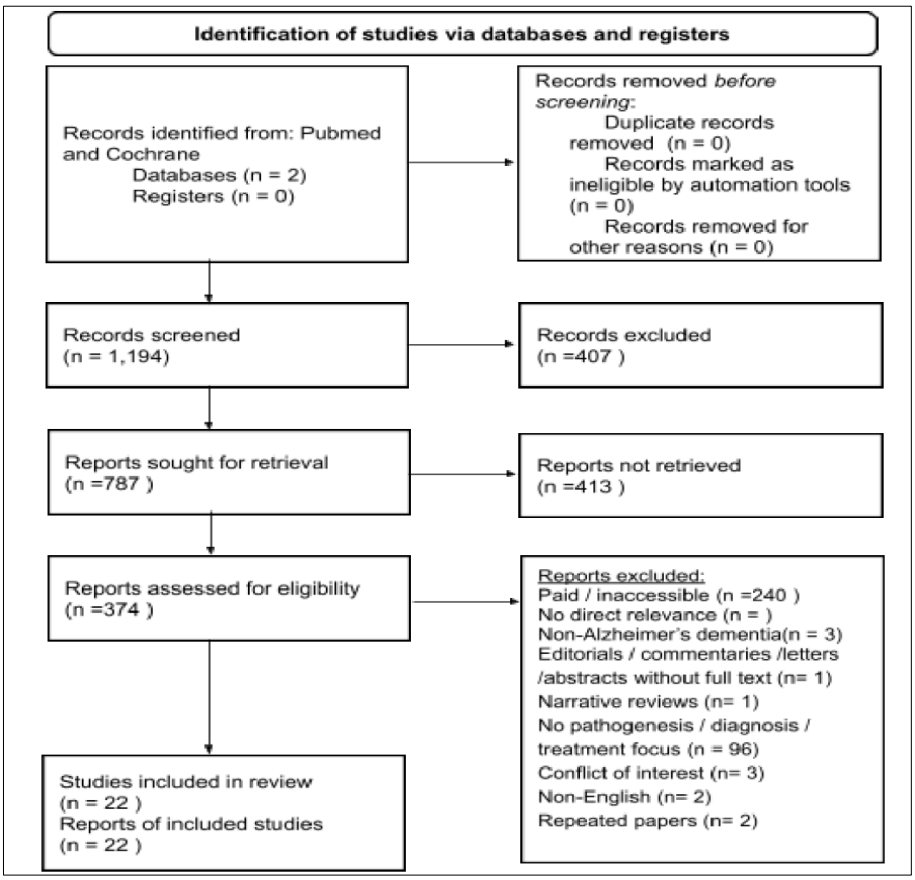


**Figure 1: PRISMA-based study selection process for the systematic review.**

**Table 1: Characteristics and qualitative assessment of the 22 studies included in this systematic review, including reference number, year of publication, principal findings, and the Alzheimer's disease pathways discussed.**

| Reference number | Year | Quality assessment | Key findings | Pathways discussed |
|---|---|---|---|---|
| **1** | 2023 | NOS 8/9, high quality | Amyloid-first versus tau-first subtypes, APOE ε4 and education influence, independent then interacting amyloid/tau spread | Amyloid-β pathway, tau pathology, genetic pathways |
| **2** | 2024 | NOS 9/9, high quality | Biomarkers diverge decades before AD: amyloid → tau → neurodegeneration → cognition; hippocampal atrophy early, cognitive decline late, APOE ε4 enriched; enables preclinical detection | Amyloid-β pathway |

Continued.

| Reference number | Year | Quality assessment | Key findings | Pathways discussed |
|---|---|---|---|---|
| **3** | 2020 | AXIS 15/20, moderate quality | DMN functional failure, striatal hyperconnectivity drives Aβ spread, network changes correlate with cognition, seed volumes correlate with cognition | Genetic pathways, synaptic dysfunction, amyloid-β pathway, tau pathology |
| **4** | 2019 | NOS 6/9, moderate quality | CSF biomarkers predict white matter integrity and progression in at-risk adults | Neuroinflammation, synaptic dysfunction, amyloid-β pathway, tau pathology |
| **5** | 2020 | NOS 7/9, moderate quality | Amyloid+ tau+ normal+ linked to earlier onset, high P-tau/T-tau predicted faster cognitive and IADL decline especially in APOE ε4 carriers, Aβ42 and ChEI response not predictive | Tau pathology, genetic pathways |
| **6** | 2018 | AXIS 14/20, moderate quality | DMN functional failure, striatal hyperconnectivity drives Aβ spread, network changes correlate with cognition | Amyloid-β pathway, tau pathology, synaptic dysfunction |
| **7** | 2020 | AXIS 15/20, moderate quality | Female APOE ε4 carriers show higher tau and regional atrophy despite, indicating sex-specific vulnerability and tau-driven degeneration | Tau pathology, genetic pathways, mitochondrial dysfunction, neuroinflammation |
| **8** | 2021 | NOS 9/9, high quality | Age and baseline cognition are main predictors, tau predicts earlier AD onset/death but not nursing home placement (NHP) or survival | Amyloid-β pathway**,** tau pathology, genetic pathways |
| **9** | 2024 | AXIS 18/20, high quality | Tau rises earlier, subcortical in DS, fusiform/medial temporal in ADAD, APOE ε4 higher in ADAD | Amyloid-β pathway, tau pathology, neuroinflammation/microglia, mitochondrial dysfunction and oxidative stress, metabolic/growth factor dysregulation, genetic pathways |
| **10** | 2018 | NOS 3/9, low quality | let-7b and let-7e elevated in AD CSF, packaged in extracellular vesicles, induce TLR7-mediated neurotoxicity; may serve as biomarkers | Neuroinflammation/microglia , synaptic dysfunction |
| **11** | 2018 | ARRIVE 2.0-, high quality | Showed oligodendrocyte DNA damage and senescence causing myelination loss and white matter deficits | Mitochondrial dysfunction, genetic pathways, neuroinflammation/microglia |
| **12** | 2020 | NOS 3/9-, low quality | AD and delirium CSF showed overlapping synapse/microglia protein elevations; AD had tau-specific, delirium had inflammatory changes | Amyloid-β pathway, neuroinflammation/microglia, synaptic dysfunction |
| **13** | 2025 | JBI checklist-moderate | SNAP-25 (CSF/plasma) and VAMP-2 (CSF) are elevated early in AD, specific to AD-related synaptic dysfunction; link amyloid/tau pathology to neuronal degeneration | Synaptic dysfunction |
| **14** | 2022 | NOS 9/9-, high quality | Higher IGF-1 linked to larger hippocampi and fewer white matter hyperintensities; benefits were reduced with high CRP, suggesting inflammation moderates its effect | Metabolic/growth factor dysregulation |
| **15** | 2020 | Q-Genie assessment: 59/77, high quality | AD is driven by microglial and endolysosomal dysfunction, with genetic variants affecting phagocytosis and protein clearance | Amyloid-β pathway, neuroinflammation/microglia, genetic pathways |
| **16** | 2020 | NOS 9/9-, high quality | Baseline tau-PET predicts future cortical atrophy and clinical decline in AD, with variant-specific patterns; amyloid-PET shows weak predictive value | Tau pathology |
| **17** | 2024 | AXIS 18/20-, high quality | Tau-related cognitive decline occurs mainly in women, showing greater vulnerability in preclinical Alzheimer's disease | Tau pathology, genetic pathways |

Continued.

| Reference number | Year | Quality assessment | Key findings | Pathways discussed |
|---|---|---|---|---|
| **18** | 2022 | NOS 9/9-, high quality | Soluble TREM2 rises early; protects against amyloid/tau pathology, slows atrophy and cognitive decline; potential AD biomarker/therapeutic target | Neuroinflammation/microglia, amyloid-β pathway, tau pathology, genetic pathways |
| **19** | 2021 | NOS 8/9-, high quality | Hippocampal subfields, especially the presubiculum, show accelerated atrophy from normal aging to AD; correlates with memory/attention decline, CSF tau levels, and earlier AD onset | Tau pathology, amyloid-β pathway, synaptic dysfunction |
| **20** | 2024 | Q-Genie assessment: 62/77, high quality | APOE ε4 drives AD risk; shared and novel loci confirmed; GRS predicts AD, influenced by ancestry | Genetic pathways, metabolic/growth factor dysregulation |
| **21** | 2022 | NOS 8/9-, high quality | β-amyloid patterns vary by variant, with PET and CSF measures often discordant | Amyloid-β pathway, genetic pathways |
| **22** | 2021 | ARRIVE 2.0-, high quality | Aβ accelerates tau spread from the medial temporal lobe into cortex via brain networks, acting as a catalyst for AD progression | Metabolic/growth factor dysregulation |

APOE: apolipoprotein e; ε4 allele is associated with higher ad risk; β-amyloid (Aβ), a peptide that aggregates extracellularly forming plaques in AD; DMN: default mode network; functional failure refers to impaired activity or connectivity within the brain's default mode network, which is involved in self-referential thinking, memory processing, and internal mental states; IADL=instrumental activities of daily living, referring to complex everyday tasks such as managing finances, medications, shopping, meal preparation, and transportation; ChEI=cholinesterase inhibitor, a class of drugs used to improve cognitive symptoms in patients with Alzheimer's disease and other dementias; LET-7 (leukemia-associated transcript 7 microRNA family): a conserved family of microRNAs involved in regulating cell differentiation, proliferation, and immune signaling; in the CNS, extracellular LET-7 can act as a danger-associated molecular pattern (DAMP); TLR7 (toll-like receptor 7): a pattern recognition receptor expressed in immune and neural cells, recognizing single-stranded RNA (ssRNA) and mediating innate immune responses; aberrant activation contributes to neuroinflammation and neurotoxicity; GWAS (genome-wide association studies): a study approach examining genetic variants across the genome to identify associations with traits or diseases; Newcastle-Ottawa scale (NOS): tool for assessing quality and risk of bias in observational cohort and case-control studies; ARRIVE 2.0 (animal research: reporting of in vivo experiments): guidelines for transparent reporting of animal research; AXIS (appraisal tool for cross-sectional studies): designed to evaluate quality and bias in cross-sectional research; JBI checklist (Joanna Briggs Institute): critical appraisal tools tailored to different study types, here applied for biomarker studies; Q-Genie (quality of genetic studies): tool to evaluate methodological quality of genetic association studies

## RESULTS

### *Amyloid and tau pathways*

Evidence from the reviewed studies challenges the classical "linear amyloid cascade" model. Instead, findings suggest a multifactorial framework where Aβ and tau can follow distinct trajectories. Aksman et al reported diverging pathways (amyloid-first versus tau-first), influenced by APOE genotype and moderated by educational background.[1] Jia et al demonstrated that amyloid abnormalities often appear up to 20 years before symptom onset, followed by tau changes about a decade later and then measurable neurodegeneration.[2] Wattmo and colleagues further highlighted tau burden, not amyloid, as the best predictor of disease acceleration and survival outcomes, especially among APOE ε4 carriers.[5,8]

### *Network dysfunction linking proteinopathy to connectivity failure*

Changes at the brain network level emerged as a critical mediator of disease progression. Functional imaging revealed that the default mode network (DMN) deteriorates early, with some compensatory activity paradoxically hastening pathology. Chang et al. observed that breakdown in connectivity networks facilitated faster spread of amyloid and tau, while Rabipour et al showed that APOE ε4 carriers already demonstrate altered memory-related functional networks before symptoms develop.[2,3] Tse et al confirmed that DMN disruption in mild cognitive impairment corresponds to cognitive decline, underscoring connectivity failure as a central mechanism.[11]

### *Neuroinflammation and glial activity*

Several studies reinforced inflammation as an active driver rather than a secondary process. Racine et al linked white matter degeneration to both traditional CSF biomarkers and markers of inflammation like YKL-40.[4] Peters van Ton et al showed overlap between inflammatory processes in delirium and AD, suggesting shared vulnerability pathways.[12]

Mechanistically, Derkow et al demonstrated that extracellular vesicle–associated microRNAs, such as LET-7, trigger TLR7-mediated toxicity.[10] Collectively, these findings highlight microglial and astroglial dysfunction as major contributors to progression.[15]

***Genetic background and sex differences***

Genetic predisposition and sex influenced disease course. Yan et al found that female APOE ε4 carriers had greater tau buildup and atrophy despite preserved cognition, hinting at resilience mechanisms.[7] Wisch, Chhatwal, and others noted that autosomal dominant and Down syndrome cases follow distinct biomarker trajectories, marked by rapid tau accumulation and subcortical involvement.[9,21] These results emphasize the heterogeneity of AD across genetic backgrounds.

***Synaptic dysfunction***

Synaptic decline was consistently identified as central to pathology. Racine et al. observed neurogranin levels tracking with early white matter changes.[4] Gaetani et al validated synaptic proteins such as SNAP25 and VAMP2 as novel fluid biomarkers.[13] Morenas-Rodríguez et al argued that these markers improve diagnostic precision in atypical or early cases beyond traditional Aβ and tau assays.[19]

***Mitochondrial and oligodendrocyte dysfunction***

Emerging pathways broaden the model of AD. Tse et al reported that DNA damage in oligodendrocytes leads to senescence and white matter loss prior to amyloid deposition.[11] Yan et al associated mitochondrial dysfunction with accelerated tau pathology in female APOE4 carriers.[7] These findings suggest that metabolic stress and glial aging are integral to disease progression.

***Integrated model***

Across 22 studies, the evidence supports a shift from a single amyloid-driven pathway to a multidimensional model. Amyloid changes occur first, but tau and synaptic dysfunction are stronger predictors of decline. Genetic variation, sex, and inflammatory processes shape disease trajectory. This integrated framework suggests that personalized, multimodal interventions guided by biomarkers and genetic risk are more likely to be effective.[1–22]

## DISCUSSION

Historically, the pathogenesis of AD has been primarily explained by the amyloid cascade hypothesis, which states that abnormal production and aggregation of Aβ protein initiate a cascade leading to neurodegeneration, including the formation of extracellular amyloid plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein. This model has dominated research for decades, but its limitations have become apparent, as it does not fully account for the complexity of AD or consistently translate into effective therapies.[1,5,7,9]

Over time, additional hypotheses have emerged, including the neuroinflammation hypothesis, which highlights the role of activated microglia and chronic inflammation in driving disease progression, and the infectious hypothesis, which suggests that pathogens may trigger or exacerbate AD pathology, with Aβ acting as an antimicrobial peptide.[1,3,4,6,8,10]

Other models incorporate genetic, vascular, and environmental factors, recognizing that AD is a multifactorial disorder with contributions from immune dysfunction, metabolic changes, and possibly infectious agents.[5,7-9]

The pathogenesis of AD represents a multifactorial cascade, beginning with a convergence of genetic, biological, and environmental risk factors. Genetic predisposition, including APOE ε4 and rare mutations in APP and PSEN1/2, sets the stage for early proteinopathy, while sex differences, particularly female vulnerability, modulate disease trajectory.[7] Age remains the most significant non-modifiable risk factor, and vascular and metabolic conditions such as hypertension, diabetes, and obesity, further exacerbate neuronal vulnerability. Lifestyle and environmental factors, including diet, physical activity, and cognitive engagement, interact with these intrinsic risks to influence disease onset and progression.[8,12]

At the molecular and cellular level, these risk factors precipitate a series of pathogenic processes. Aβ accumulation leads to extracellular plaque formation, while hyperphosphorylated tau aggregates into intracellular neurofibrillary tangles, together driving synaptic dysfunction and neurotransmission deficits. Concurrently, neuroinflammation, mediated by dysregulated microglia and astrocytes, amplifies neuronal injury and contributes to network destabilization.[4,10,12,15] Mitochondrial and metabolic dysfunction further compound oxidative stress and energy deficits, creating a milieu conducive to progressive neurodegeneration.[7,11]

These cellular alterations culminate in network-level dysfunction. Breakdown of intrinsic connectivity networks (ICNs), particularly DMN, impairs coordinated brain activity, while degeneration of white matter tracts including the cingulum, corpus callosum, and temporal lobe pathways disrupts structural connectivity. Functional MRI studies reveal altered connectivity patterns that precede overt cognitive symptoms, highlighting the early network-level impact of molecular pathology.[3,6,11]

Integration of biomarker data provides a window into these processes before clinical manifestations arise. Cerebrospinal fluid (CSF) markers, such as reduced Aβ42 and elevated p-tau, total tau, and neurofilament light chain, alongside PET imaging and fluid biomarkers like neurogranin, SNAP25, and VAMP2, enable detection of preclinical changes.[13] Cognitive and digital assessments

complement these measures, capturing subtle functional decline.

Clinically, the disease progresses through distinct stages: a preclinical phase with molecular abnormalities, mild cognitive impairment (MCI) characterized by subtle deficits, and AD dementia marked by significant cognitive and functional impairment. The rate of decline and prognosis are influenced by genetic factors, sex, systemic and metabolic health, and the resilience of synaptic and network architecture. Understanding this complex interplay opens avenues for personalized interventions, emphasizing combination therapies targeting multiple mechanistic pathways rather than single-pathway approaches.

In summary, Figure 2 shows the framework of AD as a multidimensional disease. By linking risk factors to molecular events, network dysfunction, and clinical outcomes, it highlights opportunities for early detection, risk stratification, and targeted intervention, ultimately supporting a more precise and personalized approach to disease management.

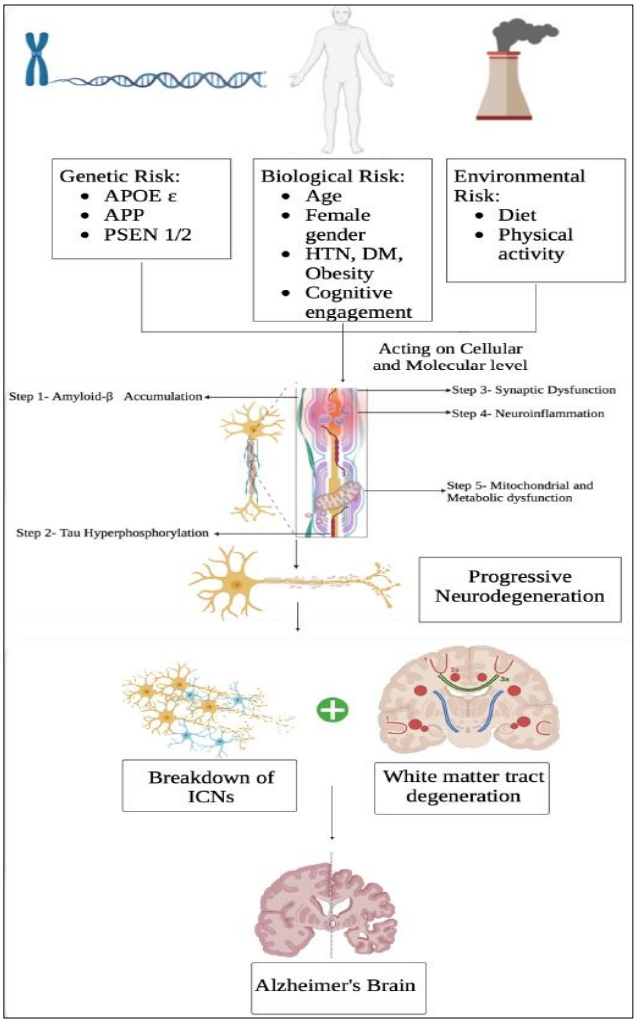


**Figure 2: Multimodal mechanistic pathway of Alzheimer's disease pathogenesis.**

## CONCLUSION

Our findings highlight that AD pathogenesis cannot be fully explained by a single pathway. Alterations in intrinsic connectivity networks, Aβ deposition patterns, tau spread, and other molecular and cellular factors, together with risk factors, collectively contribute to disease progression. This supports the concept of a multimodal pathogenesis, emphasizing the interplay between network dysfunction, proteinopathies, and neuroinflammatory processes.

Future research should focus on integrated, multimodal assessments combining neuroimaging, molecular biomarkers, genetic study and functional network analysis to better predict disease trajectory. Additionally, potential interventions targeting multiple pathogenic pathways simultaneously such as combination therapies addressing amyloid, tau, and network dysfunction may hold greater promise than single-target approaches. Recognizing and addressing the complex, multifactorial nature of AD is crucial for developing effective therapeutic strategies.

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