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Alzheimer's Disease (AD): Environmental Modifiable Risk Factors

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Abstract:

Introduction: Alzheimer's disease (AD) is a pervasive, complex and heterogeneous neurodegenerative disorder characterized by progressive cognitive decline, and the accumulation of amyloid plaques and neurofibrillary tangles. Despite extensive research, its multifactorial etiology, involving both genetic and environmental components, remains complex and not fully understood.

Objectives: This study aims to explore the interaction between genetic predispositions and non-genetic risk factors in the development of AD. It seeks to identify key modifiable risk factors and evaluate their impact on disease onset and progression, while emphasizing the importance of a multidisciplinary approach in understanding and mitigating AD.

Materials and Methods: A comprehensive literature review was conducted using databases such as PubMed, ScienceDirect, and Google Scholar. The study focused on analyzing review articles, meta-analyses, original and clinical studies relevant to AD's risk factors. Data were synthesized to identify significant patterns and interactions affecting AD onset and progression.

Results and Discussion: Genetic factors, including mutations in APP, PSEN1, and PSEN2, and allelic variants such as APOE4, contribute significantly to AD risk. Non-genetic factors, including advanced age, female sex, harmful behaviors (e.g., smoking, chronic alcoholism), chronic stress, exposure to solvents and pesticides, and associated diseases (e.g., obesity, diabetes, traumatic brain injury, hypertension, hypercholesterolemia), also play crucial roles. The study highlights the interaction between these factors, noting that while genetic predispositions establish a baseline risk, environmental and behavioral influences can modulate the disease's onset and progression.

Conclusion: Understanding the multifactorial nature of AD requires addressing both genetic and modifiable risk factors. Effective management and prevention strategies should focus on reducing exposure to harmful environmental factors and modifying lifestyle behaviors. Enhancing public awareness and implementing preventive measures are critical for mitigating the impact of AD and improving patient outcomes. Further research is essential for developing targeted therapies and preventive strategies.

Keywords: neurodegenerative conditions, Alzheimer's disease, environmental risk factors, multifactorial disorders

Introduction

General Overview – Multifactorial Diseases and the Interaction between Environment and Heredity

Situated within the extensive spectrum of neurodegenerative disorders, Alzheimer's disease (AD), first described in 1906 by the renowned psychiatrist and pathologist Alois Alzheimer as a "disease of forgetting," is recognized for its heterogeneity, diversity of hypotheses surrounding its etiology, and

numerous genetic mutations, epigenetic modifications, and biochemical alterations. The disease progresses irreversibly from early stages characterized by deficits in information storage and encoding to advanced phases marked by progressive functional, cognitive, and behavioral decline. The eponymous condition, AD, is initially detected through short-term memory impairment, progressive decline, and deterioration in reasoning, memory, and visual perception. As the disease progresses to moderate or severe stages, additional symptoms may emerge, including agitation, anxiety, apathy, delusional ideas, irritability, depressive states, delirium, hallucinations, and insomnia. AD is unequivocally characterized by a broad etiology, cerebral atrophy associated with mitochondrial dysfunction, neurotrophin depletion, and the accumulation of senile plaques and intraneuronal neurofibrillary tangles. These pathological features are linked to autosomal-dominant mendelian mutations (APP on chromosome 21, PSEN1 on chromosome 14, PSEN2 on chromosome 1), rare autosomal-recessive mutations (in the conducted studies, a mutation specifically identified as A673V was found in the APP gene, associated with this mode of inheritance in descendants) or the presence of specific allelic variants (APOE4, MAPT, APOJ, SORT1). [1–6]

AD is regarded as a conformational neurodegenerative disorder primarily characterized by protein abnormalities (misfolded proteins - structure is altered). The disease is influenced by genetic factors as well as non-genetic factors including physiological, biological, demographic, behavioral, pathological, and environmental elements. The principal cause of the disorder is the aberrant polymerization and processing of normally soluble proteins. [7]

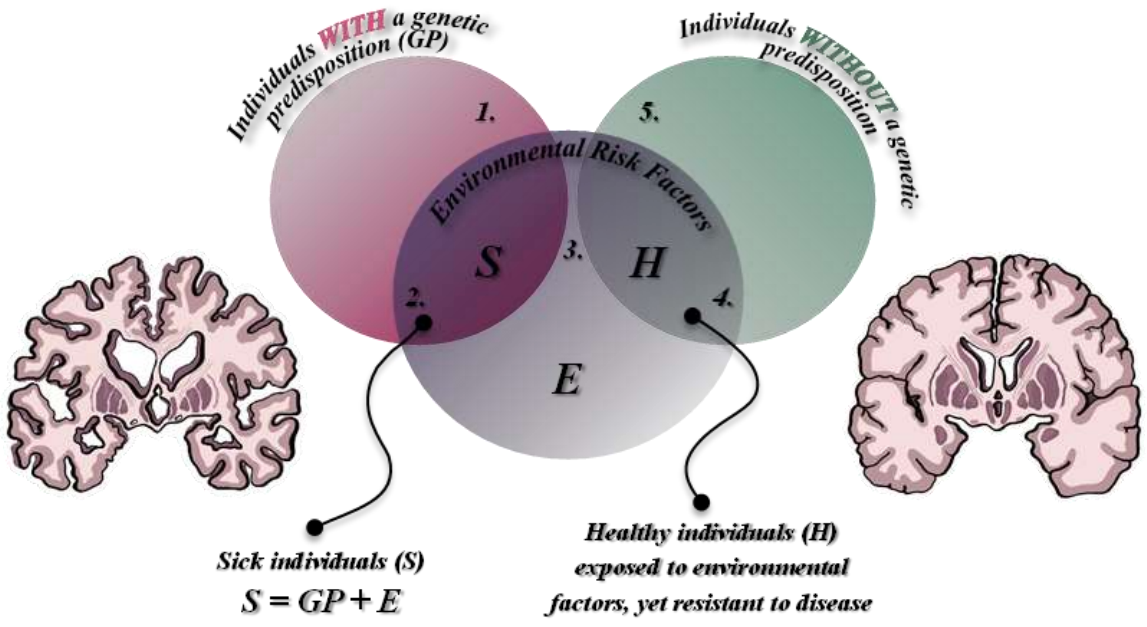

Figure 1. Interaction of Heredity and Environment in the Determinism of Multifactorial Diseases; S=Sick individual; H=Healthy individual; E=Environmental risk factors; GP=Genetic predisposition; 1=Individuals with genetic predisposition to Alzheimer's disease (GP); 2=Individuals diagnosed with Alzheimer's disease, affected by the interplay of environmental and hereditary factors; 3=Environmental factors exposure; 4=Healthy individuals exposed to environmental risk factors but resistant to disease; 5=Individuals without genetic predisposition;

Characterized as a polygenic, neurodegenerative, multifactorial disease, AD arises under the influence of both genetic and non-genetic factors, including physiological, behavioral, demographic, environmental, and pathological risk factors. Multifactorial conditions manifest within human organisms—unique biological entities—as a result of interactions between heredity and environment, or sometimes due to one alone (Figure 1). In these rare and exceptional cases, genes may exhibit a monogenic determinism, being transmitted through maternal or paternal autosomal-dominant mendelian inheritance (e.g., APP on chromosome 21, PSEN1 on chromosome 14, PSEN2 on chromosome 1) or autosomal-recessive inheritance (e.g., APP - A673V).

The environment plays a pivotal role in modulating, shaping the expression of the genetic makeup (predispositions), influencing both the onset of AD and the age at which symptoms first appear. Meanwhile, heredity is associated with the degree of risk, reflecting an individual's susceptibility to being diagnosed with AD (typically between the fifth and tenth decade of life) or another related, investigated condition throughout their lifetime.

It is observed that the transition from a state of vulnerability (hereditarily transmitted susceptibility) to an actual disease occurs as a result of the continuous interaction between two major classes of factors. The disease becomes the outcome of a complex, bilateral interaction. An essential aspect of the determinism process is that, to induce a disease, environmental factors must surpass a certain threshold of activation (exceed a triggering threshold), which varies according to the specific condition and the individual organism.[8–12]

The mechanisms of interdependence between genetic and non-genetic factors thus provide additional explanations regarding patients with intact health. Human entities with hereditary genetic predispositions can maintain their state of health in the absence of environmental factors with triggering potential. Similarly, the preservation of intact health can also be observed in patients exposed to harmful environmental risk factors, who, unlike the previously described individuals, possess a heightened level of genetic resistance.

Research focusing on the heritability of AD has revealed that genetic factors contribute between 60% and 80% to its onset, whereas environmental factors account for only 20% to 40% of the risk in shaping an individual's likelihood of developing the condition.[4,13]

Epidemiology of Alzheimer's Disease

With the ongoing global aging of the population, reflected in increased life expectancy, scientific research has increasingly focused on identifying the factors that lead to the onset of AD, as well as understanding its mechanisms and exploring potential treatments. The rising incidence and mortality rates associated with AD support these efforts and underscore the need for continued investigation and intervention.[14,15]

AD is a major global health concern, characterized by its high prevalence and significant impact on affected individuals and healthcare systems. Epidemiological studies provide crucial insights into the distribution, determinants, and patterns of this neurodegenerative disorder. AD is the most common form of dementia (50-70%), affecting a large number of individuals (millions of people) worldwide. Prevalence rates increase with age, with a substantial rise in the number of cases among individuals aged 65 and older. The incidence of AD also escalates with advancing age, and it is projected to rise significantly as the global population ages.

According to data from the Global Burden of Disease (GBD) database over a 30-year period (from 1990 to 2019), the incidence of AD increased by approximately 147.95%, rising from 2.92 million new cases

in 1990 to 7.24 million new cases in 2019. During the same period, prevalence (which includes all existing cases, not just new ones) rose by 160.84%. It was reported that in 1990, only 20.3 million people were diagnosed with AD and other dementias. By 2016, this number had increased to 43.8 million, with projections suggesting that by 2050, nearly 131 to 152 million people will be diagnosed with these chronic neurological conditions. [7,16–18]

According to current statistics published by the World Health Organization (WHO), the number of individuals diagnosed with dementias of various etiologies has exceeded 55 million globally. Of these, 60% are from countries with low and middle incomes. Furthermore, an additional 10 million cases are diagnosed annually, which equates to one new case every 3.2 seconds. [19]

The neurodegenerative disorder AD, the most prevalent chronic neurological condition with specific manifestations included in the spectrum of dementia syndromes, affects approximately 60-70% of the aforementioned population. This corresponds to an estimated 33 to 38.5 million cases worldwide.

This condition causes significant issues, becoming one of the foremost debilitating diseases affecting individuals. It affects cognitive, neurological, and motor functions, leading to a complete loss of independence for patients. Moreover, AD is ranked as the seventh leading cause of global mortality, with approximately 1.6 million deaths, and the second leading cause in high-income developed countries, with around 814,000 deaths, according to reports published in 2019. Analysis of published data over the years reveals a persistent increase in mortality rates. The number of deaths recorded in 2019 (1.6 million) is approximately 2.73 times higher than that reported in 2000 (584,000). Consequently, AD has advanced rapidly, climbing 13 positions in the global ranking of causes of death. In both Europe (497,000 deaths in 2019) and the Americas (390,000 deaths in 2019), the statistics underscore a concerning reality, with Alzheimer's disease being the third leading cause of death annually. The mortality rate and prevalence have increased exponentially over time. Although in 2000 the Americas had 44,000 fewer deaths caused by Alzheimer's disease compared to Europe, both incidence, prevalence, and mortality rates have increased. By 2010, the totals had grown to approximately equal values: 263,000 cases in the Americas and 270,000 in Europe. Over the following 9 to 10 years, the number of diagnosed patients in Europe increased, with deaths nearly doubling (1.84 times higher than in 2010), whereas in the Americas, deaths rose by 1.7 times. As a result, by the end of this period, Europe experienced a difference of 107,000 deaths from AD compared to the Americas, a figure 2.43 times higher than recorded 19 to 20 years earlier.[14–18,20–27]

In Romania, data from European Union reports for 2023 indicate that only 0.8% of deaths were attributed to Alzheimer's disease (AD) and other forms of dementia, equivalent to 2,361 patients out of a total of 295,232 deaths that year. However, incidence, prevalence, and mortality rates specific to this country are not well-documented, with no conclusive statistics or comprehensive data monitoring programs available across all counties. It is estimated that approximately 35,000 individuals with a confirmed diagnosis of AD are registered in medical records. Nevertheless, the Romanian Alzheimer Society estimates that over 80% of those affected by neurodegenerative processes specific to this disease remain undiagnosed (even among patients receiving treatment and evaluation in hospitals, a significant number were diagnosed with unspecified dementias due to the absence of thorough investigations necessary for differential diagnosis).

Motivation and Objectives

The assertion by French military surgeon Ambroise Paré, "There are no diseases, only patients" (as cited by Conf. MD. Covic M., 1981), along with the awareness of the profound impact of Alzheimer's disease

on individuals, has fostered a desire to delve deeper into its study. This includes investigating potential triggering mechanisms, the role of the immune system, changes in the nervous system, genetic variations, mutations, and their variability across populations. Addressing this intricate pathology requires a multidisciplinary approach.

The aim of the conducted study was to identify non-genetic, modifiable risk factors—demographic, physiological, pathological, behavioral, and environmental—that significantly impact the health of people and contribute, alongside genetic predispositions, to the initiation of neurodegenerative processes specific to AD.

The aspiration to engage in future research, driven by a desire to pursue the path of empirical scientific knowledge, coupled with the awareness that "nothing in life is to be feared, it is only to be understood," and that now is the opportune time "to understand more, so that we may fear less," as the renowned Polish scientist and Nobel laureate Marie Curie once stated, has guided the development of this work. shaped the creation of this work.

This study involved a thorough analysis of the relevant, specialized literature, reviewing, synthesizing data and findings published in scientific articles, and distilling the essential insights drawn from these sources.

Materials and Methods

The conducted study involved a preliminary stage of reviewing specialized literature, following the format of an academic "literature review" article. The methodology consisted of analyzing previously conducted and published studies and research. The information synthesized and condensed in this study was selected from materials obtained from university library collections and from databases, search engines such as PubMed included in MEDLINE, ScienceDirect, and Google Scholar. The inclusion criteria were represented by the type of analyzed material (books, documents, review articles, systematic reviews, meta-analyses, original or clinical studies) and the year of publication, with the search being conducted using phrases or keywords like "Alzheimer's disease," "environmental factors," or "modifiable risk factors," utilizing filters.

Results and Discussion

Alzheimer's disease (AD) is characterized by a complex, vast etiology that can be influenced by both genetic and environmental factors. Genetically, mutations on chromosomes 14, 1, 19, and 21 are significant, with many cases following an autosomal-dominant inheritance pattern. Specifically, mutations on chromosomes 21, 14, and 1 are often linked to a monogenic mode of transmission. In addition to genetic predispositions, exposure to harmful substances such as aluminum, pesticides, and organic compounds, as well as infectious agents like the herpes virus and slow viruses, can contribute to the development of AD. Traumatic brain injuries, cerebrovascular amyloidosis, and vascular incidents in mixed dementia cases are also recognized as contributing factors. The pathological mechanisms of AD include acute-phase inflammatory responses, the formation of amyloid plaques, and the accumulation of neurofibrillary tangles composed of tau proteins. A critical aspect of AD is the significant, pronounced neurochemical cholinergic deficit, marked by reduced levels of acetylcholinesterase and acetylcholine. Structural and functional impairments in mitochondria—key organelles for oxidative phosphorylation and energy production—due to neurofibrillary accumulations, metabolic disruptions, the proliferation of apolipoprotein E4, and imbalances in neurotransmitters like noradrenaline, dopamine, and serotonin further contribute to the initiation and progression of neurodegenerative processes characteristic of AD. [5,6,28]

There is a broad spectrum of environmental risk factors with a high potential to induce neurodegenerative processes. Environmental factors thus play a fundamental role in the etiology of AD, influencing both early-onset (EOAD) and late-onset (LOAD) forms of the condition. These factors contribute to the manifestation and triggering of genetic predispositions, as well as to the reduction of the age at onset, accounting for 20-40% of the risk, according to previously presented data (heritability in LOAD ranges between 60%, 70%, and 80%). A diverse range of non-genetic factors derived from the environment—including occupational conditions (such as exposure to aluminum, pesticides, and organic substances), harmful personal behaviors and habits (chronic alcoholism, nicotine addiction), and unforeseen, adverse incidents (chronic intoxications, carbon monoxide poisoning, and exposure to heavy metals), as well as infectious agents and associated diseases—can contribute to the onset of dementia symptoms, particularly those characteristic of AD.

- **Demographic and Physiological Risk Factors**

Advanced age, female sex, and a low level of formal education, which imply a reduced number of interneuronal connections and a limited cognitive reserve, contribute to an increased risk of developing AD. [29]

Gender

One significant physiological risk factor is female sex, particularly among patients in their eighth or ninth decade of life. This aspect has been highlighted both statistically (with 60-70% of Alzheimer's disease cases being female) and pathologically. Although β-amyloid accumulations are quantitatively similar in both sexes, women exhibit a higher percentage of TAU proteins. [19,30]

Moreover, statistical data reinforce the hypothesis that female sex is a significant physiological risk factor for AD. This condition, along with multiple forms of dementia, rank as the fifth leading cause of death annually, with approximately 1.1 million women succumbing to these diseases and their related complications each year. [14,15]

Statistics published in 2023 by the Alzheimer's Association in the United States indicate that approximately 6.7 million Americans aged 65 and older have been diagnosed with various forms of dementia, with 60-70% of these cases being AD, predominantly of the late-onset type. This data suggests that 1 in 9 individuals over this age is affected by this neurodegenerative disorder. The gender disparity observed in these statistics underscores that AD predominantly affects women, with only one-third of the diagnosed cases being male, while the remaining 4.1 million cases are female. [21–27,31]

Age

It is well-established that the prevalence of AD increases with advancing age. The percentage of individuals diagnosed with AD ranges from 5-10% among those aged 60 to 69 years in developed countries, exceeding 25% for those who experience onset after the age of 70.

The consideration of age as a physiological risk factor is supported by 2016 statistics from the United States published in the DSM-V-TR, which indicated that approximately 5.4 million individuals were diagnosed with AD. Of these, around 200,000 were diagnosed before the age of 65, corresponding to 3.7% of the total. Among patients with dementia, only 11% were diagnosed with AD after the age of 65, with 32% of these individuals being over 85 years old and 81% over 75 years old. This data highlights a progressive increase in the incidence rate of AD up to the mid-ninth decade of life, followed by a subsequent decline in the percentage of diagnoses.[32–34]

Origin

Ethnoracial origin is recognized as a significant risk factor for AD. In 2016, the prevalence of AD diagnosis varied significantly based on racial and ethnic background. Specifically, rates ranged from 3.5% to 14.4% of the total dementia cases in the United States, depending on factors such as race, age, comorbidities, associated diseases, and the methodologies used in studies. The highest prevalence rates were observed among individuals of Caribbean Latino descent and African Americans. [32–34]

- **Behavioral, Physiological, and Environmental Risk Factors**

The risk of developing AD is also elevated in individuals who engage in harmful behaviors that compromise their overall health, such as chronic alcoholism and smoking.

Alcohol and Nicotine

In individuals diagnosed with AD, there is a notable presence of cholinergic deficits in the brain, attributed to reductions in acetylcholine and acetylcholinesterase, as well as, in some instances, a decrease in specific nicotinic receptors for acetylcholine. Conversely, smoking induces an upregulation of nicotinic receptors and an enhancement of cholinergic metabolism. Although nicotine can stimulate the release of acetylcholine and increases the number of nicotinic receptors, oxidative stress, free radicals, altered inflammatory immune responses, and activation of phagocytes contribute to exacerbated oxidative and degenerative effects. [35–37]

Solvents and Pesticides

In the etiopathology of AD, it is well established that factors such as organic solvents (benzene, toluene), organophosphorus pesticides, and exposure to aluminum have detrimental effects on the central nervous system and trigger neurodegenerative processes. [36]

Metals

Recent studies suggest that a variety of metals may contribute to the pathogenesis of AD both through interactions with other types of metals and the disruption of cellular homeostasis, leading to multiple imbalances. Aluminum, however, remains the most extensively investigated risk factor, having been shown to elevate mortality rates associated with AD among those exposed over prolonged periods, such as miners inhaling aluminum particles, dust. Additionally, metals such as mercury, zinc, copper, cadmium, magnesium, and manganese have been included in this risk category. Furthermore, the additive effects of these metals contribute synergistically: lead, arsenic, and cadmium together enhance the formation of Aβ peptides and, consequently, "senile" plaques in the hippocampus and frontal cortex by activating the "amyloidogenic cascade".[38]

Recent researches have linked the homeostasis of metals to the conformational alterations of β-amyloid proteins and the dysfunction of transporters such as transferrin and DMT1 within the blood-brain barrier. These disruptions are induced by fluctuations, changes in metal concentrations, which are heavily influenced by external environmental factors. [39]

Vitamins

In the context of Alzheimer's disease (AD), multiple studies have been conducted to distinguish it from other dementias caused by nutritional deficiencies, such as those of folates, vitamin B12, B1, and B3. These studies have examined the nutritional status and parameters of diagnosed patients, the role of vitamin complexes, and how they influence the progression of the disease. The investigations concluded that, apart from calcium deficiency and severe malnutrition, there are no other significant risk factors. However, recommendations have been made for the regular administration of vitamin complexes (which

play a minor role in enhancing cognitive functions and reducing the formation of senile plaques) containing vitamins K, A, D, and E when deficiencies are detected, as a significant proportion of the analyzed cohorts showed low plasma levels of these vitamins.[38]
Although the adjunctive effect of vitamins has not been definitively proven, and no major nutritional risk factors have been identified, studies emphasize that oxidative stress combined with malnutrition and homocysteine-related vitamins can synergistically increase a patient's risk of developing Alzheimer's disease (AD). [38]

- **Pathological and Physiological Risk Factors**

Comorbidities

The risk of developing AD is also elevated in individuals with associated conditions such as obesity, type 2 diabetes mellitus, dyslipidemia, hypercholesterolemia, hypertension, or a history of traumatic brain injuries. [35,36]

Obesity

In patients with obesity, which is recognized as a modifiable risk factor, an increased rate of neuronal apoptosis and necrosis has been observed within the central nervous system. This is attributed to the loss of neuroplasticity resulting from metabolic alterations induced by weight gain. The body mass index (BMI) is thus directly proportional to the risk of developing these neurodegenerative processes. [38]

Diabetes mellitus

The association between AD and diabetes mellitus, particularly type 2 diabetes, is significantly influenced by the glycemic and insulin (essential neuromodulator) fluctuations that can induce the onset of neurodegenerative processes. Insulin resistance, hyperinsulinemia, and hyperglycemia, leptin, adiponectin, IL-6 (Interleukin 6), resistin and TNF-α (tumor necrosis factor) can potentiate the formation of β-amyloid plaques, especially in individuals who are homozygous or heterozygous for the ε4 risk allele. In the latter case, involving a patient with type 2 diabetes, there is a notable interdependence between the onset of AD and hyperinsulinemia: elevated insulin levels can interfere with the clearance of amyloid-β peptides by competing for the IDE (insulin-degrading enzymes), while excess adipocytes contribute to this process through the production of cytokines and adipokines, making the likelihood of developing AD in diabetics twice as high compared to non-diabetic individuals. Furthermore, RAGE (receptor for advanced glycation endproducts (AGEs)) in diabetic patients may serve as cell-surface receptors for amyloid-β peptides, promoting the formation of extracellular neuritic plaques and intracellular neurofibrillary tangles. [35,36,38,40]

Traumatic Brain Injuries (Craniocerebral Trauma)

Craniocerebral injuries inherently involve the disruption of the blood-brain barrier, alterations in the immune system due to the presence of normal brain antigens, and the loss of plasma proteins. Additionally, the trauma-induced lesions result in an upregulation of the APP gene expression as part of the acute phase response to neuronal damage. [38]

Infections

Although infections that lead to conditions such as meningitis, encephalitis, tuberculosis, neuroborreliosis, parasitosis, and meningoencephalitis, along with their pathogenic agents, are considered exclusion criteria in the differential diagnosis of AD, studies illustrate how the Herpes simplex virus (HSV) contributes to

the pathogenesis of AD. Antibodies generated against specific viral antigens accumulate in the cerebrospinal fluid (CSF), leading to the formation of abnormal neurofibrillary aggregates of TAU proteins. Additionally, upon detection of the infection by the immune system, astrocytes and pericytes are activated, resulting in the enlargement of amyloid deposits. [38,41]

Conclusions

Although the disease is irreversible, with decline occurring at varying rates, existing research indicates that approximately one-third of dementia cases might be preventable or their onset delayed. This can be achieved through the identification and management of modifiable risk factors, ongoing population monitoring, testing, and recognizing both genetic and non-genetic determinants. Reporting on epidemiological trends plays a vital role in this complex process. [14–18,20,42–44]

The study highlights the importance of developing preventive evaluation programs and implementing early-stage medication in order to slow or reduce the progression of neurodegeneration. Every incremental finding, every newly identified aspect, and each validation or refutation of prior hypotheses or published results, regardless of their scale or importance in the international scientific community, progressively contribute to the characterization of these processes, the identification of interdependencies and causal relationships, and the potential for highly specific treatment of all patients.

Thus, the selection of this research topic was driven by the desire to identify factors that have the potential to initiate the neurodegenerative processes characteristic of Alzheimer's disease. Limited public awareness about Alzheimer's disease often results in a lack of preventive measures throughout an individual's life and delays in seeking medical assistance until symptoms have significantly worsened. Establishing a therapeutic regimen that addresses both cognitive and non-cognitive symptoms is crucial for attempting to mitigate or decelerate the progression of the disease. However, it is important to acknowledge that the effectiveness of such interventions remains uncertain in the context of this progressive condition.

The study underscores the necessity of exploring this multifaceted condition from a multidisciplinary perspective, focusing on the various mechanisms by which genetic components and modifiable risk factors influence the development of Alzheimer's disease. Addressing and mitigating modifiable behavioral risk factors, reducing exposure, and treating associated conditions can potentially lower the risk of developing neurodegenerative diseases such as AD. For demographic and physiological risk factors, monitoring and testing are essential stages in disease management, both for establishing a diagnosis and for implementing preventive measures.

References

1. Burns A, Byrne JE, Maurer K. Alzheimer's disease. Lancet [Internet]. 2002;360:163–5. Available from: www.thelancet.com
2. Hippius H, Neundörfer G. The discovery of Alzheimer's disease. Dialogues Clin Neurosci. 2003;5(1):101–8.
3. Maurer K, Volk S, Gerbaldo H. Auguste D and Alzheimer's disease. THE LANCET. 1997;349:1546–9.
4. Soria Lopez JA, González HM, Léger GC. Alzheimer's disease. In: Handbook of Clinical Neurology. Elsevier B.V.; 2019. p. 231–55.
5. Szalontay AS. Actualități în boala Alzheimer. Iași: Editura Gr. T. Popa; 2014.

6. Szalontay AS, Chiriță V, Chiriță R. Boala Alzheimer - Management Clinico-Terapeutic. Iași: Editura U.M.F. “Gr.T.Popa” ; 2005.
7. Tiwari S, Atluri V, Kaushik A, Yndart A, Nair M. Alzheimer’s disease: Pathogenesis, diagnostics, and therapeutics. Vol. 14, International Journal of Nanomedicine. Dove Medical Press Ltd.; 2019. p. 5541–54.
8. Tudose C, Maniu M, Maniu C. GENETICĂ UMANĂ. Iași: Editura CORSON; 2000.
9. Covic M. Curs de genetică medicală. Iași: Institutul de Medicină și Farmacie, Disciplina de Biologie si genetică medicală; 1981.
10. Covic M. Lucrări practice de biologie medicală. Iași; 1976.
11. Covic M, Stefănescu D, Sandovici I. Genetică medicală. Editura Polirom; 2004.
12. Covic M, Ștefănescu D, Sandovici I. Genetică Medicală. Polirom; 2017.
13. Reitz C, Rogaeva E, Beecham GW. Late-onset vs nonmendelian early-onset Alzheimer disease: A distinction without a difference? Neurol Genet. 2020;6(5).
14. Gustavsson A, Norton N, Fast T, Frölich L, Georges J, Holzapfel D, Kirabali T, Krolak-Salmon P, Rossini PM, Ferretti MT, Lanman L, Chadha AS, van der Flier WM. Global estimates on the number of persons across the Alzheimer’s disease continuum. Alzheimer’s and Dementia. 2023 Feb 1;19(2):658–70.
15. Li X, Feng x., Sun X, Hou N, Han F, Liu Y. Global, regional, and national burden of Alzheimer’s disease and other dementias, 1990–2019. Frontiers in Aging Neuroscience - Alzheimer’s Disease and Related Dementias [Internet]. 2022; Available from: http://ghdx.
16. GBD 2019 Dementia Forecasting Collaborators. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. Lancet Public Health. 2019;7.
17. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet . 2020;396:1204–22.
18. GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;369:1223–49.
19. Scheltens P, Blennow K, Breteler MMB, de Strooper B, Frisoni GB, Salloway S, Van der Flier WM. Alzheimer’s disease. The Lancet. 2016 Jul 30;388(10043):505–17.
20. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet . 2020;396:413–46.
21. Alzheimer’s Association. 2018 Alzheimer’s disease facts and figures. Alzheimer’s and Dementia. 2018 Mar 1;14(3):367–429.
22. Alzheimer’s Association. 2015 Alzheimer’s disease facts and figures. Alzheimer’s and Dementia. 2015 Mar 1;11(3):332–84.
23. Alzheimer’s Association. 2009 Alzheimer’s disease facts and figures. Alzheimer’s and Dementia. 2009 May;5(3):234–70.
24. Alzheimer’s Association. 2019 Alzheimer’s disease facts and figures. Alzheimer’s & Dementia [Internet]. 2019 Mar;15(3):321–87. Available from: https://alz-journals.onlinelibrary.wiley.com/doi/10.1016/j.jalz.2019.01.010

25. Alzheimer's Association. 2013 Alzheimer's disease facts and figures. Alzheimer's and Dementia. 2013 Mar;9(2):208–45.
26. Alzheimer's Association. 2010 Alzheimer's disease facts and figures. Alzheimer's and Dementia. 2010 Mar;6(2):158–94.
27. Alzheimer's Association, Thies W, Bleiler L. 2011 Alzheimer's disease facts and figures. Alzheimer's and Dementia. 2011 Mar;7(2):208–44.
28. Masters CL, Bateman R, Blennow K, Rowe CC, Sperling RA, Cummings JL. Alzheimer's disease. Nat Rev Dis Primers. 2015 Oct 15;1.
29. Oboudiyat C, Glazer H, Seifan A, Greer C, Isaacson RS. Alzheimer's disease. Semin Neurol. 2013;33(4):313–29.
30. Scheltens P, De Strooper B, Kivipelto M, Holstege H, Chételat G, Teunissen CE, Cummings J, van der Flier WM. Alzheimer's disease. The Lancet. 2021 Apr 24;397(10284):1577–90.
31. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's and Dementia. 2011;7(3):263–9.
32. American Psychiatric Association. DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS FIFTH EDITION - DSM-5-TR. Vol. V. 2022.
33. American Psychiatric Association. DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS - FOURTH EDITION - DSM-IV-TR. 2010.
34. American Psychiatric Association. DSM-5-TR. 2022.
35. Mayeux R. Early Alzheimer's Disease. New England Journal of Medicine. 2010 Jun 10;362(23):2194–201.
36. Mayeux R, Stern Y. Epidemiology of Alzheimer disease. Cold Spring Harb Perspect Med. 2012;2(8).
37. Wenk GL. Neuropathologic Changes in Alzheimer's Disease. J Clin Psychiatry. 2003;64(9):7–10.
38. Armstrong RA. Risk factors for Alzheimer's disease. Vol. 57, Folia Neuropathologica. Termedia Publishing House Ltd.; 2019. p. 87–105.
39. Calabrò M, Rinaldi C, Santoro G, Crisafulli C. The biological pathways of Alzheimer disease: a review. AIMS Neurosci. 2021;8(1):86–132.
40. Razay G, Wilcock GK. Hyperinsulinaemia and Alzheimer's Disease. Age and Agein. 1994;396–9.
41. Itzhaki RF, Lathe R, Balin BJ, Ball MJ, Bearer EL, Braak H, Bullido MJ, Carter C, Clerici M, Cosby SL, Del Tredici K, Field H, Fulop T, Grassi C, Griffin WST, Haas J, Hudson AP, Kamer AR, Kell DB, Licastro F, Letenneur L, Lövheim H, Mancuso R, Miklossy J, Otth C, Palamara AT, Perry G, Preston C, Pretorius E, Strandberg T, Tabet N, Taylor-Robinson SD, Whittum-Hudson JA. Microbes and Alzheimer's disease. Vol. 51, Journal of Alzheimer's Disease. IOS Press; 2016. p. 979–84.
42. Gao Y, Liu X. Secular trends in the incidence of and mortality due to Alzheimer's disease and other forms of dementia in China From 1990 to 2019: An age-period-cohort study and joinpoint analysis. Front Aging Neurosci. 2021;13(709156).
43. Gao X, Chen Q, Yao H, Tan J, Liu Z, Zhou Y, Zou Z. Epigenetics in Alzheimer's Disease. Front Aging Neurosci. 2022 Jun 23;14.
44. Gauthier S, Albert M, Fox N, Goedert M, Kivipelto M, Mestre-Ferrandiz J. Why has therapy development for dementia failed in the last two decades. Alzheimers Dement . 2016;12:60–4.