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Posted Date: 26 June 2024

doi: 10.20944/preprints202406.1892.v1

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Review Article

Factors Contributing to Alzheimer's Disease in Older Adult Populations: A Narrative Review

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Abstract: Introduction: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and memory loss, predominantly affecting older adults. Understanding the multifaceted factors contributing to AD is crucial for developing effective prevention and intervention strategies. This narrative review synthesizes current literature on the various factors influencing the development and progression of AD in older adult populations.

Methods: A comprehensive search was conducted across electronic databases including PubMed, Web of Science, and PsycINFO using relevant keywords such as "Alzheimer's disease," "risk factors," "genetics," "environmental factors," and "lifestyle." Studies published between 2000 and 2023 were included, focusing on factors associated with AD in individuals aged 65 years and older.

Results: The review identified several key factors contributing to AD in older adults. Genetic predisposition, particularly the presence of apolipoprotein E (APOE) ε4 allele, emerged as a significant risk factor. Environmental factors such as air pollution, pesticides, and heavy metals were also implicated. Furthermore, lifestyle factors including physical inactivity, poor diet, and smoking were associated with increased AD risk. Chronic conditions such as diabetes and cardiovascular diseases were found to exacerbate cognitive decline in older adults. **Conclusions:** This narrative review highlights the complex interplay of genetic, environmental, and lifestyle factors in the development and progression of Alzheimer's disease among older adults. Understanding these factors is crucial for targeted interventions aimed at reducing AD risk and improving cognitive health outcomes in aging populations. Future research should focus on longitudinal studies and personalized medicine approaches to elucidate specific mechanisms underlying AD pathogenesis and to develop effective preventive strategies.

Keywords: Alzheimer's disease, older adults, risk factors, genetics factors, environmental factors, lifestyle factors

1. Introduction

As the population ages, more people are being diagnosed with Alzheimer's disease, and the number is expected to grow. Approximately 60-80% of dementia cases are caused by Alzheimer's disease (Alzheimer's Association, 2022). People suffering from Alzheimer's disease are increasing rapidly today. There are more than 6 million Americans living with Alzheimer's disease. It is estimated that by 2050, this number will rise to nearly 13 million (Alzheimer's Association, 2022).

Alzheimer's disease (AD) dementia refers to a particular onset and course of cognitive and functional decline that results in death (Alzheimer's Association, 2019). In 1906, a clinical psychiatrist and neuroanatomist, Alois Alzheimer, presented "A peculiar severe disease process of the cerebral cortex" at the 37th Meeting of South-West German Psychiatrists in Tubingen, Germany (Hippius & Neundörfer, 2003). At that time, he described the case of Auguste Deter, a 51-year-old woman with

cognitive disturbances, disorientation, delusions, and other behavioral changes whom he had first encountered in 1901. The death of Mrs. Deter occurred 4.5 years later in 1906 (Lopez et al., 2019).

In 1984, clinical diagnostic criteria for AD dementia were revised and further refined in 2011 and 2018 to reflect the use of biomarkers and the new ability to assess preclinical stages of the disease (McKhann et al., 2011; Jack et al., 2018). It was not until the mid-1980s that the molecular identities of Alzheimer's disease's two defining pathologies, beta amyloid peptide found in plaques and hyperphosphorylated tau protein found in neurofibrillary tangles (NFTs), were identified (Lopez et al., 2019). Following these early discoveries, neuropathological assessment of AD has evolved to also recognize multiple comorbid neuropathologies that contribute to clinical dementia (Hyman et al., 2012; Montine et al., 2012). In the United States, Alzheimer's disease is considered to be the most prevalent form of neurodegenerative dementia, with a disproportionate impact on minority populations (Alzheimer's Association, 2019).

After President Obama signed the National Alzheimer's Project Act (NAPA) into law in 2011, the US developed a national plan to address AD in 2012 (Lopez et al., 2019). According to the plan, six ambitious goals are outlined to prevent future cases of Alzheimer's and related dementias, as well as to meet the needs of the millions of Americans who are currently affected by these diseases (U.S. Department of Health and Human Services, 2018). A few examples include preventing and effectively treating Alzheimer's disease and related dementias by the year 2025, improving care quality and efficiency, providing greater support for people with these diseases and their families, enhancing public awareness and engagement, improving data collection to track progress, accelerating action to promote healthy aging and reduce Alzheimer's and related dementia risk factors (Lopez et al., 2019).

2. Related Work

There is still some controversy regarding the pathophysiology of AD. Generally, the "amyloid-cascade hypothesis" places the accumulation of beta amyloid at the center of the process (Querfurth & LaFerla, 2010). A type 1 transmembrane protein, amyloid precursor protein (APP), is produced by a variety of cell types. There are two pathways through which APP can be sequentially cleaved in the central nervous system. Both of these pathways require cleavage by β -secretase as the second step. The first pathway, non-amyloidogenic, involves APP being first cleaved by α -secretase, producing an extracellular product called APPa and a membrane-bound 83 amino acid fragment called C83. In the process of cleaving C83 by β -secretase, another secreted fragment called p3 is produced, leaving behind the membrane-bound APP intracellular domain (AICD). The amyloidogenic pathway begins with APP being cleaved by β -secretase (also known as BACE-1) to produce the secreted extracellular product (Lopez et al., 2019).

Recent epidemiological studies have highlighted significant trends in the prevalence and demographics of Alzheimer's disease (AD). For instance, it is projected that the number of individuals affected by AD will nearly double by 2050 (Alzheimer's Association, 2022). The rising prevalence underscores the urgent need for effective prevention and management strategies.

Advancements in neuropathological research have elucidated key pathological hallmarks of AD, including beta-amyloid plaques and neurofibrillary tangles composed of hyperphosphorylated tau protein (Lopez et al., 2019). Understanding these molecular mechanisms is crucial for developing targeted therapies that mitigate disease progression.

Genetic studies have identified several susceptibility genes associated with AD, such as the APOE $\epsilon 4$ allele and mutations in the amyloid precursor protein (Kanatsu & Tomita, 2017; Van Cauwenbergh et al., 2016). These genetic variants contribute to the differential risk and onset of AD across populations.

Research has highlighted significant ethnic disparities in AD prevalence, with higher rates observed among Hispanic and African American populations (Alzheimer's Association, 2019). Socioeconomic factors, including access to healthcare and educational attainment, also influence AD risk and outcomes.

Various modifiable risk factors, such as hypertension, diabetes mellitus, physical inactivity, and smoking, have been implicated in the pathogenesis of AD (McGrath et al., 2017; Wang et al., 2012; Zhong et al., 2015; Islam et al., 2023). Understanding the impact of these factors on neurodegeneration is critical for developing preventive interventions. Recent studies have evaluated diverse intervention strategies aimed at preventing or delaying AD onset. These include lifestyle modifications such as physical exercise, cognitive training, and dietary interventions (Serrano-Pozo & Growdon, 2019). Early detection and personalized treatment plans are essential for optimizing outcomes in AD management.

3. Research Design

This narrative review aims to synthesize and evaluate existing literature on the relationship between genetic factors, modifiable risk factors, and the incidence of Alzheimer's disease (AD) in older adults. The review focuses on providing a comprehensive overview of current knowledge, identifying gaps in the literature, and suggesting directions for future research. A systematic approach was employed to identify relevant studies, searching databases such as PubMed, MEDLINE, PsycINFO, and Google Scholar using keywords including "Alzheimer's disease," "genetic factors," "modifiable risk factors," "APOE," "hypertension," "diabetes," "physical activity," "smoking," "diet," and "cognitive decline." peer-reviewed articles were considered to ensure a thorough review.

Studies were included based on the following criteria: they were published in English between 2000 and 2023, focused on older adults aged 50 and above, investigated the relationship between genetic factors (e.g., APOE genotype) and modifiable risk factors (e.g., lifestyle, health conditions) with the incidence of AD, and provided data on cognitive outcomes or AD diagnosis. Studies were excluded if they were case reports, editorials, or commentaries, did not include primary data or detailed methodological information, or focused on populations with pre-existing dementia diagnoses.

A narrative synthesis approach was employed to analyze the data, grouping studies based on common themes such as genetic predisposition (e.g., APOE genotype) and specific modifiable risk factors (e.g., physical activity, diet, cardiovascular health). The relationships between these factors and AD incidence were critically evaluated. As this is a review of existing literature, no new ethical approval was required; however, the review adhered to ethical standards by accurately reporting findings, acknowledging sources, and discussing potential biases and limitations.

4. Results and Discussion

Results

Genetic Factors for Alzheimer's Disease

In most cases, the apolipoprotein E (APOE) gene has been closely associated with the incidence of Alzheimer's disease (Kanatsu and Tomita, 2017). Other genes implicated in the disease include presenilin1, presenilin 2, and mutations in the amyloid precursor protein (Cauwenberghs et al., 2016). An individual becomes susceptible to AD as a result of mutations in the genes mentioned above (Khan et al., 2020).

Modifiable Risk and Protective Factors

Age

Approximately 5.8 million Americans live with a diagnosis of Alzheimer's disease as of 2019. By 2050, the number of people with Alzheimer's disease is expected to increase to 13.8 million (2019 Alzheimer's disease facts and figures, 2019). Age-related Alzheimer's disease prevalence increases with age, with 3% of those 65-75 years old, 17% of those 75-84 years old, and 32% of those over 84 years old affected (2019 Alzheimer's disease facts and figures, 2019).

Sex

Women have a 20% lifetime risk of developing AD and men have a 10% lifetime risk at the age of 45. According to Petersen et al. (2018), nearly two-thirds of AD patients are women, and one-third are men, due to both genetic factors and women's longer life expectancy (Petersen et al., 2018).

Ethnicity

The risk of developing AD is one and a half times greater for Hispanics and African Americans. Since 2000, reported deaths from AD have increased 145%, and AD is now the fifth leading cause of death in the United States after age 64 (Petersen et al., 2018).

Hypertension

Several longitudinal studies have shown that midlife hypertension increases the risk of all-cause and Alzheimer's disease dementia (McGrath et al., 2017). In a pathological study, hypertension was associated with an increase in amyloid plaques and NFTs, as well as decreased brain weight (indicating significant atrophy) (Serrano-Pozo and Growdon, 2019).

Diabetes mellitus

The results of longitudinal epidemiological studies have yielded conflicting results in regards to whether diabetes mellitus (DM) in midlife increases the risk of developing late-onset dementia and Alzheimer's disease. A few studies have demonstrated such an association (Wang et al., 2012), while others have failed to detect it (Serrano-Pozo and Growdon, 2019).

Hypercholesterolemia

According to one study, serum cholesterol levels in midlife were positively associated with the development of AD 21 years later (Solomon et al., 2007).

Smoking

More recent evidence from 37 prospective cohort studies confirms that smoking increases the risk of all-cause dementia and vascular dementia, whereas AD risk is significantly increased only among non-carriers of APOE 4 (Zhong et al., 2015).

Alcohol drinking

An extensive Norwegian population-based study found that in contrast to infrequent alcohol consumption (1–4 times in the last 14 days), frequent alcohol consumption (5 times in the last 14 days) has been associated with increased risk of Alzheimer's disease and vascular dementia up to 27 years later (Langballe et al., 2015).

Obesity and diet

There is a strong association between midlife obesity, measured by anthropometric parameters such as body mass index and waist-to-hip ratio, and late-life dementia, independent of other vascular or socioeconomic risk factors (Serrano-Pozo & Growdon, 2019).

Exercise

It is well established from epidemiological longitudinal prospective studies that a low level of physical activity is associated with an increased risk of developing Alzheimer's disease dementia; conversely, a high level of physical activity is associated with a reduced risk (Serrano-Pozo & Growdon, 2019).

Education attainment, leisure, and social activities

The level of education is inversely correlated with the risk of developing dementia due to Alzheimer's disease (Xu et al., 2016). Recreational cognitive and physical activities have also been linked to a reduced risk of dementia. In contrast, loneliness and single or widowed/widower marital status have been associated with an increased risk of developing dementia (Sommerlad et al., 2018).

Table 1. Summary of Modifiable Risk Factors for Alzheimer's Disease.

Risk Factor	Association with AD	Citation
Hypertension	Increases risk, linked to amyloid plaques and NFTs	(McGrath et al., 2017)
Diabetes Mellitus	Mixed findings, some studies show association	(Wang et al., 2012)
Hypercholesterolemia	Elevated midlife levels associated with increased risk	(Solomon et al., 2007)
Smoking	Increases risk among non-APOE ε4 carriers	(Zhong et al., 2015)
Alcohol Consumption	Frequent consumption linked to increased risk	(Langballe et al., 2015)
Obesity	Midlife obesity increases risk independently	(Serrano-Pozo & Growdon, 2019)
Physical Activity	High activity levels associated with reduced risk	(Serrano-Pozo & Growdon, 2019)
Education	Higher education levels reduce risk	(Xu et al., 2016)
Cognitive Activities	Engagement reduces risk	(Sommerlad et al., 2018)

Discussion

Although it is still unclear whether vascular and psychosocial factors are involved in the pathogenesis and clinical manifestation of AD, primary prevention appears to be possible due to the fact that most vascular factors, psychosocial factors, and lifestyle factors can be modified or managed (Qiu et al., 2007). The management of midlife, high blood pressure and obesity, high blood sugar level, and diabetes is one intervention strategy that targets vascular pathways. Furthermore, by adequately managing heart failure and avoiding very low blood pressure, it is possible to delay clinical expression of the dementia syndrome, especially in elderly people, by preventing recurrent cerebrovascular disease and maintaining sufficient cerebral blood perfusion.

As a second strategy, individuals can maintain an active and socially integrated lifestyle by creating extensive social networks and participating regularly in social, physical, and intellectual activities, which may reduce the risk or delay the onset of Alzheimer's disease (Fratiglioni, 2004). Overall, it is likely that the most effective strategy is to encourage people to implement multiple preventive measures throughout their lives, including obtaining a high level of education during childhood and early adolescence, actively controlling vascular factors (Habib et al., 2021) and disorders during adulthood, and maintaining a mental, physical, and socially active lifestyle during middle age and later in life.

The purpose of tertiary prevention is to prevent functional disability in patients suffering from Alzheimer's disease, and to improve their quality of life as much as possible. People with mild dementia may benefit from cognitive training by maintaining cognitive function, slowing down cognitive decline, and improving their wellbeing (Qiu et al., 2009).

6. Conclusions and Future Scope

The purpose of this review is to identify risk factors associated with Alzheimer's disease in older adults worldwide. In order to advance Alzheimer's disease research, it is important to focus on the following key areas. The importance of raising awareness of older adults' health and health needs cannot be overstated. The prevalence of Alzheimer's disease is higher among aging populations due to several factors that should be considered in future research. In order to provide dementia care to older patients, more exposure and knowledge is necessary, such as patient panels and cultural competency training. Future research should prioritize longitudinal studies that comprehensively assess both genetic and lifestyle factors over time to better understand their causal relationships with AD. Additionally, exploring the molecular mechanisms underlying the interaction between genetic predisposition and modifiable risk factors can provide deeper insights into AD pathogenesis. Interventions that combine lifestyle modifications with pharmacological treatments targeting specific genetic pathways hold promise for more effective prevention and management of AD. Further, the development and implementation of public health strategies promoting healthy lifestyles from an early age could contribute to a significant reduction in AD incidence.

Data Availability

The study analyzed all data from publicly available literature cited in the manuscript's references. Researchers looking for specific datasets or more information should refer to these original sources for complete access and retrieval information.

Study Limitations

This review has several limitations that should be considered. First, the reliability of our findings hinges on the quality and accuracy of data reported in the literature we reviewed, which may vary across studies. Second, there is a potential for publication bias, where studies with negative results or smaller sample sizes may be underrepresented. Third, methodological variability among included studies, including differences in study design and definitions, may impact the comparability and synthesis of results. Finally, our review focused on studies published between 2000 and 2023, which may have excluded more recent developments or emerging research in the field.

Author Contributions: **Jalal Uddin:** Conceptualized and designed the study, conducted data collection and analysis, drafted the manuscript, and critically revised it for important intellectual content. **Tazveen Fariba:** Provided guidance and supervision throughout the study, offered critical feedback on the manuscript's content and structure, and contributed to the final approval of the version to be submitted. **Shahida Sultana Shumi:** Reviewed and proofread the manuscript, and contributed to the final approval of the version to be submitted. **Farhana Khandoker:** Reviewed and proofread the manuscript, and contributed to the final approval of the version to be submitted. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Acknowledgments: The authors gratefully acknowledge the School of Public Health, University of Nevada, Las Vegas, for their invaluable support and resources that facilitated the completion of this manuscript.

Conflict of Interest: The authors declare no conflicts of interest related to this manuscript.

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Jalal Uddin is a Master of Public Health student in the Social and Behavioral Health Department at the University of Nevada, Las Vegas (UNLV). With a Bachelor of Science in Physiotherapy from Bangladesh, Jalal's research interests span Alzheimer's disease, Parkinson's disease, and other neurological conditions in older adults, alongside issues affecting gender and racial minorities. Motivated by a passion for reducing health disparities, Jalal actively contributes as a Graduate Research Assistant, adept in data analysis using SPSS and SAS. His work includes designing survey methodologies, collaborating with organizations like the Alzheimer's Association, and American Public Health Association.



Tazveen Fariha is an emerging researcher with a Master of Public Health from the University of Creative Technology from Bangladesh, and upcoming pursuit of a PhD in Public Health at the University of Nevada Las Vegas (UNLV) starting Fall 2024. Currently serving as an Academic Coordinator at Chattogram International Nursing College, she oversees course planning and faculty supervision while contributing to nursing education advancements. Tazveen's research focuses on mental health among nursing students and empathy in nursing practice, with recent conference presentations and publications in nursing journals highlighting her commitment to advancing healthcare education and research.

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Her diverse background reflects a strong commitment to advancing public health.
