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Sex-Based Variations in Alzheimer's Disease: From Susceptibility to Therapeutic Outcomes

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ABSTRACT: ***Background:*** *Alzheimer's disease (AD) shows distinct differences between women and men in prevalence, disease progression, and therapeutic response. Women express a greater risk of AD onset, influenced by increased longevity and hormonal factors, and typically experience faster cognitive decline along with heightened susceptibility to AD-associated depression and anxiety. Current therapies—primarily cholinesterase inhibitors and memantine—offer only symptomatic relief without modifying disease progression.* ***Objective:*** *To review sex-specific differences in Alzheimer's disease and evaluate the current understanding of therapeutic response variations between men and women, with an emphasis on identifying opportunities for sex-tailored interventions.* ***Methods:*** *A narrative review of the literature on AD prevalence, progression, and treatment outcomes across sexes was conducted. Particular attention was given to pharmacological therapies (cholinesterase inhibitors, memantine), lifestyle factors, and sex-specific risk determinants such as cardiovascular health and hormonal fluctuations.* ***Results:*** *Evidence suggests that women are more vulnerable to AD onset and progression compared to men. Limited studies indicate potential therapeutic advantages of specific medications for women, though robust, sex-stratified clinical trials remain lacking. Non-pharmacological strategies, including lifestyle adjustments in diet, exercise, and cognitive engagement, show promise in alleviating symptoms for both sexes.* ***Conclusions:*** *Sex differences significantly influence AD onset, clinical course, and therapeutic response. While current treatment remains largely non-disease-modifying, emerging sex-specific findings underscore the need for personalised medicine approaches. Further research is required to clarify sex-specific mechanisms, optimise therapeutic strategies, and address disparities in care access, ultimately improving management of AD in both women and men.*

KEYWORDS: *Alzheimer's disease; Anxiety; Behavioural symptoms; Cognitive function; Cognitive stimulation; Depression; Hormonal fluctuation*

INTRODUCTION

A clinical condition known as dementia causes a person to lose the capacity to perform instrumental and/or fundamental daily tasks. Memory, language, executive and visuospatial function, personality, and conduct are among the cognitive domains that exhibit a steady decrease. Alzheimer's disease (AD) is the predominant etiology of dementia. By far, it causes approximately 80% of dementia diagnoses [1]. Nearly fifty-five million individuals worldwide currently exhibit memory loss, and more than sixty per cent of them reside in low and middle-income countries. Every year, reports show

over ten million new cases. Cognitive decline may arise from numerous cerebral traumas and disorders. Alzheimer's disease, the predominant variant of cognitive impairment, may contribute to sixty to seventy percent of instances [2]. The AD is a predominant source of impairment and dependency that affects the older population and currently ranks as the sixth most prevalent cause of mortality globally. Family and close companions provided the equivalent of five hours of care and supervision per day, accounting for a quarter of the global dementia economy, which spent more than a trillion US dollars in 2019. Women are more frequently affected by cognitive impairment, both in direct and indirect ways. Women additionally contribute 70% of the care hours for patients having AD, but they also have higher mortality and years of disability-adjusted life due to dementia [3]. Its causes are varied, its manifestations are diverse, and its impact on prevalence, risk factors, and outcomes is heterogeneous based on sex [4]. There are no known therapies for AD, along with the probable deviation of memory loss associated with normal pressure hydrocephalus (NPH), and current treatments are insufficient to reduce the disease's course [5]. A significant area of research has focused on identifying modifiable risk factors for AD. Unfortunately, age and sex, which are the two best indicators of AD, do not fit into this group [6]. The change in risk of dementia was related to the interaction of sex with age throughout development. The brain is affected in a way that is sexually dimorphic from conception onward [7].

In relation to long-term health outcomes, this encourages risk and resilience. In this study, the present state of knowledge about the individual and combined impacts of sex on AD risk, prevention, and therapy will be reviewed. In a nutshell, sex is the division of people into sex chromosomal complements, where males have one X and one Y chromosome and females have two X chromosomes. An individual's sex is referred to as their psychosocial and cultural self-identification as male or female [8]. Researchers in the past have examined the risk factors for dementia development that are particular to both sexes; however, dementia research has not always clearly defined the distinction between sexuality as a physiological factor (SABV) and sex as a cultural construct/personal characteristic [9]. Given that a person's biology is influenced by their sex and vice versa, boundaries can be blurry. In a similar vein, a person's sex does not necessarily match their biological sex [10]. The investigation will concentrate on sex and sexuality disparities in AD among people who have expected chromosomal complements for males (XY) and females (XX) and are not changing their sex or sexual identity through exogenous hormones or surgery, despite the increasing desire to take medical results in transsexual and intersex categories into account. As emphasized above, this review demonstrates the relationship between AD and different sexes. Several databases, such as PubMed, carried out a thorough survey for this purpose. The keywords like Alzheimer's disease, Depression, Hormonal fluctuation and Cognitive stimulation were used to obtain the most appropriate article to support the study. On the other hand, articles stating the relationship between sex and AD, its causes and natural remedies of AD were also referred to accomplish the study. Furthermore, the remaining articles that had irrelevant or mismatched keywords were disregarded for this analysis. Every publication was evaluated and cited in accordance with its applicability and suitability for the conversation at hand. The terms used to search PubMed are listed in Table 1. A total of 200 articles were discussed in depth to find out how sex and sex were related to AD. In addition, causes of AD and natural treatments were also discussed.

Table 1. Keywords used for the literature review and the number of articles retrieved

Keywords	PubMed
Alzheimer's disease	70817
Alzheimer's Disease and Depression	3772
Alzheimer's Disease and Anxiety	1662
Alzheimer's Disease and Hormonal Fluctuation	18
Alzheimer's Disease and Cognitive Stimulation	1468

SIGN AND SYMPTOMS

AD is characterised by memory loss, which first shows as trouble remembering recent events or conversations. The condition worsens, causing a more noticeable cognitive impairment that makes it harder for patients to retain details and think coherently [11], [12]. Even though people may be conscious of their own memory problems at first, as the illness progresses, friends and family start to notice more clearly. These symptoms worsen due to the underlying brain abnormalities linked to AD,

which eventually result in a greater deterioration in memory and cognitive abilities [13].

Memory

AD causes memory loss that goes beyond everyone's normal lapses and affects everyday functioning at home and at work [14], [15]. AD patients may ask the same questions or make the same statements repeatedly, forget recent discussions, appointments, or events, misplace objects in strange places, get lost in familiar environments, and finally find it difficult to remember the names of loved ones and everyday objects (Figure 1). They might also find it difficult to communicate their ideas, find the appropriate words, or participate in discussions. As the illness progresses, these symptoms progressively get worse, severely lowering cognitive function and general quality of life [16], [17].

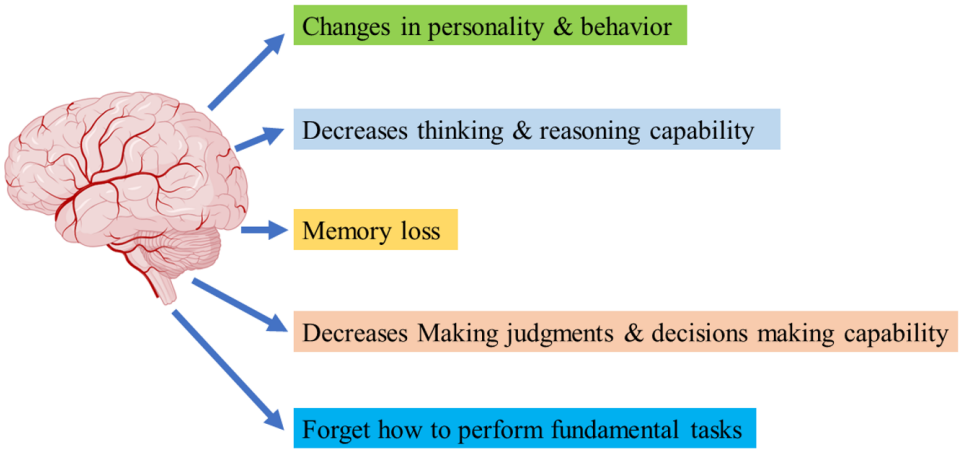

Figure 1. Memory impairment symptoms of an Alzheimer's patient

Thinking & Reasoning

AD causes cognitive impairment, especially when it comes to abstract thinking like mathematical calculations [18]. It becomes very difficult to multitask, which makes it tough to handle finances, balance cheque books, and make on-time bill payments [19]. As the illness worsens, people may become less able to understand and apply numerical concepts, which can be very problematic for money management and other duties that need numerical comprehension [20].

Making Judgments & Decisions

The ability to make good decisions and judgments in day-to-day situations declines with Alzheimer's disease. This downturn could show itself as poor social choices or incorrect weather-appropriate attire [21]. People may also find it difficult to deal with everyday issues, such as controlling food burning on the stove or making choices while driving, which reflects the growing difficulties people encounter in getting by in daily life [22].

Planning & Performing Familiar Tasks

Activities that need consecutive steps get harder as Alzheimer's disease worsens. Even simple things like cooking or playing a beloved game might become intimidating. As the medical condition advances, people may ultimately forfeit the capacity to do basic activities like dressing and taking a shower, underscoring the significant influence the illness has on day-to-day life [23].

Changes in Personality & Behavior

Brain abnormalities associated with Alzheimer's disease can have a substantial impact on moods and behaviors. These abnormalities can lead to a range of issues, such as depression, decreased interest in activities, social withdrawal, mood swings, increased suspicion of others, episodes of rage or aggression, changes in sleep patterns, wandering tendencies, lowered inhibitions, and the emergence

of delusions, such as false beliefs about stealing [24]. These behavioural and mental changes are common as the disease progresses and can have a substantial impact on the individual's quality of life and interactions with others.

Preserved Skills

Despite considerable impairments in memory and cognitive abilities, people with Alzheimer's disease frequently maintain certain skills as their symptoms deteriorate. These retained abilities may include activities such as reading or listening to literature, storytelling, remembering, singing, listening to music, dancing, drawing, or participating in crafts. These talents may last longer since they are associated with brain regions impacted later in the illness process, allowing people to continue engaging in meaningful and enjoyable activities [25].

Quality of Life

The impact of clinical symptoms on an AD patient's quality of life, as well as their capacity to carry out everyday tasks, engage in social activities, and obtain medical attention, is also influenced by their sex. A multidimensional scale called the health-related quality of life (HrQoL) is used to assess how patients' lives are affected by illness and treatment. A recent study that looked at the connections between sociodemographic factors and three HrQoL domains—physical functioning, cognitive, and socioemotional—did not find evidence of a widespread sex effect [26]. But whereas male sex primarily impacted the HrQoL cognitive domain, female sex turned out to be a poor predictor of physical functioning and socioemotional HrQoL. On the other hand, female patients in prospective research on a cohort of patients with idiopathic AD in Germany reported more issues in every category except self-care [27]. Simultaneously, long-term research aimed at examining the impact of AD onset on life satisfaction revealed a significant decline in life satisfaction in males over their later years, but not in women [26].

Respect, honesty, compassion, and decency should be shown to people suffering from dementia, while also ensuring their safety and privacy are protected. Support is essential to improving a person's quality of life during the early stages of dementia, and as the illness worsens, suitable social and physical settings are required to preserve quality of life. Understanding the progression of dementia and effective communication are important factors to take into account. You should also consult with the person or their close associates to determine preferences, promote independence, identify strengths, offer choices, monitor general health, ensure safe and familiar living spaces, foster companionship and relationships, tailor care to the needs of each individual, value the person with dementia as an individual, interpret behaviors as meaningful communication, and recognize the interconnectedness of the person with dementia and other aspects of their life [28].

CAUSES OF ALZHEIMER'S DISEASE

Genetics

Genetic contributions to Alzheimer's disease (AD) involve both rare deterministic mutations and common risk variants. Early-onset familial AD (FAD), comprising <5% of cases, arises from autosomal dominant mutations in *APP* (amyloid precursor protein), *PSEN1* (presenilin 1), and *PSEN2* (presenilin 2) genes on chromosomes 21, 14, and 1, respectively. These mutations enhance amyloid-beta (Aβ) production, particularly the neurotoxic Aβ42 isoform, by altering γ-secretase cleavage, leading to amyloid plaques and early symptoms before age 65. Over 300 *PSEN1* mutations alone have been identified, with variable penetrance and phenotypes including spastic paraparesis [29], [30].

Late-onset sporadic AD (95% of cases, onset >65) is polygenic, with APOE ε4 on chromosome 19 as the strongest risk allele: one copy triples risk (OR ~3), two copies raise it 12-fold, and it promotes Aβ aggregation, tau hyperphosphorylation, and neuroinflammation. Genome-wide association studies (GWAS) have pinpointed >70 loci, including TREM2 (microglial function), *ABCA7* (lipid transport), and *SORL1* (endosomal trafficking), collectively explaining ~20-30% heritability. Rare variants like TREM2 R47H impair microglial phagocytosis of Aβ, exacerbating pathology [29], [31]. Figure 2 illustrates the factors involved in AD.

The AD is characterised by amyloid-beta accumulation, tau hyperphosphorylation, neuroinflammation, and synaptic dysfunction-autophagy was impacted in a sex-specific manner via hormones, genetics such as APOE ε4, and cellular responses. Women have an increased lifetime risk associated

in part with longer life expectancy and loss of menopause-related estrogen, and men manifest different compensatory responses [32], [33].

Male-Specific Pathways in AD: In male AD hippocampus (CA1 subfield), estrogen signalling pathway (hsa04915) is up-regulated, possibly as a neuroprotective feature to the neurodegeneration process, but clearly down-regulated GABAergic synapse (hsa04727) and insulin secretion (hsa04911). Shared pathways such as IL-17 signalling (hsa04657) and MAPK signalling (hsa04010) activate in both sexes, but males display sex-specific stress-response enrichments after separating the sexes. Microglial immunometabolism is sex-specific, and men exhibit endophenotypes that can contribute to progression [33], [34].

Female-Specific Pathways in AD: Female AD cases demonstrate upregulated female-specific pathways in CA1, including: HIF-1 signalling (hsa04066), calcium signalling pathway (hsa04020), and Epstein-Barr virus infection-related (hsa05169); and downregulated dopaminergic synapse hsa04728). Astrocytes exhibit a higher level of changed cell death pathways in men than women, and women carrying APOE $\varepsilon 4$ show greater tau pathology and hippocampal atrophy through estrogen-APOE interaction. Glutamatergic synapse (hsa04724) was downregulated in both of them; however, oxytocin signalling (hsa04921) included sex differences [32], [34]–[36].

1 Familial Alzheimer's Disease (FAD)

A tiny portion of Alzheimer's cases are due to familial AD (FAD), which is brought on by genetic mutations in particular genes such as the presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*), and amyloid precursor protein (APP). These mutations cause aberrant proteins to be produced, such as amyloid-beta, which build up in the brain and aid in the onset of Alzheimer's disease [37], [38].

2 APOE Gene

The most prevalent kind of Alzheimer's disease, known as late-onset Alzheimer's disease (LOAD), has a substantial hereditary risk factor associated with the APOE gene. The APOE gene's $\varepsilon 4$ allele is linked to a higher risk of Alzheimer's disease, whereas the $\varepsilon 2$ allele might be protective [39], [40].

3 Polygenic Risk Scores

Genome-wide association studies (GWAS) have connected Alzheimer's disease to several genetic variants. Even while these variations have small effects on their own, when together, they raise a person's total genetic risk. The Polygenic Risk Score (PRS) evaluates a person's genetic susceptibility to Alzheimer's disease by combining data from several genetic variants [41], [42]

4 Gene Expression and Regulation

AD can change the expression and control of genes related to several biological processes, such as inflammation, neuronal survival, and synaptic function. Variations in gene expression could be involved in the pathophysiology of the illness [43], [44].

5 Epigenetic Modifications

Epigenetics modulates AD via DNA methylation, histone modifications, and non-coding RNAs, bridging genetics, environment, and ageing. Global hypomethylation and site-specific hypermethylation occur in AD brains; for instance, *PSEN1* promoter hypermethylation reduces expression, while *APP* hypomethylation boosts transcription. DNMT1/3a deficits in neurons link to oxidative stress-induced hypomethylation. Histone acetylation decreases (e.g., H3K9ac, H4K12ac) due to HDAC2 upregulation, repressing neuroplasticity genes like BDNF, while HAT inhibitors show therapeutic promise [30], [45].

MicroRNAs (miRNAs) dysregulate post-transcriptionally: miR-29a/b downregulation elevates BACE1 (Aβ-generating enzyme), miR-107 targets BACE1/ kinases, and miR-132/124 loss impairs neuronal survival. Long non-coding RNAs (lncRNAs) like BACE1-AS stabilise BACE1 mRNA. These changes, influenced by ageing, APOE status, and lifestyle, offer biomarker potential (e.g., blood miR-34c/circulating DNA methylation) and drug targets like HDAC inhibitors or miRNA mimics. Epigenome-wide studies reveal reversibility, unlike fixed genetics, supporting intervention strategies [30], [46].

Age

AD predominantly affects older individuals, and advancing age is the primary risk factor for the development of the condition.

1 Age as a Primary Risk Factor

Advancing age is the single most substantial risk factor for AD. The incidence of AD increases dramatically with age, with the majority of incidents occurring in adults aged 65 and older [47], [48]. Estimates suggest that the frequency of Alzheimer's approximately multiplies every five years after the age of 65, with the highest incidence rates observed in individuals over 85 [38].

2 Age-Related Modifications in Neuronal Functioning and Structure

Ageing is connected with various functionally and structurally changes in the brain, including loss of neurons and decreased density of synapses, and changes in neurotransmitter networks. These age-related changes may contribute to the increased susceptibility to AD [49], [50].

3 Interaction between Age and Other Risk Factors

Age interacts with other risk factors for Alzheimer's disease, such as genetics, lifestyle factors, and cardiovascular health. The cumulative effect of age and these risk factors may exacerbate the risk of developing AD [51], [52].

4 Age-Related Biomarkers and Pathological Changes

Ageing is associated with the accumulation of pathological changes in the brain, including the deposition of amyloid-beta plaques and the formation of neurofibrillary tangles composed of hyperphosphorylated tau protein. These pathological changes are hallmark features of AD [53], [54].

5 Age-Related Cognitive Decline

While cognitive decline is a normal part of ageing, Alzheimer's disease represents a more severe and progressive form of cognitive impairment. Age-linked cognitive decline may interact with AD's pathology, leading to accelerated cognitive deterioration in older individuals [55], [56].

Brain Abnormalities

AD is defined by significant brain abnormalities, including the buildup of amyloid plaques, neurofibrillary tangles, and synaptic dysfunction. These pathological changes contribute to the progressive neurodegeneration observed in individuals with the disease.

1 Amyloid Plaques

Amyloid plaques are deposits outside of cells, mostly consisting of amyloid-beta protein (Figure 2). These plaques disrupt neuronal function and contribute to Neuronal degeneration and synaptic destruction in the brain. Amyloid deposition is one of the hallmark pathological features of AD [57]. Jack *et al.* provide an overview of the role of amyloid imaging in Alzheimer's disease diagnosis and research [53].

2 Neurofibrillary Tangles

Neurofibrillary tangles are intracellular clumps of increased phosphorylated tau protein. These tangles damage the cellular structure of nerves and impair cellular function. Tau pathology correlates closely with neuronal loss and cognitive decline in AD [58]. Nelson *et al.* discuss the correlation between Alzheimer's neuropathologic changes, including neurofibrillary tangles, and cognitive status [54].

3 Synaptic Dysfunction

Synaptic dysfunction and loss are early and prominent features of Alzheimer's disease. Dysfunction of connections between neurons hinders neuronal communication and leads to cognitive deterioration. Synaptic dysfunction may occur before the advent of amyloid and tau pathology [59], [60]. Selkoe *et al.* provide insights into the role of synaptic dysfunction in Alzheimer's disease pathogenesis [59].

4 Neuronal Loss

AD is distinguished by the progressive loss of neurons, particularly in the following regions of the brain associated with memory and cognitive function, such as the hippocampus and neocortex. Neuronal loss correlates with the severity of cognitive impairment in individuals with AD [59], [61]. Selkoe *et al.* discuss the relationship between neuronal loss and AD progression [59].

5 Inflammatory Responses

Chronic neuroinflammation is a prominent feature of AD and contributes to disease progression. Activated microglia and astrocytes release neurotoxic compounds and cytokines that promote inflammation, exacerbating neuronal damage and dysfunction, providing early evidence of AD-related inflammation of the neurons [62], [63].

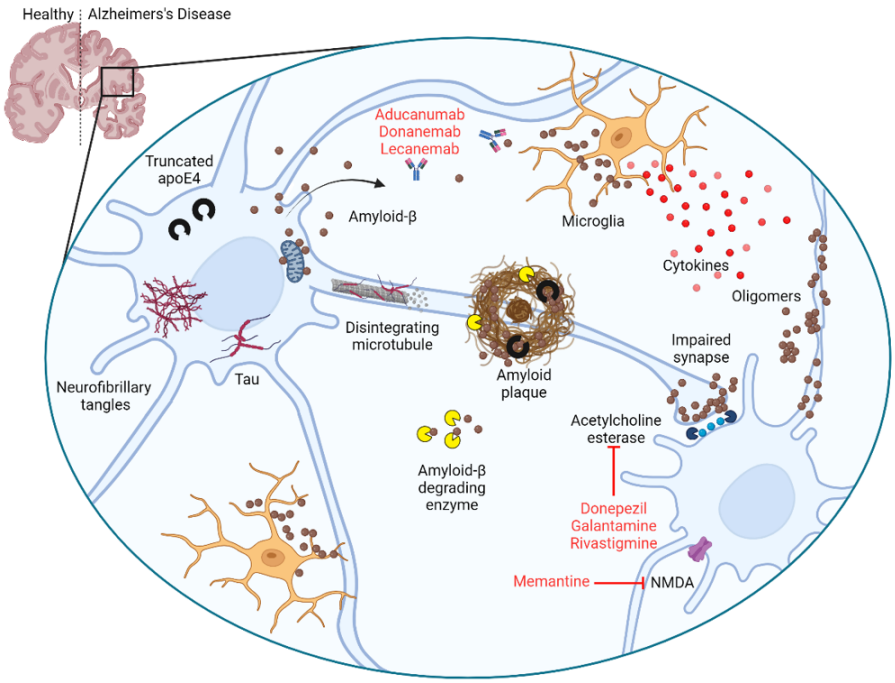

Figure 2. Factors involved in Alzheimer's disease

Environmental Factors

While AD, having a substantial hereditary element, external factors additionally play a role in its progression. and progression.

1 Air Pollution

Exposure to air pollutants, especially nitrogen dioxide and fine particulate matter (PM2.5) (NO_2), has been linked to an increased risk of cognitive decline and AD. Air pollutants can induce neuroinflammation, oxidative stress, and vascular dysfunction, all of which are implicated in AD pathology [64], [65].

2 Pesticides and Heavy Metals

Some studies suggest that exposure to certain pesticides and heavy metals, such as lead and mercury, may be associated with an elevated risk of AD. Pesticides can disrupt neurotransmitter systems and induce oxidative stress, while heavy metals can accumulate in the brain and promote neurotoxicity [66], [67].

3 Occupational Exposures

Occupational exposures to chemicals and toxins, such as solvents and heavy metals, have been implicated in AD risk. Certain occupations, such as farming and manufacturing, may involve higher levels of exposure to neurotoxic substances, increasing the risk of cognitive impairment and AD later in life [68], [69].

4 Diet and Nutrition

Healthful eating and nutrition perform a vital role in mental well-being and may influence AD risk. Eating food that is packed with fatty substances, processed sugars, and refined carbohydrates has been connected to a higher risk of cognitive decline and AD. Conversely, the risk has been linked to an increased risk of cognitive decline and AD may be decreased by following a Mediterranean-style diet high in vegetables, whole grains, fruits, and healthy fats [70], [71].

5 Social and Cognitive Engagement

Social isolation and limited cognitive stimulation have been related to an increased risk of cognitive deterioration and AD. Participating in social activities, maintaining social connections, and engaging in Social Activities intellectually stimulating pursuits may help retain cognitive function and lower the risk of AD [72], [73].

Lifestyle Factors

The role of lifestyle factors in Alzheimer's disease has attracted significant interest in recent months, with research suggesting that certain habits and behaviours may influence the risk of developing the disease. Here are some key lifestyle factors and their consequences on Alzheimer's disease.

1 Physical Activity

Consistent exercise has been associated with a lower risk of Alzheimer's disease. Exercise improves blood circulation to the brain, encourages the development of fresh neurons, and reduces inflammation, all of which can potentially safeguard against cognitive deterioration [74]–[76].

2 Healthy Diet

Following a Mediterranean-style meal that contains lots of veggies, whole grains, fruit, fish, and Healthful fats (such as olive oil and nuts) have been linked to a lower risk of Alzheimer's disease. This diet offers vital vitamins and minerals that support cognitive wellness and decrease inflammation [77], [78].

3 Cognitive Stimulation

Engaging in mentally stimulating activities, such as reading, puzzles, and learning new skills, may help preserve cognitive function and reduce the risk of Alzheimer's disease. Keeping the brain active and challenged can build cognitive reserve, which may delay the onset of symptoms [79], [80].

4 Social Responsibility

Maintaining social relationships and engaging in social activities might have a protective effect against Alzheimer's disease. Social interaction stimulates the brain, reduces stress, and may help preserve cognitive function [81], [82].

5 Quality Sleep

Restful sleep is necessary for neural wellness and cognitive performance. Poor sleep quality or sleep disorders may enhance the chance of developing Alzheimer's disease by impairing memory consolidation and increasing inflammation in the brain [83].

6 Stress Management

Chronic stress has been related to cognitive impairment and a greater likelihood of memory loss. Dealing with stress with methods of calmness, awareness, and interaction may assist in protecting against cognitive impairment [84].

7 Heart Health

Factors that contribute to heart health, such as maintaining normal blood pressure, cholesterol levels, and weight, may also benefit brain health and reduce the risk of Alzheimer's disease. What's good for the heart is often good for the brain [85].

8 Elimination of Detrimental Chemicals

Restricting alcohol intake and abstaining from tobacco use, and lowering vulnerability to hazardous substances may help mitigate the probability of Alzheimer's disease by protecting brain health and reducing inflammation [86].

Cardiovascular Health

Conditions impacting cardiovascular health, including hypertension, diabetes, and obesity, and high lipid concentration, are associated with an elevated risk of Alzheimer's disease. Maintaining heart health may also help preserve brain function.

1 Vascular Hypothesis

De la Torre, J.C. proposes that vascular factors contribute significantly to the development and progression of AD. Poor cardiovascular health, including conditions like hypertension, atherosclerosis, and diabetes, may lead to reduced cerebral blood flow, thereby increasing the risk of AD [87].

2 Shared Risk Factors

Kivipelto, M. *et al.* prove that several risk factors, such as hypertension, high cholesterol, diabetes, obesity, and smoking, are shared between cardiovascular disease (CVD) and AD, suggesting a common underlying mechanism or pathway linking these conditions [88].

3 Reduced Blood Flow

Cardiovascular issues can lead to reduced cerebral blood flow, which may result in hypoperfusion and hypoxia in the brain. Chronic hypoperfusion contributes to the accumulation of amyloid-beta plaques and tau tangles, key pathological features of AD [89].

4 Impact on Brain Structure

Cardiovascular risk factors can lead to structural alterations in the brain, including white matter lesions and cerebral atrophy. which are associated with both dementia with vascular involvement and cognitive decline in AD [90].

5 Inflammation and Oxidative Stress

Cardiovascular risk factors promote oxidative stress and inflammatory processes, which lead to neuronal dysfunction and neurodegeneration, accelerating the progression of AD [91].

6 Treatment Implications

Managing cardiovascular risk factors through lifestyle modifications and medical interventions may help minimise the incidence of AD or halt its growth in affected individuals [52].

Head Trauma

Head trauma, particularly repetitive or severe traumatic brain injury (TBI), has been linked with an increased chance of acquiring AD and other kinds of memory loss.

1 Increased Risk of Alzheimer's Disease

Investigations have demonstrated that individuals with a history of head trauma, especially moderate to severe TBI, have a higher risk of developing AD later in life. This probability may be further elevated if the brain injury occurs repeatedly or at a younger age [92].

2 Accelerated Brain Ageing and Pathological Changes

Head trauma can lead to chronic neuropathological changes in the brain, including the accumulation of tau protein tangles and beta-amyloid plaques, which are hallmarks of AD. Additionally, TBI can accelerate brain ageing processes, potentially contributing to cognitive decline and dementia [93].

3 Neuroinflammation and Neurodegeneration

Head trauma triggers neuroinflammatory responses and cellular processes that contribute to neurodegeneration. Chronic inflammation and neuronal damage may promote the development and progression of AD pathology in individuals with a history of TBI [94].

4 Interaction with Genetic Risk Factors

Genetic variables, including the existence of the APOE $\varepsilon 4$ allele, may interact with head trauma to further increase the risk of developing AD. Individuals with both a history of head injury and genetic susceptibility may have a particularly elevated risk of dementia [95].

5 Potential Prevention Strategies

Preventive measures, such as promoting safety practices to reduce the risk of head injury and providing adequate medical care following TBI, may help mitigate the chance of acquiring AD in vulnerable populations [96].

Inflammatory and Immune Responses

Chronic inflammation in the brain and dysregulation of the immune system may contribute to the advancement of memory loss. Immune system dysfunction could lead to the advancement of memory loss and neuronal damage.

1 Chronic Neuroinflammation

Chronic neurological inflammation is a significant characteristic of Dementia and memory loss. Microglia, the resident immune cells of the brain, become triggered and generate inflammatory substances, cytokines, and chemokines in response to the presence of amyloid-beta plaques and tau tangles. This sustained inflammatory response contributes to neuronal dysfunction and degeneration [64].

2 Role of Immune Cells

Dysregulation of T lymphocytes, particularly an increase in pro-inflammatory Th17 and Th9 subsets, has been seen in the peripheral blood and minds of people with AD. These immune cells trigger inflammation of the brain and may exacerbate neuronal damage in the AD brain [97].

3 BBB (Blood-Brain Barrier) Dysfunction

In AD, chronic inflammation can lead to dysfunction BBB (Blood-Brain Barrier), impairment, allowing the invasion of distal immune system cells and molecules entering the brain regions. This exacerbates neuroinflammation and contributes to the progression of neuronal damage and cognitive decline [98].

4 Role of Genetic Factors

Genetic variants associated with inflammation and immune response, such as polymorphisms in genes encoding cytokines and complement proteins, may modulate the risk of developing AD and influence disease progression by affecting the intensity of neuroinflammatory processes [99].

5 Therapeutic Implications

Targeting neuroinflammation and immune dysregulation has shown up as a possible therapy method for AD. Strategies aimed at modulating immune responses, such as anti-inflammatory drugs or immunomodulatory agents, are being investigated for their potential to decrease the progression of the condition and enhance memory and thinking in AD patients [100].

Neurotransmitter Imbalance

Neurotransmitter imbalance, particularly involving acetylcholine (ACh) and glutamate, plays a crucial role in memory loss (AD).

1 Acetylcholine Deficiency

The cholinergic theory posits that a lack of the neurotransmitter acetylcholine (ACh) plays a crucial role in the decline of thinking observed in AD. Absence of cholinergic neurones, especially those that go to the hippocampus within the basal forebrain and neocortex, contributes to memory impairment and cognitive deficits in AD patients [101].

2 Excitotoxicity of Glutamate

Abnormalities of the neurotransmitter glutamate, leading to excitotoxicity, are implicated in the pathogenesis of AD. Impaired glutamate clearance and excessive glutamate release contribute to neuronal damage and cell death, particularly in vulnerable areas like the brain and hippocampus [102].

3 Impact on Synaptic Function

Imbalances in neurotransmitter systems, including ACh and glutamate, disrupt synaptic function and plasticity in AD. Dysfunction of synaptic transmission and impaired synaptic connectivity contribute to cognitive deficits and neuronal dysfunction in AD pathology [103].

4 Neurotransmitter Receptor Alterations

Alterations in neurotransmitter receptor expression and function, including changes in cholinergic and glutamatergic receptor subtypes, contribute to synaptic dysfunction and cognitive impairment in AD. Targeting these receptors with pharmacological interventions represents a potential therapeutic strategy for AD treatment [104].

5 Therapeutic Implications

Pharmacological interventions targeting neurotransmitter systems, such as cholinesterase inhibitors to increase ACh levels or NMDA receptor antagonists to modulate glutamatergic transmission, are currently used in the treatment of AD to alleviate symptoms and improve cognitive function in affected individuals [105].

EPIDEMIOLOGIC EVIDENCE FOR SEX DIFFERENCES IN AD

According to many reports, women are more likely to experience AD than males [106], [107]. Women make up over two-thirds of AD cases in the US. One common explanation that has been put forth is that, on average, women outlive men by 4.5 years. In most global subpopulations, there are more women than men who are at least 85 years old. However, the biggest risk factor for AD is advanced age. It is challenging to determine the actual variations in the possibility of developing AD between identically aged men and women, and the results have been inconsistent [72]. While some studies found no correlation among sexes, evolution, and prevalence, or found none at all, many showed greater age-corrected figures and/or quicker advancement in women. It's also crucial to remember that, even in the absence of a difference, sex disparities in mechanisms may still exist. Even while a disease may have the same prevalence, men and women may experience it in different ways.

The contradictory results across those various studies could be attributed to a multitude of factors, such as 1. variations in standards for inclusion and exclusion; 2. statistical power and sample size; 3. Research design and type (cross-sectional study, prospective cohort, or retrospective cohort) [72]; 4. Cultural variations impacting stress management techniques, nutrition, and exercise [72]; and 5. Historically disparate methods of classification and diagnosis of AD cases [108], [109]. Since many different criteria had been employed in previous research and a final diagnosis of AD could only be acquired at autopsy, categorisation bias was a significant concern in ascertaining the true incidence of AD in men and women. But because of the developments in amyloid PET and CSF tau and amyloid for clinical applications, AD dementia may now be clearly diagnosed. As a result, it is now possible to reduce the differences in the frequency of AD between men and women throughout studies [110].

According to the estimated lifetime risk for AD based on data from the Framingham Heart Study, for men and women at age 45 was one in ten (10%) and one in five (20%), respectively, with the chances for both sexes being slightly greater by age 65 (Figure 3). All estimates of incidence and prevalence were greater for women than for males, according to a recent meta-analysis of 22 studies on sex differences, even if the differences were not statistically significant [1], [110]. Longevity continues to be a significant factor in the increased incidence of AD in females compared to males, as evidenced by other studies like the Cache County Memory Study [111]. When combined with the challenges associated with estimating incidence, the growing body of evidence from preclinical and medical studies lends credence to the idea that biological mechanisms particular to sex contribute to diverging AD risk. These biological mechanisms are a significant addition to the epidemiologic perspective and warrant further, more thorough research in the future [112], [113].

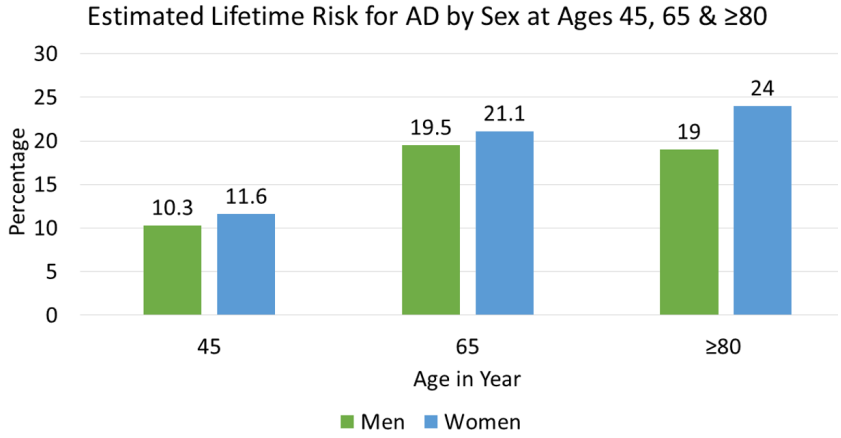

Figure 3. Graphical representation of AD patients according to age between men and women

IMPACT OF SEX ON AD PATHOPHYSIOLOGY

Impact of Sex Hormones in AD

It is commonly known that sex hormones play a part in ageing and AD processes, as well as brain growth [27], [28], [114], [115]. Research on both humans and animals has provided evidence for the functional roles that sex hormones, including androgens, progesterone, and estrogens, play in behavior and thought processes [27], [116]. Age-related reductions in sex hormone levels were

connected to greater odds of AD and memory impairment, with numerous neuroprotective effects implicated [27], [115]. For instance, age-associated declines in both the periphery and the cerebral levels of testosterone are connected to an enhanced vulnerability to establishing AD in males, while decreased lifetime exposure to estrogens is connected to an increased chance of acquiring AD in females (Figure 4). Additionally, it has been documented those ageing causes modifications to downstream signalling cascades and sex hormone receptors [115]. For instance, ageing and AD have been shown to enhance the expression of non-functional splicing variants of estrogen receptor alpha in the hippocampal regions, with higher expression levels in female senior participants than in male subjects [117], [118].

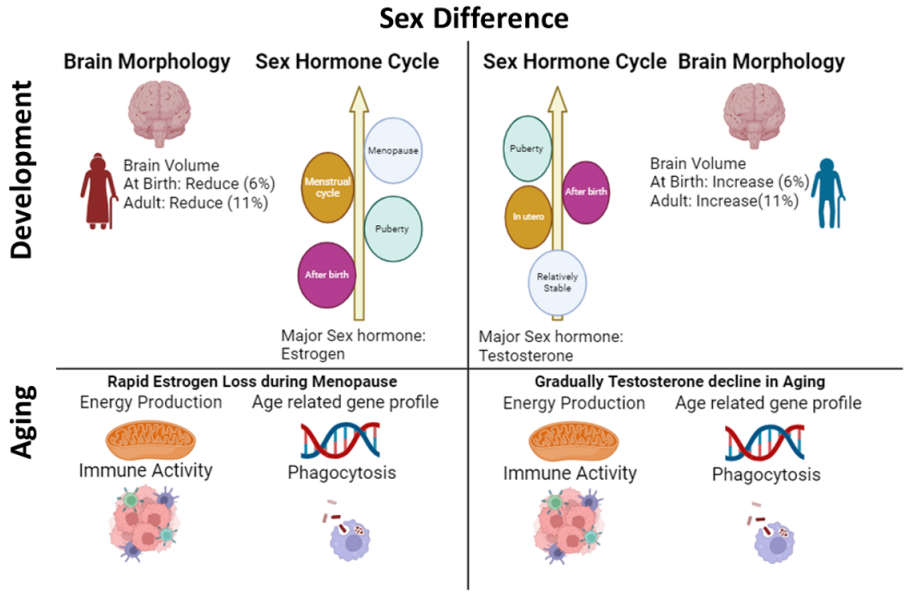

Figure 4. Impact of sex difference on AD pathophysiology

Furthermore, research has revealed that polymorphisms in the estrogen receptor are linked to Cognitive loss and the onset of AD in women, especially in those who carry the APOE $\varepsilon 4$ gene [119], [120]. APOE $\varepsilon 4$ interacts with sex: multiple genetic and biomarker studies report that carrying the APOE $\varepsilon 4$ allele confers a larger relative risk for clinical AD in women than in men, particularly in mid-late life and in certain age windows. This is one of the best-reproduced sex-specific genetic findings in AD (meta-analyses and pooled analyses show stronger effect sizes for women). Strength of evidence: moderate to strong for an interaction in many cohorts, but the effect size and age range vary across studies. Confounders: differences in sample ancestry and age structure, selective survival of $\varepsilon 4$ carriers, and under-representation of non-White populations in genetic studies mean the interaction may not generalise to all groups [24], [121]. These findings imply that as people age and AD develops, the brain becomes less sensitive to sex hormones. However, the outcomes of treatment with sex hormones in clinical trials for AD are highly debatable [27], [106]. Numerous research investigations failed to reveal any therapeutic results, notwithstanding prior research demonstrating that alternative estrogen treatment protects from AD in females [107]. It has been demonstrated that beginning hormone replacement therapy within the vital perimenopausal window may reduce the risk of dementia, but beginning months or years after menopause may raise the risk. Hormone therapy may be ineffective due to factors other than medication time, such as diminished response at downstream signalling and brain receptor cascades. All of these findings point to the intricate role that sex hormones play in AD [108].

Impact of Sex Chromosomes in AD

Sex chromosomes may play a role in the heterogeneity of AD, according to accumulating research. For instance, somatically acquired X chromosomal aneuploidy has been linked to neurodegenerative processes and brain ageing, according to molecular cytogenetic studies. Compared to younger women (age 16), elderly women (age 65) have an X chromosome loss frequency that is more than 100 times higher [122]. Among neurones located in the hippocampal and cerebellum of AD patients, the fre-

quencies of X chromosomal aneuploidy were doubled [39]. Moreover, there is a strong correlation between ageing and AD and premature centromere division (PCD), a genetic mechanism linked to increased aneuploidy (Figure 4).

In the anterior cortex neurons of people with AD, the standard amount of PCD on the X chromosome is about three times more than in control participants [123]. On the X chromosome of AD patients, as well as on the chromosomes of peripheral lymphocytes from men and women over the age of, significantly greater percentages of PCD were found [41], [124]. Conversely, protective effects against AD could be explained by an additional X chromosome, most likely through increased activation of proteins that avoid X inactivation [125]. In comparison to males, females express more X-linked genes due to about fifteen per cent of X-linked genes that evade this inhibition. For instance, human intellectual disability has been linked to mutations with loss of function in the histone demethylase gene KDM6A [11]. Conversely, deletion of KDM6A in CD41 T cells lowered clinical illness and decreased neuropathology in autoimmune conditions, including multiple sclerosis [12], suggesting that KDM6A plays cell type-specific functions in human illnesses [13]. Relentlessly, a recent study on mice showed that Kdm6a2/2 animals had synaptic plasticity and memory problems, and that giving hAPP mice an extra X chromosome gives resilience to AD-related vulnerability in mice, most likely by upregulating KDM6A expression [14], [15]. Another gene implicated in cell-cell recognition crucial to central nervous system function, PCDH11X, is an example of an X-inactivation escapee linked to sex differences in developing AD [16], [17]. It was proposed that PCDH11X uses epigenetic pathways to evade X inactivation [16]. After examining 2356 AD patients and 2384 control participants, researchers discovered a single nucleotide polymorphism (rs5984894) in the PCDH11X gene that was linked to a greater incidence of AD in women [18]. However, the link between PCDH11X polymorphisms and AD was not supported by two further genome-wide association studies [19], [20]. Furthermore, the X chromosome has a large number of genes related to immunological functions [21]. Owing to partial and random inactivation of one of the two X chromosomes, females' immunological responses are more diverse than those of males [22]. To fully comprehend how X chromosomes regulate neuroinflammation, more research is required. Furthermore, the most prevalent acquired mutation in elderly men is loss of chromosomal Y (LOY) [23]. According to a recent study using five transcriptomic datasets, there is a consistent degree of extreme downregulation of chromosome Y. Age and the extreme downregulation of chromosome Y associated with AD are found to interact significantly, suggesting that chromosome Y's extreme downregulation contributes to men's age-related increased risk of AD [26]. When combined, these research streams provide evidence for the significance of sex chromosomes in sex-specific susceptibilities and/or resilience in the ageing of the brain and neurodegenerative processes. The long-ignored functions of related genes and sex chromosomes in the pathogenesis of AD may point to new avenues for future research to comprehend the molecular mechanisms behind sex variations in AD.

CLINICAL DIFFERENCES OF ALZHEIMER'S DISEASE IN MALE AND FEMALE

According to a recent meta-analysis, the prevalence of AD is increasing with age in both sexes, although males are experiencing a greater increase in the 60-69 and 70-79 decades of life. Certain findings indicate that women are more likely than men to have the clinical manifestation of AD [126]. Comprehending the reasons behind the disparity in the correlation between AD pathogenesis and dementia in males and females may provide crucial hints regarding the pathophysiology of AD or may result in sex-specific preventive treatment approaches. Though not unexpected, the sexual dimorphism in the clinical manifestation of AD pathogenesis was stronger than expected, and its causes remain unclear. Men may be more susceptible to dementia than women due to other types of pathology. Heart disease is known to affect males more frequently than women [122], [126]. Some data also point to a higher prevalence of Parkinson's disease and Lewy bodies in men [123], [127]. Cognitive impairment can be a result of any of the three disorders. Women were more likely to have infarcts or Lewy bodies than men in our sample, and even after adjusting for the existence of Lewy bodies and the occurrence of either infarct or stroke, there was still a higher correlation between AD pathophysiology and clinical AD in women.

Another hypothesis states that women might be more susceptible to AD pathology due to a relative deficiency of certain safeguards, such as postmenopausal women's low estrogen levels. For instance, evidence from experiments using mice devoid of estrogen receptors implies that estrogen upregulation plays a critical role in shielding the brain from harm [124], [128]. Lastly, the complicated interaction between the APOE genotype and other biological pathways may be one of numerous variables changing the pathway from pathology to clinical disease in women, even if we statistically corrected for the effect of possessing an $\varepsilon 4$ allele. To investigate these and other options, further investigation

is required [125]. One study discusses data from randomised placebo-randomised controlled trials (RCTs) evaluating presently available therapies for AD, specifically drugs that inhibit cholinesterase (ChEIs) with memantine, to explore potential sex and sex inequalities in their efficacy, safety, and tolerance. A review of the literature was conducted. They evaluated 48 eliminated studies of possible interest, encompassing nearly all presently reported experiments on the four medications in question. Most of the RCTs recruited a higher proportion of female participants to reflect the higher prevalence of AD among women [129].

Elevated cortisol levels, indicative of hypothalamic–pituitary–adrenal (HPA) axis dysregulation, have been consistently implicated in accelerating neurodegeneration in Alzheimer's disease (AD). Emerging evidence suggests that these effects display notable sex differences. Women with AD often exhibit higher basal cortisol levels and a more pronounced association between cortisol elevation and hippocampal atrophy, which may partly explain their faster cognitive decline compared to men [130], [131]. Postmenopausal oestrogen loss further amplifies HPA axis reactivity, lowering neuronal resilience to cortisol-induced damage. In contrast, while men with AD also show increased cortisol, the relationship between cortisol levels and cognitive impairment appears less robust, potentially due to differences in neuroendocrine aging trajectories or cortisol receptor sensitivity. Overall, current knowledge indicates that cortisol dysregulation disproportionately impacts women, reinforcing the need for sex-specific neuroendocrine biomarkers and targeted therapeutic strategies in AD [132].

DISEASE PREDICTORS AND RISK FACTORS OF AD

Age remains the most significant threat to memory impairment, but it's crucial to understand that dementia is not a natural byproduct of ageing on a biological level. Furthermore, not all cases of dementia are limited to the elderly; a significant proportion of instances include youthful onset memory loss, which is characterised by the emergence of signs before the age of 65. According to research, people who adopt a healthy lifestyle practice—such as engaging in consistent workouts, quitting smoking, consuming alcohol in moderation, keeping an appropriate weight, following a nutritious diet, and managing blood pressure, lipid profile, and levels of sugar in the blood—can reduce their risk of cognitive decline and dementia. Additional risk factors include exposure to air pollution, depressive disorders, loneliness in society, a lack of education, and intellectual inactivity [27], [28].

The risk of depression is twice as high in women as in males [114]. Because depression and memory are associated with some of the same brain regions, it can have an impact on cognition throughout the lifespan. Certain studies show that the potential danger of AD dementia in both men and women has been increased by depression [106], with estimations of a 70% increased risk for AD dementia in midlife [107]. Therefore, a medical diagnosis of depressive disorders may have a greater overall influence on the likelihood of AD dementia in women since women experience a higher lifetime prevalence of depression. Men are more likely than women to have sleep apnea generally, but after menopause, women are much more likely to suffer from sleep apnea. This is in contrast to depression [133]. Cognitive decline and an elevated risk of Alzheimer's dementia have been linked to sleep apnea and poor-quality sleep. The overall impact of this risk factor may be stronger in men due to the higher prevalence of sleep apnea in this population. It is noteworthy that not enough research has been done to determine whether sex affects the relationship between sleep apnea and AD dementia [117].

Developing is more likely to occur in both men and women. Alzheimer's disease dementia occurs when there is less schooling [118]. Women are more at risk of AD dementia due to low education since they have had fewer options (lower frequency) to pursue higher education over the past century. Independent of women's access to education, a study has also shown that poorer education may have a bigger negative impact on AD dementia in women [119]. In the United States, women have recently had better educational outcomes than men. Dementia prevalence could be declining more in women than in men in some countries. The slow advancements in women's education over the previous century may help to explain this [120]. AD dementia is more common in men without a spouse or who are widowed than in women [134]. One reason could be that historically, women have been in charge of taking care of their families' health (such as making sure spouses or partners have frequent checkups from doctors, making sure everyone eats a good diet, etc.), at the price of their own well-being. Furthermore, unmarried women are more likely than unmarried men to visit the doctor and participate in communal events, both of which are good for the brain. These findings may account for some of the variation in risk, despite the fact that they are somewhat stereotyped and not true in all circumstances. Carers of elderly, single, or widower males should be aware of this elevated danger and promote social interaction and routine checkups to lower it [134].

Menopause and pregnancy are unique to women. Roughly 12 per cent of pregnancies are affected by hypertensive pregnancy disorders (HPD). A higher risk of HPD has been associated with cognitive impairment and brain shrinkage decades after pregnancy [135]. It has not yet been investigated, nevertheless, whether certain forms of HPD and the risk of AD dementia are related. For women who reach middle age, menopause is a common occurrence. There is information relating the phase of menopause to a reduction in memory for speech [136], and an elevated Early menopause has been associated with an increased risk of dementia (either medically or naturally appearing) [135]. In particular, bilateral oophorectomy performed before menopause has been linked to an accelerated ageing process and an elevated risk of dementia due to the sudden loss of ovarian hormones [136]. To reduce the risk of AD dementia in women, there is still considerable disagreement on the use and type of estrogen-containing hormone therapy (17β-estradiol patch versus conjugated equine estrogens, for example) [137]. recent clinical trials and observational studies have not found an association (positive or negative) with cognitive decline or dementia risk when hormone therapy is started within 5 years of menopause, despite initial results from the Women's Health Initiative Memory study demonstrating that women who were randomized to start taking estrogen treatment beyond a certain age of 65 were at greater Concern about memory loss [138]. These newest studies indicate that it is suitable for relieving symptoms of menopause (which includes hot flashes or sleep and mood disturbances) without the risk of an increased risk of dementia. However, further research is certainly needed.

CURRENT THERAPY FOR AD

AD (Alzheimer's disease) treatment is, in fact, intricate and comprises a variety of individualized components. The following are some essential elements of a multifactorial management strategy for AD:

Estrogen Therapy

By improving hippocampal and prefrontal cortex function, lowering neuroinflammation, stopping estrogen receptor deterioration, lowering oxidative brain damage, and increasing cholinergic and serotonergic activity, estrogen helps prevent dementia. The window phase hypothesis states that early medication, during the first five years after menopause, increases the effects of estrogen in preventing dementia. However, some research has demonstrated that estrogen has negative effects on the brain, including the Women's Health Initiative Memory Study (WHIMS) [139].

Patient Counselling

Doctors, caregivers, and patients must have open lines of communication in order to properly diagnose and treat conditions, as well as to identify symptoms and offer guidance. An effective and genuine communication of thoughts and feelings facilitates a team-based approach to Alzheimer's disease management. Healthcare providers can obtain important insights into the patient's condition by creating a setting where worries and observations are freely expressed. This enables the provision of individualized interventions and support. In addition, patients and caregivers can have the knowledge and tools they need to deal with the difficulties brought on by the illness, which promotes empowerment and understanding. To put it simply, open communication improves the overall quality of life for those with Alzheimer's disease and establishes the groundwork for comprehensive treatment [140].

Behavioural Approaches

It's critical to form predictable and simple surroundings for people with Alzheimer's disease, which includes established habits and communication techniques. These strategies include remaining composed in conversations, providing entertaining activities, speaking honestly, and only declining requests when someone's safety is jeopardised. Making timely plans for legal and medical decisions is also crucial, as is addressing behavioural and cognitive issues with therapies like memory psychological treatment. Exercise, light, and musical assistance can all help to enhance general well-being and cognitive performance. Caretakers and medical professionals can boost the standard of living and effectively manage symptoms of AD patients by combining these approaches to provide the best possible care and assistance [141].

Caregiver Support

Caregivers must incorporate scheduled, brief relaxation breaks to prevent burnout and preserve their well-being. To provide caregivers with information regarding how dementia affects behaviour, function, and cognition, psychoeducation is essential. Setting reasonable goals and developing plans to avoid circumstances that could aggravate symptoms or endanger safety and well-being are further benefits of this instruction. To exchange experiences and get help when needed, caregivers are also urged to create support networks, whether through friends, family, or support organizations. Prioritizing caregiver self-care, offering thorough education, and building up support systems can help caregivers better manage the difficulties of caring for people with dementia while still preserving their resilience and well-being [140], [142].

Pharmacological Interventions

The only AD medications accepted by the Food and Drug Administration are the Glutamate blockers (memantine, galantamine, donepezil, and rivastigmine), which are AChEIs. AChEIs seek to prevent the degradation of acetylcholine in AD sufferers by blocking the acetylcholinesterase enzyme in the synaptic cleft [143]. AChEIs therefore enhance central cholinergic neurotransmission and ultimately appear to reduce cognitive decline, at least during the first year of treatment. Even a short-term cessation of these drugs results in a rapid decline and increases the risk of nursing home admission, albeit there is still a probability of additional deterioration [144].

Since Individuals who began receiving AChEI six months later saw a higher level of neurological impairment compared to those who started it immediately after diagnosis, it is suggested to start treatment as quickly as feasible [96]. All three AChEIs have shown their therapeutic efficacy in delaying deterioration, preserving, or even increasing everyday life activities and cognition in randomised, placebo-controlled studies that lasted up to 52 weeks or more [140], [145]. Additionally, longer-term open-label extension trials indicate the advantages of longer-term care [140]. Glutamatergic transmission is inhibited by memantine, a low-affinity, noncompetitive, open-channel blocker of NMDA receptors, and kidneys have a 70-hour half-life. continue to be its main elimination mechanism. The Food and Drug Administration (FDA) has authorised this as a monotherapy or in combination with an AChEI for intermediate to severe AD. Memantine, also a treatment, has proven to have both short- and long-term benefits for persons with mild to severe AD, according to several tests assessing cognitive ability, psychomotor and mental signs of memory loss, as well as tasks of everyday life (BPSD) [146].

It is possible to utilise memantine and an AChEI together because of their complementary mechanisms of action. With frequently synergistic effects and no increase in negative effects, patients benefit from their combination [140], [141].

NATURAL REMEDIES FOR MEMORY LOSS (ALZHEIMER'S DISEASE)

Even though there is no remedy for the condition, some natural remedies and lifestyle changes may help alleviate symptoms or slow down its progression. Especially when dealing with a complex condition like AD, it's imperative to contact a healthcare expert before attempting any novel remedies

Dietary Changes

Dietary changes play a crucial part in the therapy and supervision of AD. While presently no solution for AD, certain dietary strategies have been shown to support brain health, potentially slowing the progression of cognitive decline and improving an excellent life for those with the disease.

1 Mediterranean Diet

High intakes of fruits, vegetables, whole grains, legumes, nuts, and olive oil, moderate intakes of fish, poultry, and dairy products, and low intakes of red meat and sweets are the hallmarks of the Mediterranean diet. Studies have consistently linked adherence to the Mediterranean diet with a reduced risk of cognitive decline and AD. This diet is rich in antioxidants, anti-inflammatory chemicals, and beneficial fats that may help promote brain cells and support cognitive function [147].

2 DASH Diet

The Dietary Protocols for Avoiding Hypertension (DASH) regimen has a focus on veggies, fruit, whole-grains, and protein-packed meats and dairy products with lower-fat content while minimising sodium, fats that are saturated fats, and sugar additives. The DASH diet has been linked to a decreased risk of AD and mental decline, much like the Mediterranean diet. It may aid in lowering inflammation, along with oxidative stress in the brain and supports cardiovascular health, which is strongly associated with brain health [148].

3 Antioxidant-Rich Foods

Antioxidants aid in preventing oxidative damage to brain cells, which is linked to the onset and advancement of AD. Consuming meals strong in antioxidants, which include green leafy vegetables, berries, and vibrantly colored fruits and vegetables, may help maintain neurological function and lower the risk of memory decline [149], [150].

4 Moderate Alcohol Habit

: Some studies suggest that moderate alcohol use, particularly red wine, may reduce the risk of AD. However, excessive alcohol consumption should be avoided as it might negatively impact brain health [151].

Regular Exercise

Regular exercise is increasingly recognized as an important component of the treatment and management of AD. Being active has been found to offer several benefits for brain health and cognitive function, and it may help delay the onset of AD and enhance the standard of life for affected individuals.

1 Improvement in Cognitive Function

Exercise has been associated with improvements in many elements of mental functioning, particularly recall, focus, and executive function, in both healthful elderly persons along with people with AD. Aerobic exercise, in particular, has been shown to enhance cognitive performance by promoting neuroplasticity and neurogenesis in the brain [152].

2 Reduction in Disease Progression

While exercise cannot cure AD, research suggests that it may help slow the progression of the disease and delay the onset of symptoms. Regular physical activity has been associated with a lower risk of developing AD and may help preserve cognitive function in individuals who already have the condition [153].

3 Enhancement of Brain Health

Exercise enhances brain health by boosting the flow of blood to the brain, promoting the release of neurotrophic factors, and decreasing irritation and cellular oxidative damage, all of which are important for maintaining neuronal function and protecting against neurodegeneration. These effects may help mitigate the pathological processes underlying AD [154].

4 Improvement in Mood and Behavior

AD is often accompanied by changes in mood and behavior, including depression, anxiety, and agitation. Exercise has been shown to have emotion-enhancing effects and may lessen signs of anxiety and depression in patients with AD. Additionally, regular activity can provide a sense of accomplishment and social interaction, which may improve overall well-being [155].

5 Enhanced Quality of Life

Engaging in consistent physical activity can enhance physical function, mobility, and independence in persons with AD, leading to a better overall standard of life. Exercise programs tailored to the individual's abilities and preferences can help maintain functional capacity and promote a sense of autonomy and dignity [156].

Mental Stimulation

Mental stimulation is a crucial component in the therapy and supervision of AD. Engaging in intellectually stimulating activities has been demonstrated to have various rewards for healthy brains and cognitive performance, and it may help slow the progression of AD, improve symptoms, and enhance overall quality of life for affected individuals.

1 Maintenance of Cognitive Function

Mental stimulation helps keep the brain active and engaged, which can help preserve cognitive function and delay the onset of cognitive decline in individuals with AD. Activities such as reading, puzzles, word games, and learning new skills stimulate different areas of the brain and promote neuroplasticity, the brain's ability to adapt and reorganize in response to learning and experience [157].

2 Enhancement of Memory

Memory loss is a common symptom of AD, but engaging in memory-stimulating activities can help improve memory function and retention. Activities that require active retrieval of information, such as reminiscing, storytelling, and memory exercises, can strengthen neural connections and improve memory recall in individuals with AD [158].

3 Promotion of Social Interaction

Social engagement is important for cognitive and emotional well-being, and participating in group activities and social interactions can help individuals with AD feel connected, supported, and stimulated. Group operations, including group discussions, crafts and artistic endeavours lessons, and music therapy sessions, provide an opportunity for social contact and meaningful interactions with others, which can increase mood, minimise feelings of loneliness, and promote general quality of life [159].

4 Reduction of Behaviour-based Symptoms

Alzheimer's disease is often accompanied by behavioural and psychological symptoms, feelings of anxiousness, agitation, and sadness. Engaging in mentally stimulating activities can help distract people from unsettling ideas and emotions, reduce agitation and restlessness, and improve overall mood and well-being [160].

5 Improvement in Quality of Life

Participating in mentally stimulating activities that are enjoyable, meaningful, and customised to the person's interests and abilities can enhance overall quality of life for those with AD. Mental stimulation provides a sense of purpose, achievement, and contentment, and it can aid individuals in maintaining a sense of identity and autonomy despite the challenges of the disease [161].

Social Engagement

Social engagement serves a critical function in the treatment and management of the condition. Maintaining social connections and participating in meaningful social activities can have significant benefits for brain health, memory capacity, including general well-being in persons with AD.

1 Cognitive Stimulation

Social interactions provide opportunities for cognitive stimulation, as they often involve conversation, problem-solving, and engagement with others. Regular social engagement can help keep the brain active and engaged, promoting neuroplasticity and supporting cognitive function in individuals with AD [162].

2 Emotional Support

Social connections and relationships provide emotional support and companionship, which are important for emotional well-being and resilience in individuals with AD. Having a strong support network of family, friends, and caregivers can contribute to the reduction of feelings of loneliness, depressive thoughts, and fear, and enhance overall mood and quality of life [163].

3 Enhanced Quality of Life

Engaging in social activities that are enjoyable, meaningful, and personalized to the individual's interests and abilities can enhance overall quality of life for individuals with AD. Social engagement provides opportunities for recreation, leisure, and cultural enrichment, and it can help individuals maintain a sense of identity, purpose, and connection to the world around them [164].

4 Reduction of Behavioural Psychology Symptoms

AD is often accompanied by psychomotor and mental symptoms such as restlessness, aggression, and wandering. Social engagement can help reduce these symptoms by providing individuals with meaningful activities and interactions that distract them from distressing thoughts and behaviors, and promote feelings of calm and security [165].

5 Delay of Disease Progression

Some research suggests that maintaining strong social connections and engaging and intriguing in regular workouts could be beneficial in delaying the onset of AD and slowing its progression. Social engagement has been associated with a lower risk of memory loss and dementia in older persons, underscoring the necessity of keeping engaged in society throughout the lifespan [166].

Sleep Quality

Sleep errors are widespread in individuals with AD and can have significant implications for cognitive function, disease progression, and general quality of life. Addressing sleep quality is an important aspect of the treatment and supervision of memory loss.

1 Understanding Sleep Changes

AD often disrupts sleep patterns, leading to alterations in sleep-wake cycles, nighttime awakenings, and daytime sleepiness. These changes may result from underlying neuropathological changes in the brain, alterations in neurotransmitter systems, or disturbances in the circadian rhythm. Understanding the specific sleep disturbances experienced by individuals with AD is essential for developing targeted interventions [167].

2 Building a Comfortable Sleep Environment

Optimising the sleep environment can help promote better sleep quality in individuals with a memory decline. This may include maintaining a consistent sleep schedule, minimizing noise and light disturbances, ensuring comfortable bedding and room temperature, and reducing factors that may cause discomfort or anxiety during the night. Creating a calm and soothing bedtime routine can help indicate to the body that it is appropriate to sleep [168].

3 Addressing Sleep Disorders

Sleep-related conditions, including sleeplessness, restlessness in the legs, and periodic movement of the limbs, are common in persons with dementia and may aggravate cognitive impairment and behavioural symptoms. Identifying and treating underlying sleep disorders through pharmacological and non-pharmacological therapies, including CPAP (continuous positive airway pressure), for sleep apnea or medications for insomnia, may help enhance sleep quality & general well-being [169].

4 Promoting Activities with Availability to Sunlight During the Day

Regular physical engagement and exposure to daylight during the day can help balance the rhythm of sleep and wakefulness, along with encouraging more restful sleep quality in individuals with AD. Encouraging daytime activities, such as exercise, outdoor walks, and personal participation in social and cognitive stimulation, can help maintain circadian rhythms and improve sleep efficiency. Contact with sunshine, particularly in the morning, may also assist in synchronizing the body's internal clock and promote daytime alertness and nighttime sleepiness [170].

5 Managing Behavioural Symptoms

Behavioural symptoms such as worry, aggressive behaviour, and restlessness can disrupt sleep and contribute to sleep disturbances in patients with memory loss. Addressing these symptoms through behavioural interventions, environmental modifications, and, when necessary, pharmacological treatments, may restore sleep quality and overall management of the disease [171].

Stress Reduction

Stress reduction techniques can play a valuable role in the treatment and management of AD. Chronic stress has been associated with cognitive decline and exacerbation of AD symptoms, while stress reduction strategies can help improve overall well-being and potentially slow disease progression. Here are some stress reduction techniques and their benefits, supported by research:

1 Mindfulness Meditation

People with loss of memory and those who care for them have been found to have less stress, worry, and despair when they practice mindfulness meditation, which is focusing on the here and now without passing judgment. In addition to improving emotional resilience and general quality of life, mindfulness techniques can assist people in managing the difficulties posed by the illness [172].

2 Relaxation Techniques

For those with AD, relaxation methods like gradual relaxation of muscles, prolonged respiration, and guided visualisation may assist with decreased levels of stress and encourage relaxation. These methods are simple to adopt into everyday activities and may help decrease tension, nervousness, and sleeplessness difficulties [173].

3 Active Living

Habitual exercise has been demonstrated to lower stress and increase mood in patients with cognitive decline. Exercise increases the production of chemicals called endorphins that function as natural mood boosters, and it can help individuals cope with stressors more effectively. Additionally, physical activity has numerous other benefits for brain health and cognitive function [174].

4 Social Support

People suffering memory impairment and their caretakers might experience less stress and loneliness by keeping up social ties and getting support from friends, family, and support groups. Social support offers opportunities for socialization, practical help, and emotional validation, all of which can strengthen coping strategies and boost general well-being [175].

5 Cognitive Enhancement

Participating in intellectually invigorating tasks such as puzzles, games, and creative arts can assist distract persons with memory loss from stressors and provide a sense of accomplishment and enjoyment. Cognitive stimulation promotes brain Wellness. Programs might reduce cognitive operate and resilience to stress over time [161].

HERBAL SUPPLEMENTS

Several herbal supplements have been examined regarding their possible advantages in AD. However, it's vital to remember that data from science confirming their effectiveness is often limited, and they must be used carefully and under the advice of someone with medical training. Here are some herbal supplements that have been investigated:

Ginkgo Biloba

Ginkgo biloba is among the most widely used supplements from natural sources for cognitive advancement. Certain research indicates that it may enhance cognition and recall in persons with Alzheimer's disease, though results have been mixed. Because of its acceptable blood-thinning effects, *Ginkgo biloba* must be used with prudence, particularly in people on drugs that inhibit coagulation.

1 Meta-Analysis by Birks *et al.* (2015)

: This meta-analysis evaluated the efficacy of *Ginkgo biloba* for enhancing cognition and dementia, including Alzheimer's disease. The investigation included several randomly assigned trial designs and concluded that *Ginkgo biloba* showed some promise in enhancing cognitive function and performing everyday activities in individuals with memory loss. However, the authors also highlighted the need for further high-quality studies to confirm these findings [176].

2 Systematic Review and Meta-Analysis by Weinmann *et al.* (2019)

This comprehensive study and meta-analysis assessed the outcomes of *Ginkgo biloba* in dementia, including Alzheimer's disease. The review included 21 randomized controlled trials and found that *Ginkgo biloba* extract may have some beneficial effects on Memory retention as well as tasks of daily living in adults having intermediate to moderate cognitive decline. However, the authors emphasized the need for further well-designed studies to validate the results and identify the appropriate dosage and duration of treatment [177].

Turmeric

Turmeric, specifically its primary ingredient is curcumin, has attracted recognition for its potential therapeutic effects in AD (Alzheimer's disease) due to its anti-inflammatory and antioxidant qualities.

1 Review by Aggarwal *et al.* (2007)

This review discusses the potential therapeutic effects of curcumin, the active component in turmeric, combating several ailments, notably neurodegenerative disorders like AD. It explores curcumin's anti-inflammatory and antioxidant properties, as well as its ability to modulate various signalling pathways implicated in neurodegeneration [178].

2 Clinical Trial by Baum *et al.* (2008)

This clinical trial investigated the efficacy of curcumin in patients with AD. It was a six-month randomised, placebo-controlled, double-blind pilot study. Although the study found no substantial changes in both cases, curcumin and placebo collections based on cognitive outcomes, it did observe trends toward improvement in some measures. The authors noted the need for larger trials to confirm these findings [179].

3 Review by Chin *et al.* (2020)

An overview of curcumin's neuroprotective qualities in memory loss is given in this assessment. It discusses the mechanisms underlying curcumin's potential benefits, including its antioxidant, anti-inflammatory, and anti-amyloid characteristics. The review also addresses the challenges associated with curcumin, such as its poor bioavailability and rapid metabolism, and explores strategies to enhance its efficacy as a therapeutic agent [180].

Huperzine A

The potential therapeutic benefits of (Huperzine A), a naturally occurring alkaloid molecule for memory decline, have been investigated.

1 Review by Wang *et al.* (2011)

An outline of the developments in research on huperzine A is given in this review, with particular attention to its pharmacological characteristics, modes of action, and its medical uses. It discusses Huperzine A's ability to inhibit acetylcholinesterase (AChE) and its neuroprotective effects, which have been linked to its possible effectiveness in treating Alzheimer's disease [181].

2 Clinical Trial by Xu *et al.* (1995)

This clinical research examined the efficacy of Huperzine A in people with cognitive decline. It was a randomly allocated, double-blinded, placebo-controlled study that evaluated the effects of medication Huperzine A on mental processes, memory, and activity. The study found that Huperzine, when compared to a placebo, a therapy produced notable changes in behaviour and cognitive performance, indicating that it may be used as a medicinal agent for Alzheimer's disease [182].

3 Review by Rafii *et al.* (2011)

This review describes a phase II clinical trial of Huperzine A in patients with mild to moderate Alzheimer's disease. The trial assessed the safety, tolerability, and efficacy of Huperzine A treatment over 16 weeks. While the study did not meet its primary endpoint of demonstrating a significant difference in cognitive function between the Huperzine A and placebo groups, it did observe trends toward improvement in some cognitive measures, suggesting potential benefits that warrant further investigation [183].

Bacopa Monnieri

The traditional Ayurvedic herb *Bacopa monnieri*, also referred to as Brahmi, has been researched for its possible therapeutic benefits in addressing Alzheimer's disease (AD) along with other cognitive disorders.

1 Review by Aguiar and Borowski (2013)

This comprehensive review provides an overview of the neuropharmacological effects of *Bacopa monnieri*, focusing on its potential as a nootropic agent. It discusses *Bacopa monnieri's* ability to enhance cognitive function, including memory and learning, through various mechanisms such as antioxidant activity, cholinergic modulation, and neuroprotection. The review also highlights *Bacopa monnieri*'s potential therapeutic applications in age-associated dementia and neurodegenerative illnesses like dementia [184].

2 Clinical Trial by Calabrese *et al.* (2008)

This clinical trial investigated the Impacts of a standard *Bacopa monnieri* extract on cognitive function, depression, and anxiousness in the elderly. It was a (randomised, double-blind, placebo-controlled study) that evaluated the cognitive effects of *Bacopa monnieri* supplementation over 12 weeks. The study found that *Bacopa monnieri* supplementation led to significant improvements in cognitive abilities, particularly focus, memory of words, and cognitive processing speed, compared to a placebo, suggesting its potential as a cognitive enhancer in the elderly population [185].

3 Review by Kongkeaw *et al.* (2014)

This meta-analysis reviewed randomized controlled studies on the cognitive effects of *Bacopa monnieri* extract. It is analysed data from several studies and found that *Bacopa monnieri* supplementation was related to considerable increases in mental ability, including memory, attention, and cognitive processing speed, compared to placebo. The meta-analysis suggests that *Bacopa monnieri* may have potential as a cognitive enhancer, particularly in populations with cognitive impairment or age-related cognitive decline [186].

Ashwagandha

Ashwagandha (*Withania somnifera*), also known as Indian ginseng or winter cherry, is an adaptogenic herb traditionally used in Ayurvedic medicine for its various health advantages. Although studies on ashwagandha's potential memory loss are still in their infancy, some have looked into its neuroprotective and cognitive-boosting qualities.

1 Review by Kuboyama *et al.* (2017)

This review discusses the neuroprotective effects of Withanoside IV and its active metabolite sominone, which are compounds found in Ashwagandha. It explores their potential in attenuating neurodegeneration induced by amyloid-beta (Aβ) peptides, which are implicated in AD pathology. The review highlights the therapeutic potential of Ashwagandha and its bioactive compounds in mitigating AD-related neurodegeneration [187].

2 Study by Dubey *et al.* (2021)

This study investigated the inhibitory effects of Ashwagandha on the aggregation of human lysozyme induced by amyloid-beta (Aβ). The aggregation of proteins like lysozyme corresponds to cognitive decline pathology. The findings propose that Ashwagandha may have potential in inhibiting protein aggregation, which could be relevant to AD treatment [188].

3 Review by Cohen *et al.* (2016)

While this review focuses on Tulsi (*Ocimum sanctum*), it briefly discusses Ashwagandha and its potential neuroprotective effects. It highlights Ashwagandha's adaptogenic qualities and its involvement in reducing stress, which could indirectly benefit cognitive function and potentially contribute to AD management [189].

Sage

Sage (*Salvia officinalis*) has been explored for its prospective therapeutic properties in Alzheimer's disease (AD), particularly due to its cholinergic properties and antioxidant activity.

1 Review by Perry *et al.* (2001)

This review explores the in vitro activity of *Salvia lavandulaefolia* (Spanish sage) and its relevance to the treatment of memory loss. It investigates the effects of sage extracts on acetylcholinesterase (AChE) activity, which is targeted by conventional AD medications. The study suggests that sage may possess cholinergic properties that could be beneficial in AD treatment [190].

2 Study by Akhondzadeh *et al.* (2003)

This double-blind, randomized, placebo-controlled trial investigated the efficacy of *Salvia officinalis* extract in patients with mild to moderate AD. The study found that sage extract treatment led to significant improvements in cognitive function compared to placebo, as measured by various cognitive assessment scales. The research studies indicate that sage might have significance as a medicinal agent for AD [191].

3 Review by Howes *et al.* (2009)

This review discusses the role of phytochemicals, including those found in sage, in the therapy and prevention of dementia, including cognitive disease. It explores the neuroprotective effects of sage constituents such as rosmarinic acid and carnosic acid, which have anti-inflammatory and antioxidant qualities. The review highlights the potential of sage and its phytochemicals in mitigating neurodegeneration and cognitive decline associated with Alzheimer's disease [192].

Lion's Mane Mushroom

Lion's mane mushroom (*Hericium erinaceus*) has drawn interest due to the possibility of neuroprotective and memory-enhancing properties, making it a subject of interest in cognitive research.

1 Study by Mori *et al.* (2009)

This double-blind, placebo-controlled clinical trial examined the impact of the lion's mane mushroom (*Hericium erinaceus*) on moderate cognitive decline (MCI), a syndrome that typically precedes AD. The review found that supplementation with lion's mane mushroom led to significant improvements in mental abilities relative to placebo, as measured by various cognitive tests. The findings suggest that lion's mane mushroom may have potential in improving memory function in individuals with MCI, possibly contributing to the prevention or management of Alzheimer's disease [193].

2 Study by Wong *et al.* (2011)

While this study primarily focuses on the neurodegenerative potential of lion's mane mushroom in the treatment of peripheral nerve injury, it also discusses its implications for neurodegenerative disorders such as Alzheimer's disease. The review highlights the neuroprotective and neurodegenerative properties of lion's mane mushroom, suggesting its potential in promoting nerve growth and repair, which could be beneficial in Alzheimer's disease and other neurodegenerative conditions [194].

3 Review by Friedman (2015)

This review provides an overview of the chemistry, nutrition, and health-promoting properties of lion's mane mushroom, focusing on its fruiting bodies and mycelia and their bioactive compounds. It discusses the potential neuroprotective effects of lion's mane mushroom constituents such as erinacines and hericenones, which have been shown to stimulate nerve growth factor (NGF) synthesis and promote nerve survival and function [195].

Omega-3 Fatty Acids

Omega-3 fatty acids are believed to have been investigated for their potential therapeutic role in AD is a degenerative neurological condition marked by cognitive loss and impaired memory. Research suggests that Omega-3 fatty acids are notably DHA (docosahexaenoic acid) and EPA (eicosapentaenoic acid), may offer benefits in the prevention and treatment of memory loss.

4 Anti-Inflammatory Effects

The brain's persistent inflammation is associated with AD progression. It has been demonstrated that omega-3 fatty acids have anti-inflammatory qualities, potentially reducing neuroinflammation and its detrimental effects on cognitive function [196].

5 Neuroprotective Effects

DHA is a crucial agent of neuronal membranes and contributes to maintaining neuronal structure and function. Improved synaptic plasticity and neuronal integrity have been associated with adequate DHA levels, which may lessen cognitive loss in AD [197].

6 Modulation of Amyloid-beta Metabolism

Fish oil (Omega-3) may influence the production and clearance of amyloid-beta peptides, which can build up to create plaques in AD patients' brains. Some studies imply that omega-3 fatty acids could potentially reduce amyloid-beta accumulation, though More study is required to determine the mechanisms involved [198].

7 Cognitive Benefits

Research studies exploring the consequences of taking supplements with fish oil on cognitive function in Alzheimer's disease have yielded various outcomes. While some studies have reported improvements in cognitive performance and slower rates of cognitive decline, others have found no significant effects. Variability in study design, patient populations, and treatment protocols may contribute to these discrepancies [199].

Coconut Oil

Coconut oil has gained attention as a potential dietary intervention for AD due to its unique composition of medium-chain triglycerides (MCTs), particularly lauric acid. Some proponents suggest that MCTs may provide an alternative energy supply for the brain and may boost cognitive abilities in those with AD. The effectiveness of coconut oil in addressing dementia is currently up for debate, though, and there is limited information that promotes its implementation.

8 Potential as an Alternative Energy Source

Unlike long-chain fatty acids, MCTs are rapidly metabolised by the liver into ketone bodies, which can pass the barrier, the blood and the brain (BBB) and act as an alternate source of energy for the brain. Ketones have been proposed to deliver power to neurons that are unable to utilise glucose efficiently, as is the case in AD [200].

9 Animal and Preliminary Human Studies

Some animal studies and small-scale human trials have reported modest improvements in cognitive function following MCT supplementation, including coconut oil. However, these studies often suffer from methodological limitations, such as tiny sample sizes with the absence of stringent supervision, rendering it challenging to make solid decisions [201].

10 Mixed Clinical Evidence

Clinical trials investigating the effects of coconut oil or MCT supplementation on AD have given mixed outcomes. While some research has shown improvements in daily living activities and cognitive performance, other studies have not identified any appreciable advantages. Variability in study design, participant characteristics, and treatment protocols may contribute to these discrepancies [202].

11 Safety Concern

While coconut oil is usually considered suitable for consumption, its high saturated fat content raises concerns regarding its impact on cardiovascular health, notably in those with existing heart conditions. Long-term consumption of large amounts of coconut oil may also lead to weight gain and other metabolic issues.

CONCLUSION

Alzheimer's disease shows notable sex-based differences in both prevalence and clinical trajectory. Women not only exhibit a higher lifetime risk but also tend to experience faster cognitive decline and greater disease burden. Emerging evidence suggests that biological factors, hormonal influences, and sociocultural determinants contribute to these disparities. Although current therapies provide only limited symptomatic relief, patterns of sex-specific treatment response are beginning to surface, underscoring the need for more nuanced therapeutic strategies. Overall, these findings highlight

significant gaps in knowledge and emphasize the imperative for future research to develop tailored interventions and reduce sex-related disparities in Alzheimer's care.

SUPPLEMENTARY MATERIAL

No supplementary material is provided for this study.

AUTHOR CONTRIBUTIONS

Sourav Khawas: Conceptualization, Methodology. Kausik Bhar: Study selection and quality assessment. Nirjhar Duttagupta: Data extraction. Kishor Kumar Roy: Protocol development. Bishal Banerjee: Writing-original draft. Sayan Chatterjee: Literature search strategy. Arijit Mondal: Data extraction. Suddhasattya Dey: Formal analysis and synthesis. Saptarshy Sarkar: Study selection and quality assessment. Jhanvi Soni: Literature search strategy.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DECLARATION OF GENERATIVE AI USE

During the preparation of this manuscript, the authors used ChatGPT (OpenAI, model GPT-5.1) for language editing and text improvement. After using this tool, the authors thoroughly reviewed and revised the generated content, taking full responsibility for the accuracy and integrity of the final manuscript.

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