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REVIEW ARTICLE

A Review on Modifiable Risk Factors and Preventive Measures in Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) represents a progressive neurodegenerative disorder that primarily affects memory, language, and visuospatial abilities, with aging as the predominant risk factor. Currently affecting approximately 40 million individuals globally, AD prevalence is projected to increase substantially by 2050. While genetic mutations account for a small percentage of cases (familial AD), most cases are sporadic with multifactorial origins encompassing genetic, environmental, and lifestyle components. The neuropathological hallmarks include amyloid β plaques, tau neurofibrillary tangles, mitochondrial dysfunction, and synaptic deficits. Clinical diagnosis achieves high accuracy when established criteria are properly implemented, though effective treatments remain limited. Recent evidence points to several modifiable risk factors influencing AD onset and progression, particularly in late-onset cases. Psychosocial elements, including social engagement, cognitive stimulation through bilingualism, and emotional wellbeing, demonstrate protective effects. Pre-existing conditions like diabetes, hypertension, dyslipidemia, and obesity significantly increase risk through vascular mechanisms. Lifestyle factors such as physical inactivity, poor dietary habits, sleep disruption, alcohol consumption, smoking, and inadequate oral health further contribute to risk elevation. Prevention strategies emphasize managing vascular and metabolic conditions, promoting physical activity, adherence to beneficial dietary patterns, and addressing psychological health. Nutritional factors, particularly vitamins B6, B12, D, E, and folate, may influence AD development through oxidative stress and homocysteine pathways. Multi-domain interventions targeting these modifiable factors offer promising approaches to delay onset and reduce disease burden.

Keywords: Alzheimer's disease; Neuropathology; Risk factors; Preventive Measures; Cognitive decline.

1. Introduction

Alzheimer's disease (AD) is a neurological condition characterized by progressive degeneration predominantly affecting the hippocampus and cerebral cortex [1]. The clinical manifestation primarily presents as deterioration in cognitive domains, specifically impacting language processing, memory formation, and visuospatial abilities, which form the cornerstone of diagnostic criteria [2].

The global burden of AD is substantial, with current estimates indicating approximately 40 million affected individuals, predominantly over 60 years of age. This number is projected to double every two decades until at least 2050, presenting significant healthcare challenges [3]. While the majority of cases appear sporadically, a rare hereditary form, Familial Alzheimer's Disease (fAD), accounts for less than 0.5% of cases. These genetic cases stem from mutations in three specific genes: amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2), typically manifesting between ages 30 and 50, mostly earlier than sporadic cases [4].

The neuropathological landscape of AD is complex, characterized by several key features. These include region-specific reductions in cerebral glucose metabolism, intraneuronal neurofibrillary tangles composed of hyperphosphorylated tau protein, extraneuronal toxic amyloid oligomers, and pronounced synaptic and mitochondrial dysfunction [5]. Multiple proteins play crucial roles in early-onset AD pathogenesis, including the lipid-carrier apolipoprotein E (apoE), presynaptic α-synuclein, microtubule-associated protein tau, and Aβ peptides [6]. Notably, metal ion dysregulation, particularly involving zinc, copper, and iron in neocortical regions, contributes significantly to toxic Aβ precipitation [7]. The amyloid cascade typically initiates several decades before clinical symptoms emerge [8], with progressive accumulation of senile plaques distinguishing AD from normal aging processes [9].

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The historical context of AD dates back to 1901, when Auguste Deter became the first documented case [10]. Current therapeutic approaches primarily rely on acetylcholinesterase inhibitors for mild to moderate AD stages, aiming to enhance cognitive function [11]. However, effective treatment options remain limited, and apart from genetic cases, the fundamental disease mechanisms continue to elude complete explanation [12]. Clinical diagnosis achieves over 90% accuracy when established criteria are meticulously followed [13]. As individuals age, the neuropathological basis of clinically identified "AD dementia" exhibits increasing complexity [14], necessitating comprehensive approaches to both diagnosis and treatment. The behavioral manifestations of AD extend beyond cognitive decline, encompassing a broad spectrum of neuropsychiatric symptoms, including mood alterations, apathy, agitation, and psychotic features [15].

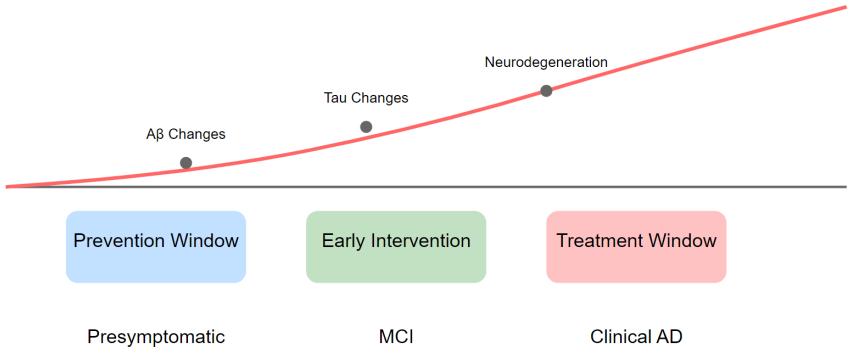

Figure 1. Timeline of AD Progression and Critical Intervention Windows

2. Epidemiology

The global impact of dementia has reached unprecedented levels, currently affecting an estimated 24 million individuals worldwide. This figure is projected to escalate dramatically through 2040, creating an immense healthcare burden [16]. Within this broader context, Alzheimer's disease emerges as the predominant form of dementia, characterized by progressive deterioration of cognitive abilities, with memory impairment typically marking its initial presentation [17]. The epidemiological landscape of AD reveals distinct patterns in disease distribution and risk factors. The lifetime risk demonstrates notable gender disparity, with estimates indicating 33.6% risk for males and 41.9% for females [18]. This gender-based difference suggests potential hormonal or sex-linked factors influencing disease development and progression.

Disease frequency is traditionally quantified through three primary epidemiological indicators: mortality, prevalence, and incidence rates [19]. These metrics provide crucial insights into disease patterns and help inform healthcare planning and resource allocation. The distribution of AD cases shows significant familial aggregation in both early- and late-onset forms, as demonstrated by multiple case-control investigations [20]. Environmental and behavioral factors play substantial roles in disease etiology and progression, as evidenced by robust epidemiological studies. AD patients frequently present with multiple pre-existing conditions compared to age-matched controls, emphasizing the importance of maintaining overall physical health in preserving cognitive function [21]. The clinical manifestation of AD encompasses a complex array of symptoms affecting multiple domains. Beyond cognitive decline, patients experience progressive deterioration in behavioral patterns and daily functioning capabilities [22]. This multifaceted presentation necessitates comprehensive care approaches addressing both cognitive and functional aspects of the disease. Current epidemiological research increasingly focuses on identifying modifiable risk factors and potential intervention points. This approach has revealed multiple promising targets for prevention and early intervention strategies, particularly in cases without clear genetic predisposition [23]. Population-based studies have identified several demographic and socioeconomic factors influencing AD risk and progression. These findings highlight the importance of considering both individual and population-level interventions in disease prevention and management [24, 25].

3. Modifiable Risk Factors

3.1. Psychosocial Factors

3.1.1. Social Interaction

Social engagement emerges as a crucial protective factor against cognitive decline in AD. Neuronal resources beyond the medial temporal lobes facilitate learning through interactive communication sessions, creating robust learning environments [26]. Research demonstrates that strong social connections significantly reduce the likelihood of age-related cognitive deterioration, though the underlying neural mechanisms require further elucidation [27].

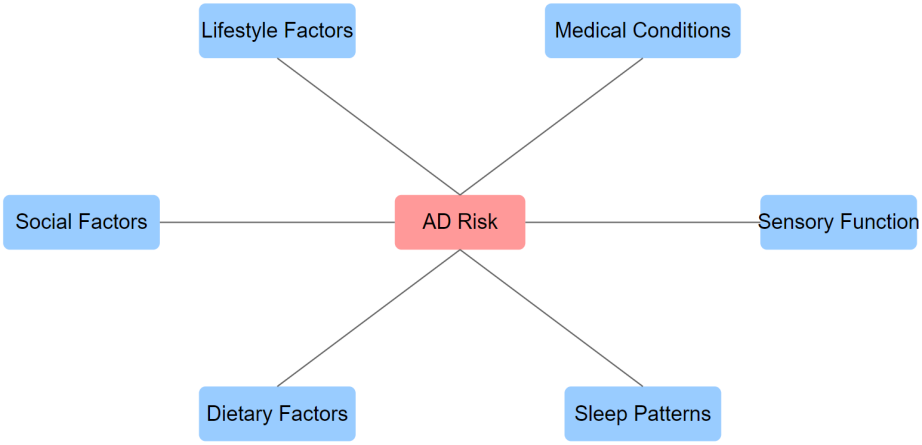

Figure 2. Modifiable Risk Factors in AD

Regular participation in social activities may delay AD onset and slow cognitive decline progression [28]. Therapeutic approaches incorporating social elements have shown promise, with oxytocin therapy demonstrating improved social and non-social memory in older adults. Research suggests oxytocin's potential role in reducing brain inflammation and alleviating memory deficits in AD patients [29].

Table 1. Major Modifiable Risk Factors for Alzheimer's Disease and Their Relative Risk

Risk Factor Category	Specific Factor	Relative Risk (95% CI)	Population Attributable Risk (%)
Cardiovascular	Hypertension	1.61 (1.16-2.24)	8.9
	Diabetes	1.73 (1.65-1.82)	3.2
	Midlife Obesity	1.91 (1.40-2.62)	7.0
Lifestyle	Physical Inactivity	1.82 (1.19-2.78)	12.7
	Smoking	1.59 (1.15-2.20)	13.9
	Low Educational Attainment	1.59 (1.35-1.86)	19.1
Psychosocial	Depression	1.90 (1.55-2.33)	10.6
	Social Isolation	1.57 (1.32-1.85)	5.9
Sensory	Hearing Loss	1.94 (1.38-2.73)	8.2

3.1.2. Cognitive Function and Bilingualism

Early exposure to multiple languages correlates with improved cerebrospinal fluid (CSF) AD biomarker profiles [30]. Bilingualism potentially contributes to cognitive reserve (CR), effectively delaying symptom onset. Studies of bilingual individuals' brains reveal greater atrophy in relevant regions while maintaining better functional capacity, supporting the protective effect of bilingualism through enhanced CR [31].

The bilingual cognitive reserve effect involves multiple cellular and molecular mechanisms. These include alterations in neuronal metabolic processes, dynamic neuronal-glial interactions, vascular system modifications, changes in myelin structure, and adaptations in neurochemical signaling pathways [32].

3.1.3. Educational Attainment

Education's influence on AD manifestation remains complex, with varying research outcomes regarding the reserve hypothesis [33]. Studies suggest that while patients with lower educational levels may demonstrate longer survival post-diagnosis [34], education's impact operates through both direct and indirect pathways, particularly via occupational status.

Research utilizing multiple regression analyses of neuroimaging data, including T1-weighted magnetic resonance imaging, FDG positron emission tomography, and floribetapir imaging, indicates that education may not directly protect brain volume in healthy controls or AD patients. However, it appears particularly beneficial during the mild cognitive impairment (MCI) stage, potentially delaying dementia onset through brain reserve mechanisms [35].

3.1.4. Stress and Depression

Depression and AD demonstrate significant comorbidity [36], with stress playing a fundamental role in disease onset and progression. Physiological stress responses substantially impact recovery capacity and quality of life, particularly in neurodegenerative conditions [37]. Several interconnected stress-related mechanisms contribute to AD pathology. The inflammatory cytokine activation, hypothalamic-pituitary axis modulation, hypothalamic-pituitary gonadal system alterations, and arginine vasopressin system changes orchestrate complex responses to various stressors. These systems trigger glucocorticoid and "oxidopamatergic" cascades in response to physical and psychological challenges [38]. Astrocytes emerge as potential therapeutic targets for both AD and stress-dependent depression, given their responsiveness to glucocorticoids and stress [39]. Stress and glucocorticoid exposure can elevate amyloid β precursor protein levels and tau phosphorylation, contributing to synaptic dysfunction and neuronal death in AD [40]. Depression affects up to 50% of AD patients, complicating care management [41]. Lifetime major depression doubles AD risk and increases AD-related neuropathology [42].

3.2. Pre-existing Conditions

3.2.1. Metabolic Disorders

The intersection of metabolic disorders with AD pathology presents a complex relationship involving multiple systemic disruptions. Diabetes mellitus, hypertension, and dyslipidemia frequently coexist in AD patients, creating a challenging therapeutic landscape [43]. In older Alzheimer's caregivers, sleep disturbances and irregular sleep durations correlate with increased prevalence of type 2 diabetes, dyslipidemia, and hypertension [44].

Hyperinsulinemia, resulting from increased adiposity and insulin resistance, shows strong associations with elevated AD risk. Multiple studies have established diabetes as a significant risk factor for AD development [45]. The relationship between these metabolic conditions and AD involves shared molecular mechanisms, particularly in butyrylcholinesterase and acetylcholinesterase-related proteins, which influence both lipid metabolism and insulin resistance [46].

3.2.2. Cardiovascular Factors

Cardiovascular pathology significantly influences AD progression through multiple mechanisms. Midlife hypertension impairs cognitive performance independently of other cardiovascular risk factors, increasing late-life dementia risk [47]. The "amyloid hypothesis" linking amyloid β accumulation to AD development intertwines with cerebrovascular pathology, particularly through risk factors including diabetes, obesity, atherogenic dyslipidemia, and hypertension [48]. Chronic brain hypoperfusion, accelerated by cardiovascular disease risk factors, precedes AD development. This relationship suggests frequent coexistence of vascular dementia with late-onset AD [49]. The Rotterdam Study revealed that repeated cerebral microbleeds significantly increase AD risk (HR 2.10, 95% CI 1.21-3.64). Similarly, arteriolosclerosis (OR 1.20, 95% CI 1.04-1.40) and severe cerebral atherosclerosis (OR 1.33, 95% CI 1.11-1.58) emerge as substantial risk factors [50].

3.2.3. Obesity

Obesity's relationship with AD involves complex molecular mechanisms extending beyond simple weight-related effects [51]. Obesity-mediated pathophysiological processes manifest in both adipose tissue and brain structures [52]. Temporal considerations prove crucial, as midlife obesity associates with a 33% greater AD risk (OR = 1.33, 95% CI = 1.03-1.62), while late-life obesity shows an inverse relationship (OR = 0.57, 95% CI = 0.47-0.68) [53].

The brain's susceptibility to oxidative stress, attributed to its high lipid content and oxygen consumption coupled with limited antioxidant defenses, makes it particularly vulnerable in obesity-related conditions [54]. Excess adipose tissue increases adipokine release, correlating with both cognitive dysfunction and structural brain abnormalities [55].

3.2.4. Hyperhomocysteinemia

Hyperhomocysteinemia (HHcy) represents a modifiable risk factor whose management may delay AD onset. This condition, characterized by elevated blood homocysteine levels, involves complex interactions with vitamin metabolism during AD's preclinical stage [56]. The methionine cycle generates homocysteine, with metabolism occurring through remethylation and trans-sulfuration pathways [57]. AD patients with HHcy demonstrate elevated fibrin(ogen) levels and increased Aβ deposits in blood vessels and brain parenchyma [58]. Folic acid shows dose-dependent effects on hippocampal dentate gyrus neurogenesis through interactions with hyperhomocysteinemia [59]. These findings suggest that enhancing homocysteine metabolism could offer preventive benefits in AD.

3.3. Traumatic Brain Injury

3.3.1. Epidemiological Evidence

Traumatic brain injury (TBI) represents a significant epigenetic risk factor in AD development, with epidemiological studies indicating β-amyloid plaques in approximately 30% of TBI-related fatalities [60]. The Danish and Swedish population studies provide compelling evidence of this association. The Danish study revealed increased AD risk among TBI patients (HR 1.16, 95% CI 1.12-1.22), while the Swedish study demonstrated even stronger correlation (OR 1.58, 95% CI 1.49-1.69). These associations proved particularly robust in cases involving severe or multiple traumatic brain injuries, during initial post-trauma months, among younger individuals, and in injuries affecting the spine or skull [61].

3.3.2. Pathophysiological Mechanisms

TBI initiates widespread disruptions in behavior, consciousness, and cognition, extending beyond focal damage to specific brain regions [62]. The pathogenic mechanisms linking TBI to dementia and neurodegeneration encompass multiple pathways. Chronic traumatic encephalopathy (CTE), a consequence of repeated concussive head injuries, manifests neuropathological changes later in life. These changes mirror symptoms and pathology observed in various neurological conditions, including amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), frontotemporal dementia (FTD), and Alzheimer's disease [63].

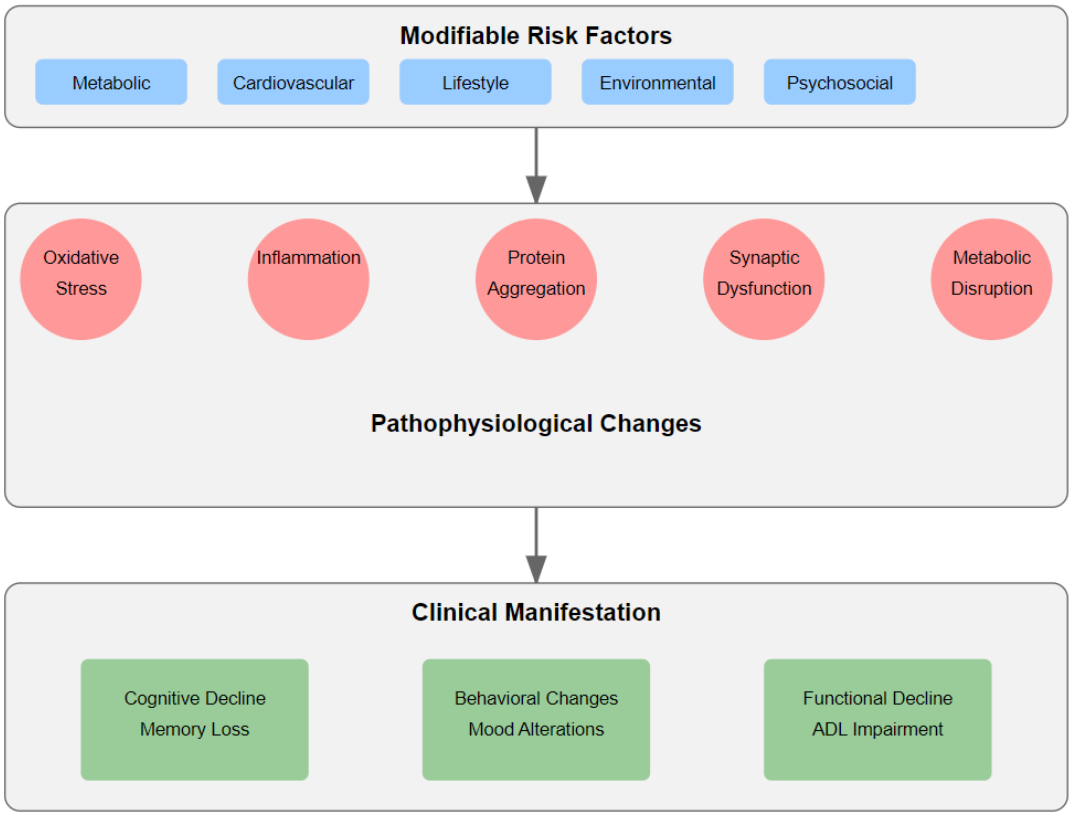

Figure 3. Neurobiological Cascade and Risk Factor Interactions in AD

3.3.3. Long-term Consequences

Long-term outcomes following TBI reveal complex patterns of neural degeneration and cognitive decline. The relationship between TBI severity and AD risk demonstrates dose-dependent characteristics, with more severe injuries correlating with higher risk profiles [64]. Age at injury plays a crucial role in determining long-term outcomes, with younger individuals showing distinct vulnerability patterns compared to older adults [65].

3.3.4. Prevention and Management

The established link between TBI and AD necessitates comprehensive prevention strategies and management protocols. These include:

- Protective measures during high-risk activities require particular emphasis, especially in occupational and recreational settings where head injuries commonly occur. Early intervention following TBI may modify long-term outcomes, suggesting a critical window for therapeutic intervention [66]. Advanced neuroimaging techniques now enable better assessment of TBI severity and prediction of long-term consequences, facilitating more targeted therapeutic approaches [67].
- The integration of cognitive rehabilitation strategies in post-TBI care has shown promise in potentially reducing AD risk. Regular monitoring of cognitive function following TBI, particularly in cases with genetic predisposition to AD, may enable earlier intervention and better outcomes [68]. Environmental modifications and lifestyle adjustments post-TBI play crucial roles in long-term cognitive preservation [69].

Current research focuses on identifying specific molecular pathways linking TBI to AD development, potentially revealing new therapeutic targets. Investigation of inflammatory responses following TBI suggests their role in accelerating AD-related pathological changes [70]. Studies of biomarker profiles in TBI patients may help predict AD risk and guide preventive interventions [71]. The interaction between genetic factors and TBI in determining AD risk represents an active area of investigation, potentially leading to personalized prevention strategies [72]

3.4. Oral Health and Hearing Impairment

3.4.1. Periodontal Disease and AD

Periodontal disease, affecting 10-15% of developed nations' populations, represents a significant polymicrobial inflammatory condition leading to tooth loss [73]. The relationship between oral health and AD manifests through various clinical parameters. Studies comparing AD patients with controls reveal significant differences in periodontal health markers. AD patients demonstrate elevated pocket depth [PD] (2.63 ± 0.56 vs. 2.29 ± 0.13; $p = 0.002$), increased bleeding on probing (BOP%) (62.65 ± 12.00 vs. 40.12 ± 10.86; $p < 0.001$), and higher plaque indices (59.06 ± 15.45 vs. 41.35 ± 7.97; $p < 0.001$) [74].

3.4.2. Hearing Loss and Cognitive Decline

Hearing impairment significantly correlates with increased dementia and AD risk in elderly populations. Both presbycusis and central auditory impairment contribute to this association [75]. The relationship between hearing loss and cognitive decline appears bidirectional, with each condition potentially exacerbating the other. This interaction suggests the importance of early hearing intervention in AD prevention strategies [76].

3.5. Lifestyle Factors and Disease Modification

3.5.1. Physical Activity

Physical activity emerges as a promising behavioral intervention for delaying AD onset [77]. Aerobic exercise particularly demonstrates positive effects on executive function and oral fluency among other cognitive domains [78]. The impact of physical activity extends beyond immediate cognitive benefits, influencing various biomarkers associated with AD and cognitive decline. Exercise-trained animal models show significant differences in hippocampal baseline Aβ levels compared to controls [79], suggesting underlying neuroprotective mechanisms [80].

Table 2. Impact of Physical Activity on AD Biomarkers and Cognitive Function

Activity Type	Frequency	Duration	Impact on Biomarkers	Cognitive Benefits
Aerobic Exercise	3-5x/week	30-40 min	↓ Aβ accumulation	Improved executive function
Resistance Training	2-3x/week	45-60 min	↓ Inflammatory markers	Enhanced memory
Moderate Walking	Daily	20-30 min	↑ BDNF levels	Better processing speed
Tai Chi/Yoga	2-3x/week	60 min	↓ Cortisol levels	Improved attention

3.5.2. Sleep Patterns and Disruption

Sleep disturbances in AD manifest through complex interactions with neurotoxic protein accumulation. Abnormal buildups of tau, α-synuclein, and amyloid β-peptide occur in sleep-related brain regions [81]. Common sleep-related complaints include:

Sleep fragmentation affects approximately 45% of AD patients, with specific disruptions including frequent awakenings (23%), early morning awakenings (11%), excessive daytime drowsiness (10%), and extended daytime napping (14%) [82]. The relationship between sleep dysregulation and AD pathology appears reciprocal, with sleep disorders promoting tau and Aβ accumulation, while increased protein aggregation further deteriorates sleep patterns [83].

Table 3. Sleep Disturbances and Associated AD Risk Factors

Sleep Parameter	Normal Range	AD Risk Pattern	Associated Biomarker Changes
Duration	7-8 hours	<6 or >9 hours	↑ Aβ accumulation
Fragmentation	<15%	>25%	↑ Tau phosphorylation
REM Sleep	20-25%	<15%	↓ Glymphatic clearance
Deep Sleep	13-23%	<10%	↑ Neuroinflammation
Sleep Latency	10-20 min	>30 min	↑ Oxidative stress

3.5.3. Alcohol Consumption

The Nord-Trundling Health study indicates that frequent alcohol consumers (≥5 times/two weeks) face 47% higher AD risk (95% CI 1.00-2.16) compared to infrequent drinkers [84]. Long-term alcohol consumption mechanisms include oxidative stress elevation, increased glutamate-induced excitotoxicity, and irreversible brain damage associated with malnutrition. While moderate ethanol concentrations may protect hippocampal neurons against β-amyloid toxicity, high consumption increases Aβ accumulation and Tau phosphorylation [85]

3.5.4. Smoking and Neurodegeneration

Smoking demonstrates complex associations with AD risk, particularly modulated by genetic factors. Research indicates heightened AD susceptibility among smokers, especially in individuals lacking the apolipoprotein E (APOE)-e4 allele [86]. Mortality rates show significant elevation in dementia patients who smoke (hazard ratio = 3.5, CI = 1.4-8.8), compared to controls (hazard ratio = 0.8, CI = 0.5-1.2), suggesting accelerated disease progression [87]. Gender-specific analyses reveal stronger negative correlations in male patients (OR 0.45, 95% CI 0.23-0.87, $p < 0.05$), while family history of dementia shows significant inverse correlation (OR 0.34, 95% CI 0.12-0.92, $p < 0.05$) [88]. Non-smokers demonstrate 18% lower AD risk compared to regular smokers [89].

3.6. Dietary Interventions

3.6.1. Dietary Patterns

Three primary dietary approaches demonstrate inverse relationships with AD risk: the MIND (Mediterranean-DASH Intervention for Neurodegenerative Delay) diet (HR 0.47, 95% CI 0.26-0.76), DASH (Dietary Approaches to Stop Hypertension) diet (HR 0.61, 95% CI 0.38-0.97), and Mediterranean diet (HR 0.46, 95% CI 0.26-0.79) [90]. Factor analysis of dietary patterns reveals specific risk associations, particularly with diets high in meat, butter, cream, various fats, eggs, and refined sugar, while showing deficiencies in vitamin C-rich fruits and vegetables [91].

Table 4. Dietary Patterns and Associated Risk Reduction in Alzheimer's Disease

Dietary Pattern	Components	Risk Reduction (%)	Study Duration (years)
Mediterranean Diet	High in vegetables, fruits, whole grains, fish	40-48	4.5
MIND Diet	Berries, green leafy vegetables, nuts	53	4.7
DASH Diet	Low sodium, high fruits and vegetables	39	4.5
Traditional Japanese	High in fish, seaweed, soy products	33	5.7

3.6.2. Micronutrient Considerations

Vitamin E intake through dietary sources, rather than supplementation, shows particular importance. Primary sources include whole grains, nuts, seeds, and green leafy vegetables, with a recommended daily allowance of 15 mg [92]. Higher vitamin D levels correlate with reduced AD risk [93]. Deficiencies in antioxidant vitamins (E and C) and B vitamins (B6, B12, and folate) may contribute to AD development through various mechanisms. The role of B vitamins extends to DNA methylation and homocysteine metabolism, with deficiencies potentially exacerbating AD through elevated homocysteine levels and subsequent oxidative damage [94]. Antioxidant vitamins demonstrate protective effects by inhibiting inflammatory signaling cascades and reducing β-amyloid-induced oxidative stress and lipid peroxidation [95].

4. Conclusion

The prevention and management of Alzheimer's disease requires addressing multiple modifiable risk factors. Current evidence supports the significance of lifestyle modifications, management of pre-existing conditions, and attention to psychosocial factors in disease prevention and progression. Early intervention in modifiable risk factors offers the most promising strategy for reducing disease burden. Current research must focus on enhancing our understanding of gene-environment interactions in AD development, while simultaneously advancing personalized prevention strategies based on individual risk profiles. Deeper investigation of novel

therapeutic targets identified through risk factor analysis, alongside implementation of effective community-based prevention programs. Technological advances in early detection and monitoring show promise in improving outcomes.

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