https://doi.org/10.33472/AFJBS.6.2.2024.1065-1075

African Journal of Biological Sciences

Research Paper Open Access

An Overview of Alzheimer's Disease

Abdallah AL-Ma'moon Sarhan, Esraa Mohamed Abd Al-Rasheed, Khaled Aly El-Sharkawy, Tamer Sabry El-Serafy

Neurology Department, Faculty of Medicine, Zagazig University, Egypt

Email: esraaabdalrasheed2020@gmail.com, eabdelrashed@medicine.zu.edu.eg

Article History

Volume 6, Issue 2, April 2024

Received:19 April 2024

Accepted: 4 June 2024

Published: 4 June 2024

doi:10.33472/AFJBS.6.2.2024.1065-1075

Abstract: Alzheimer's disease (AD) is the most common type of dementia, characterized by progressive cognitive and social decline. Clinical drug targets have heavily focused on the amyloid hypothesis, with amyloid beta (Ab), and tau proteins as key pathophysiologic markers of AD. However, no effective treatment has been developed so far, this prompts researchers to focus on other aspects of AD beyond the Ab and tau proteins. Additionally, there is mounting epidemiologic evidence that various environmental factors influence the development of dementia, and that dementia etiology is likely heterogeneous. In the past decades, new risk factors or potential etiologies have been widely studied. Here, we review general background information on Alzheimer's disease and several novel risk factors, and their links to AD that were published in recent years.

Keywords: *Alzheimer's disease; novel risk factors*

Introduction

Alzheimer's disease is a progressive, irreversible, incurable neurodegenerative disease impacting cognition, function, and behavior. Alzheimer's disease progresses along a continuum from preclinical disease to mild cognitive and/or behavioral impairment and then Alzheimer's disease dementia **(1)**.

Alzheimer's disease is the most common cause of dementia, which is a group of symptoms that has several causes and is characterized by difficulties with memory, language, problem-solving, and other cognitive skills that affect a person's ability to perform everyday activities. AD is the most common type of dementia in order of occurrence, accounting for 60–70% of all cases **(2).**

We can also see Alzheimer's disease in younger individuals, can occur occasionally in their 20s (more likely to be caused by a genetic abnormality **(2).**

Neuropathology of AD:

Two types of neuropathological changes in AD provide evidence about disease progress and symptoms: (1) positive lesions (due to accumulation), which are characterized by the accumulation of neurofibrillary tangles, amyloid plaques, dystrophic neurites, neuropil threads, and other deposits found in the brains of AD patients. In addition to (2) negative lesions (due to losses), that are characterized by large atrophy due to a neural,

neuropil, and synaptic loss. Besides, other factors can cause neurodegeneration, such as neuroinflammation, oxidative stress, and injury of cholinergic neurons **(3).**

Senile Plaques (SP): The senile plaques are extracellular deposits of beta-amyloid protein (AB) with different morphological forms, including neuritic, diffuse, dense-cored, or classic and compact type plaques. Proteolytic cleavage enzymes such as B-secretase and ɤ-secretase are responsible for the biosynthesis of AB deposits from the transmembrane amyloid precursor protein (APP) **(4).**

These enzymes cleave APP into several amino acid fragments: 43, 45, 46, 48, 49, and 51 amino acids, which reach the final forms AB 40 and AB 42; there are several types of AB monomers, including large and insoluble amyloid fibrils which can accumulate to form amyloid plaques and soluble oligomers that can spread throughout the brain**.** Amyloid B plays a major role in neurotoxicity and neural function, therefore,

The accumulation of denser plaques in the hippocampus, amygdala, and cerebral cortex can cause stimulation of astrocytes and microglia, damage to axons, and dendrites, and loss of synapses, in addition to cognitive impairment **(4).**

Neurofibrillary Tangles (NFTs): They are abnormal filaments of the hyperphosphorylated tau protein that in some stages can be twisted around each other to form paired helical filament (PHF) and accumulate in neural perikaryal cytoplasm, axons, and dendrites, which cause a loss of cytoskeletal microtubules and tubulin-associated proteins**.** The hyperphosphorylated tau protein is the major constituent of NFTs in the brains of AD patients, and its evolution can reflect NFTs morphological stages, which include: (1) pre-tangle phase, one type of NFT, where phosphorylated tau proteins are accumulated in the somatodendritic compartment without the formation of PHF, (2) mature NFTs, which are characterized by filament aggregation of tau protein with the displacement of the nucleus to the periphery part of the soma, and (3) the extracellular tangles, or the ghost NFTs stage, that results from a neuronal loss due to large amounts of filamentous tau protein with partial resistance to proteolysis**(5).**

Synaptic Loss: Synaptic damage in the neocortex and limbic system causes memory impairment and generally is observed at the early stages of AD, Synaptic loss mechanisms involve defects in axonal transport, mitochondrial damage, oxidative stress, and other processes that can contribute to small fractions, like the accumulation of AB and tau at the synaptic sites. These processes eventually lead to a loss of dendritic spines, pre-synaptic terminals, and axonal dystrophy**.** Synaptic proteins serve as biomarkers for the detection of synaptic loss, and severity, such as neurogranin, a postsynaptic neuronal protein, visinin-like protein-1 (VILIP-1), and synaptotagmin-1 **(6).**

Risk Factors of Alzheimer's Disease

There is no single cause for AD but rather it is the result of complex interactions between multiple factors, these include genetic, epigenetic, and environmental factors that act in combination to cause aberrant brain function and increase the likelihood of developing the disease **(7).**

1. Genetics and Family History:

Genetic factors were found to play a major role in the development of AD, seventy percent of the AD cases were related to genetic factors: most cases of early-onset Alzheimer's disease (EOAD) are inherited in an autosomal dominant pattern, and mutations in the dominant genes such as Amyloid precursor protein (APP) on chromosome 21, Presenilin-1 (PSEN-1) on chromosome 14, Presenilin-2 (PSEN-2) on chromosome 1, and Apo lipoprotein E (ApoE) are associated with late onset Alzheimer disease (LOAD) AD **(8).**

Early-onset familial Alzheimer's disease: which is characterized by an early-onset (<60 years old) and accounts for approximately 1-2% of AD cases, is attributed to mutations in one of three genes: those encoding amyloid-beta precursor protein (APP) and presenilins: PSEN1 and PSEN2**(2).**

Most mutations in the APP and presenilin genes increase the production of a small protein called amyloid beta (Aβ) 42, which is the main component of amyloid plaques, Some of the mutations merely alter the ratio between Aβ42 and the other major forms particularly Aβ40 without increasing Aβ42 levels **(9).**

Other genes associated with autosomal dominant Alzheimer's disease are ATP Binding Cassette Transporter A1(ABCA7), Clusterin Gene (CLU) and Bridging Integrator 1 (BIN1), Evolutionarily Conserved Signaling Intermediate in Toll pathway (ECSIT), Estrogen Receptor Gene (ESR), vitamin D receptor(VDR) gene polymorphism and Sortilin-related receptor1 **(**SORL1) **(9).**

Down syndrome, a genetic disorder caused by the presence of an extra chromosome (number 21) in the cells of affected individuals, also carries an increased risk for early-onset AD and dementia. By the age of 60, between 50-70% of people with Down syndrome develop dementia **(10).**

Late-onset familial Alzheimer's disease: which represents the rest of the AD cases corresponds to the sporadic AD variant (late-onset, >65 years old) where the etiology is not well established and in which environmental and genetic differences may act as risk factors. **(2).**

The strongest genetic risk factor for sporadic Alzheimer's disease is APOEε4 which is one of four alleles of apolipoprotein E (APOE). It plays a major role in lipid-binding proteins in lipoprotein particles and the epsilon4 allele disrupts this function **(11).**

ApoE"4 plays an important role in AB deposition as a senile plaque and causes cerebral amyloid angiopathy (CAA), which is known as a marker for AD. ApoE 4 was also shown to be associated with vascular damage in the brain, which leads to AD pathogenesis **(11).**

2.Age:

The most important risk factor and it is a complex and irreversible process that occurs through multiple organs and cell systems with a reduction in the brain volume and weight, a loss of synapses, and ventricles' enlargement in specific areas accompanied by Senile Plaques (SP) deposition and Neurofibrillary Tangles (NFT) **(12).**

Most cases of Alzheimer's disease are seen in older adults, ages 65 years or above. Between the ages of 65 and 74, approximately 5 percent of people have Alzheimer's disease. For those over 85, the risk increases to 50 percent **(12).**

Moreover, several conditions might emerge during aging due to impairment of the body's self-repair mechanisms, including in the brain such as glucose hypo metabolism, cholesterol dyshomeostasis, mitochondria dysfunction, depression, and cognitive decline, these changes also appear in normal aging, which makes it difficult to distinguish the cases in early AD **(13)**.

2. Environmental Factors:

Environmental risk factors including air pollution, diet, metals, infections, and many others may induce oxidative stress and inflammation and increase the risk of developing AD **(14).**

Air Pollution: Six air pollutants have been defined by National Ambient Air Quality Standards (NAAQSs) in the USA as a threat to human health, including ozone (O3), nitrogen oxides (NOx), carbon monoxide (CO), particulate matter (PM), sulfur dioxide (SO2), and lead. Studies on animals and cellular models have shown that exposure to high levels of air pollution can result in damage to the olfactory mucosa and bulb, in addition to the frontal cortex region, like that observed in AD **(14).**

Air pollution can cause an increase in AB42 formation, accumulation, and impaired cognitive function, there is a link between oxidative stress, neuroinflammation, and neurodegeneration, with the presence of hyper-phosphorylated tau and AB plaques in the frontal cortex **(13)**.

Diet and Nutrition: Several dietary supplements such as antioxidants, vitamins, polyphenols, and fish were reported to decrease the risk of AD, whereas saturated fatty acids and high-calorie intake were associated with increasing the risk of AD **(15).**

Food processing causes the formation of toxic secondary products (advanced Glycation end products, AGEs) from non-enzymatic Glycation of free amino groups in proteins, lipids, and nucleic acids, the toxic effect of AGEs is referred to as their ability to induce oxidative stress and inflammation by modifying the structure and function of the cell surface receptors and body proteins **(16)**.

Different studies demonstrated that elevated AGE serum level is associated with cognitive decline and progression of AD, the AGE receptor (RAGE) is in a different place within the body, including microglia and astrocytes, and was established to be overexpressed in the brain of AD patients and serve as a transporter and a cell surface receptor for AB **(13)**.

Malnutrition is another risk factor for AD. Deficiency in nutrients such as folate, vitamin B12, and vitamin D may cause a decrease in cognitive function, in addition to the fact that patients with AD suffer from problems associated with eating and swallowing, which may increase the risk of malnutrition **(17)**.

Metals: Studies demonstrated that Aluminum (Al) accumulates in the cortex, hippocampus, and cerebellum areas, where it interacts with proteins and causes misfolding, aggregation, and phosphorylation of highly phosphorylated proteins like tau protein, characteristic of AD**.** Studies revealed that acute exposure to lead was associated with AD and caused an increase in B secretase. Results have demonstrated that Cadmium ions are involved in the aggregation of AB plaques and the self-aggregation of tau in the AD brain expression and AB accumulation**.** In addition, zinc, mercury, copper, manganese, and magnesium have all been suggested as risk factors for AD **(18).**

Infections: Studies showed that the DNA of herpes simplex virus (HSV-1) was found in patients with ApoEε4 allele carriers, which explains the high risk for developing AD. HSV-1 can replicate in the brain, which can result in the activation of the inflammatory response and an increase in AB deposition, resulting in damage to neurons and the gradual development of AD **(19).**

The other study results have revealed the role of chronic bacterial infections in AD as syphilitic dementia caused by spirochete bacteria (Treponema pallidum), which are accumulated in the cerebral cortex, produce lesions like neurofibrillary tangles, which lead to devastating neurodegenerative disorders. Besides, the Chlamydia pneumonia bacterium can trigger late-onset AD by activation of astrocyte and cytotoxic microglia, disrupt calcium regulation and apoptosis, resulting in deterioration of cognitive function, and increase the risk of AD **(19).**

Recently, however, DNA from peripheral blood leucocytes and the brain of AD patients has been analyzed.
for cytomegalovirus (CMV), Epstein-Barr virus (EBS), and human herpes virus 6 (HHV-6), the data suggest that EPV and HHV-6 could be risk factors for cognitive decline and progression to AD **(7).**

COVID-19: there is also intensive research going on to analyze the possible long-term impact of COVID-19 infection on the risk of cognitive impairment and eventually dementia. Collecting user feedback and participants' experiences using digital tools and new technology e.g.-FINGERS concept) is needed **(37).**

3. Medical Factors:

Cardiovascular Disease (CVDs): Cardiovascular Diseases are recognized as an important risk factor for AD, such as stroke which is associated with an increased risk of dementia due to neural tissue loss, which enhances degenerative effect and influences amyloid and tau pathology **20)**.

Obesity and Diabetes: Increasing body fat is associated with a decreased brain blood supply which promotes brain ischemia, memory loss, and vascular dementia**.** Chronic hyperglycemia can induce cognitive impairment because of increasing amyloid-beta accumulation, oxidative stress, mitochondrial dysfunction, and neuroinflammation **(21)**.

Depression: a personal history of depression has been related to an increased risk of developing AD later in life, although this finding has not been universal **(22)**.

Several randomized control trial*s* found that treatment of depression in elderly adults results in improved cognitive function**,** though some show no improvement at all**.** Additionally, some types of anti-depressant medication (especially those with anti-cholinergic properties) can worsen cognitive function **(23).**

4. **Lifestyle factors:**

Education level and mental activity: It is observed that there is a connection between educational level and the risk of developing Alzheimer's disease. People with fewer years of education seem to be at a higher risk as they are unaware of the prevalent causes **(24)**.

The exact cause for this relationship is unknown, but it is theorized that a higher education level leads to the formation of more synaptic connections in the brain. This creates a "synaptic reserve" in the brain, enabling patients to compensate for the loss of neurons as the disease progresses **(25).**

Physical activity: Engaging in leisure time physical activity at least twice a week in midlife was associated with a greater than 50% reduction in the risk of dementia**,** Exercise strongly up-regulates antioxidant capacity, leading to reduced ongoing levels of oxidative stress and inflammatory burden **(26).**

Social activity: A complex series of relationships exists between social-environment variables and cognitive decline and dementia. In the whole population, factors such as increased engagement in social, physical, or intellectual pursuits were related to a decreased risk of dementia **(27).**

Studies have noted in elderly people that living in a home rather than in an institutional care facility can help maintain independence, family relationships, and relationships with the wider community. However, despite these benefits, older adults living alone at home may be functionally or cognitively vulnerable **(27). Smoking:** Several studies link smoking and cognitive impairment, Smoking increases total plasma homocysteine, an independent risk factor for stroke, cognitive impairment, AD, and other dementias and it can also induce oxidative stress, which is associated with excitotoxicity that may be directly or indirectly related to the neuropathology of AD **(28).**

High alcohol consumption: Moderate drinking may be associated with better cognitive function in comparison to those who are heavily alcohol consumption. However, heavy alcohol consumption can have neurotoxic effects and lead to brain damage. Many chronic alcoholics demonstrate significant brain atrophy and are associated with impaired cognitive function and increased risk of dementia **(29).**

The benefits of alcohol may be produced through its favorable effects on the cardiovascular system. Alcohol appears to reduce inflammation, increase HDL cholesterol, inhibit blood clotting**,** increase brain blood flow, and increase insulin sensitivity all of which are thought to protect against vascular disease in the body and brain, also many alcoholic drinks contain antioxidants, which may help reduce oxidative damage in the aging brain **(30).**

5. **Traumatic brain injury:** Traumatic brain injury (TBI) is the disruption of normal brain function caused by a blow to the head or penetration of the skull by a foreign object. Not all traumas to the head disrupt brain function. Moderate TBI is defined as a head injury resulting in loss of consciousness or post-traumatic amnesia that lasts more than 30 minutes. If loss of consciousness or post-traumatic amnesia lasts more than 24 hours, the injury is considered severe **(31).**

Moderate TBI is associated with twice the risk of developing AD and other dementias compared with no head injuries, and severe TBI is associated with 4.5 times the risk **(32).**

6. **Sleep:** Sleep disturbance has a complex association with AD and may be either a preclinical biomarker or a potential modifiable risk factor for AD, Patients with AD frequently experience sleep disturbances, including insomnia, abnormal sleep duration, poor nighttime sleep quality, excessive daytime sleepiness, and disrupted circadian rhythms. These sleep problems subsequently reduce the patient's quality of life and increase the risk of premature institutionalization. Exogenous melatonin has the potential to alleviate neuropathology and SD in AD by different mechanisms **(33).**
7. **Hypoxia:** Hypoxia can be caused by cardiovascular disease (CVD), hematological diseases, chronic kidney diseases (CKD), respiratory dysfunction, and environmental conditions, which could influence the central nervous system and induce neurodegeneration. Acute hypoxia can be induced by stroke, while obstructive sleep apnea syndrome (OSAS), capillary dysfunction, and CKD may lead to chronic hypoxia. Cognitive impairment may also occur in normal adults after hypoxia, Hypoxia is associated with AD. Hypoxia

facilitates the pathogenesis of AD through multiple pathways including increasing the production and accelerating the accumulation of AB, decreasing the degradation of AB, reducing the clearance of AB, elevating the hyperphosphorylation of tau, inhibiting the autophagic function, calcium-homeostasis dysregulation, aggravating neuroinflammation and oxidation stress, ruining the mitochondria function **(34).**

8. **Hearing impairment:** Hearing impairments are common among older adults: affecting up to 40% of adults aged 65 and up to 90% of adults aged>90, Hearing difficulty is commonly reported by patients with AD, Observational studies have found a consistent association between hearing loss and risk of dementia and cognitive decline **(35).**

Hearing impairments may directly affect dementia risk through brain atrophy by impairing cognitive processing abilities or by increasing cognitive load, Hearing impairments may also affect "psychosocial well-being" including social engagement, mental health, and physical activity which could lead to increased dementia risk**.** The Lancet Commission on dementia prevention in 2020 suggested that treating hearing loss may reduce dementia burden by up to 8%. However, this estimate is based on observational studies which may be biased **(35).**

The reason for the link between the two conditions is currently unknown but various hypotheses have been proposed. These include the following: common pathological mechanisms acting on the auditory pathway and brain such as vascular factors (e.g., diabetes, atherosclerosis, and hypertension); the additional cognitive load required in understanding poor auditory input interferes with other cognitive functions such as language processing and memory **(35).**

10. Loneliness: Loneliness has been reported to be associated with an increased risk of dementia; however, the extent of this relationship remains controversial **(34).**

A meta-analysis of four longitudinal studies found no association between loneliness and dementia, whereas other studies have found that loneliness is associated with an increased risk of developing dementia. Furthermore, loneliness has cross-sectionally been associated with a higher cortical amyloid burden, a neuropathological feature of AD **(32).**

Dementia was described as a great burden caused by loss of one's independence due to loss of cognitive and physical capabilities and loss of social relationships **(35).**

11. Stress: It was hypothesized that longstanding psychological stress can result in neural degeneration and AD due to pathological alterations in the hypothalamic–pituitary–adrenal axis. In recent years several epidemiological studies have been published on stress as a risk factor for AD **(34).**

12. Oral health: Several studies have supported the links between lifestyle choices, specifically engaging with oral health practices and AD development **(34).**

More recently, a Taiwanese study found a strong link between chronic periodontal disease (exposures of around 10-year period) and AD **(36).**

Clinical presentation:

The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association working group (NINCDS-ADRDA) criteria were presented in 1984. These landmark criteria for AD include a specification that the onset of dementia should be insidious and that there is a lack of other systemic or brain diseases that may account for progressive memory and other cognitive deficits. According to the NINCDS-ADRDA criteria, a definite diagnosis of AD is only to be made when there is histopathological confirmation of the clinical diagnosis **(38).**

In 2011, The National Institute of Aging–Alzheimer Association (NIA-AA) updated the guidelines published in 1984. The workgroup sought to ensure that the revised criteria would be flexible enough to be used by both general healthcare providers without access to neuropsychological testing, advanced imaging, and cerebrospinal fluid measures, and specialized investigators. They propose the following terminology for classifying individuals with dementia caused by AD: (1) Probable AD dementia, (2) Possible AD dementia, and (3) Probable or possible AD dementia with evidence of the AD pathophysiological process **(38).**

The National Institute of Aging–Alzheimer Association (NIA-AA) also proposed new guidelines to categorize the brain changes associated with AD and other dementias. The new criteria identify three stages of AD with the first occurring before symptoms and incorporate biomarker tests in cerebrospinal fluid (CSF) and blood **(39).**

The three stages of AD proposed by the new criteria:

I. Preclinical AD:

AD starts with a preclinical phase in which AD neuropathological abnormalities begin to accumulate but cognitive ability is normal **(40).**

Alzheimer's disease criteria incorporate two biomarkers, the first shows the level of Aβ accumulation in the brain, and the second shows that the neurons in the brain are injured or degenerating **(2).** Although Aβ deposition and elevated tau/phosphorylated tau are hallmarks of AD, alterations in these proteins are seen in other neurological disorders. Elevations in Aβ seem to be more specific than alterations in tau **(40).**

The NIA-AA criteria for preclinical AD propose three ordered stages; stage one is characterized by evidence of Aβ accumulation on PET Aβ imaging or CSF assays. Stage two involves cerebral amyloidosis plus evidence of neurodegeneration, such as elevated CSF tau levels or abnormalities on functional or structural neuroimaging, Stage three is characterized by amyloidosis plus neurodegeneration with evidence of very subtle cognitive decline that does not yet meet the criteria for MCI**. (40).**

Knopman used structural and amyloid imaging markers to categorize individuals according to these stages, the rate of short-term (one year) progression to MCI or dementia increased with advancing preclinical AD stage **(41)**.

II. Mild Cognitive Impairment due to AD:

Individuals with MCI have mild but measurable changes in thinking abilities that are noticeable to the person affected and to his relatives, but that do not affect the individual's ability to carry out everyday activities. Studies indicate that as many as 10-20 % of people aged 65 or older have MCI**.** Nearly half of all people who have visited a doctor about MCI symptoms will develop dementia in three or four years. Further cognitive decline is more likely among individuals whose MCI involves memory problems than among those whose MCI does not involve memory problems **(42).**

III. Dementia due to AD:

Dementia due to Alzheimer's disease, or Alzheimer's dementia, is characterized by noticeable memory, language, thinking, or behavioral symptoms that impair a person's ability to function in daily life, combined with biomarker evidence of Alzheimer 's-related brain changes. As Alzheimer's progresses, individuals commonly experience multiple types of symptoms that change with time**.** As the disease progresses, individuals experience other difficulties. Apathy and depression also may be present early in the disease. Later symptoms include impaired communication, disorientation, confusion, poor judgment, behavior changes, and, ultimately, difficulty speaking, swallowing, and walking**.** Alzheimer's disease is staged into 3 major categories according to the assessment of 6 cognitive categories: memory, orientation, judgment & problem-solving, community affairs, home & hobbies, and personal self-care **(43)**:

***Mild Alzheimer's Dementia:** most people can function independently in many areas but are likely to require assistance with some activities to maximize independence and remain safe. Handling money and paying bills may be especially challenging, and they may need more time to complete common daily tasks. They may still be able to drive, work, and participate in their favorite activities **(44)**.

***Moderate Alzheimer's Dementia:** it is often the longest stage, individuals experience more problems with memory and language, are more likely to become confused, and find it harder to complete multistep tasks such as bathing and dressing. They may become incontinent at times, and they may start having personality and behavioral changes, including suspiciousness and agitation. They may also begin to have problems recognizing loved ones **(44)**.

*__Severe Alzheimer's Dementia:__ In the severe stage of Alzheimer's dementia, individuals' ability to communicate verbally is greatly diminished, and they are likely to require around-the-clock care. Because of damage to areas of the brain involved in movement, individuals become bed-bound which makes them vulnerable to physical complications including blood clots, skin infections, and sepsis, which triggers body-wide inflammation that can result in organ failure. Damage to areas of the brain that control swallowing makes it difficult to eat and drink **(44)**.

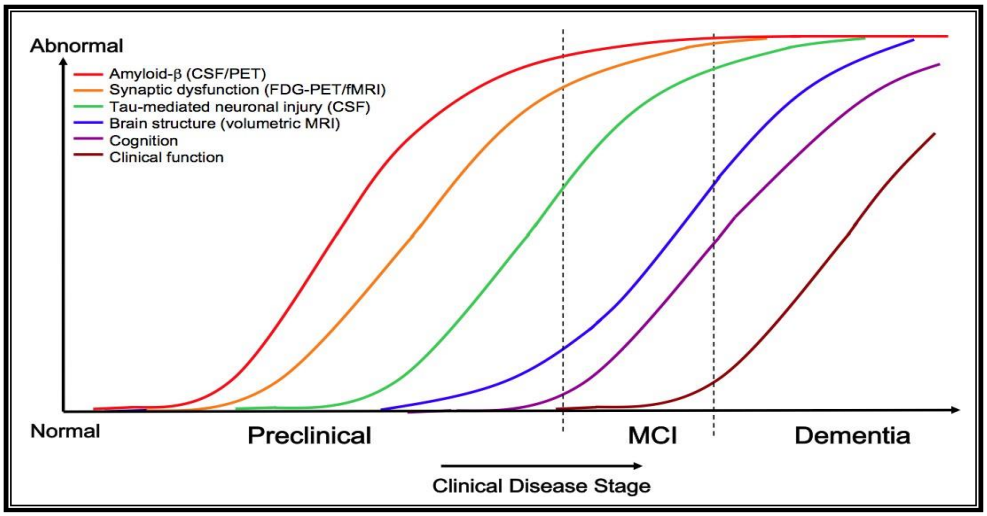

Figure (1): Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade, expanded in the preclinical phase **(45).**

Alzheimer's Disease Diagnostic Criteria:

The only method of definitively diagnosing AD is a brain autopsy. However, mental and behavioral tests and physical examinations allow physicians to make an accurate diagnosis of AD in 90 percent of cases **(25).**

There are three sets of criteria for the clinical diagnoses of the spectrum of Alzheimer's disease: the 2013 fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5))**(46).**; the National Institute on Aging-Alzheimer's Association (NIA-AA) definition as revised in 2011 and the use of supportive biomarker evidence (imaging, serum, and CSF) of AD pathology were included to aid in the delineation of AD from other forms of dementia as well as in the diagnosis of MCI due to AD)**(47)**; and the International Classification of Diseases (ICD-11)**(48).**

Three broad periods, which can span decades, define the progression of Alzheimer's disease from the preclinical phase, to mild cognitive impairment (MCI), followed by Alzheimer's disease dementia **(47). DSM -5 Criteria for the diagnosis of Alzheimer's disease (46):**

A. The criteria are met for major or mild neurocognitive disorders.

B. There is insidious onset and gradual progression of impairment in one or more cognitive domains (for major neurocognitive disorder, at least two domains must be impaired).

C. Criteria are met for either probable or possible Alzheimer's disease as follows:

For major neurocognitive disorder:

Probable Alzheimer's disease is diagnosed if either of the following is present; otherwise, **possible Alzheimer's disease** should be diagnosed.

1. Evidence of a causative Alzheimer's disease genetic mutation from family history or genetic testing.
2. All three of the following are present:

a. Clear evidence of decline in memory and learning and at least one other cognitive domain (based on detailed history or serial neuropsychological testing).

b. Steadily progressive, gradual decline in cognition, without extended plateaus.

c. No evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease, or another neurological, mental, or systemic disease or condition likely contributing to cognitive decline).

For mild neurocognitive disorder:

Probable Alzheimer's disease is diagnosed if there is evidence of a causative Alzheimer's disease genetic mutation from either genetic testing or family history.

Possible Alzheimer's disease is diagnosed if there is no evidence of a causative Alzheimer's disease genetic mutation from either genetic testing or family history, and all three of the following are present:

1. Clear evidence of a decline in memory and learning.
2. Steadily progressive, gradual decline in cognition, without extended plateaus.
3. No evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease, or another neurological or systemic disease or condition likely contributing to cognitive decline).

B. The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental, neurological, or systemic disorder.

Perspectives: There is no denying that the clinical treatment of AD is currently facing significant bottlenecks. The failure of many clinical trials suggests the importance of early diagnosis and prevention. Therefore, in recent years, researchers have been interested in thinking about AD from a broad perspective and in evaluating novel potential risk factors beyond those traditionally associated with AD such as CVD, diabetes, and education. Furthermore, our review highlights the potential importance of underappreciated health factors to healthy aging such as sleep, diet, and hearing. This new research adds further evidence to support a shift from amyloid-focused drug targets to multi-domain interventions that may help prevent AD and slow cognitive decline. However, there is still a lot of work to be done in these areas.

Conclusion: In the present review, the general background information on Alzheimer's disease and several novel risk factors and their links to AD was published in recent years.

References:

1- Porsteinsson, A. P., Isaacson, R. S., Knox, S., Sabbagh, M. N., & Rubino, I. (2021). Diagnosis of Early Alzheimer's Disease: Clinical Practice in 2021. Journal of Prevention of Alzheimer's Disease, 8(3), 371–386.

2- Deture, M. A., & Dickson, D. W. (2019). The neuropathological diagnosis of Alzheimer's disease. Molecular Neurodegeneration, 14(1), 1–18.

3- Singh, S. K., Srivastav, S., Yadav, A. K., Srikrishna, S., & Perry, G. (2016). Overview of Alzheimer's disease and some therapeutic approaches targeting A β by using several synthetic and herbal compounds. Oxidative Medicine and Cellular Longevity, 2016.

4- Jr, C. R. J., Albert, M., Knopman, D. S., Mckhann, G. M., Sperling, R. A., Carillo, M., Thies, W., & Phelps, C. H. (2011). Introduction to revised criteria for the diagnosis of Alzheimer's disease: National Institute on Aging and the Alzheimer Association Workgroups. Alzheimer Dement., 7(3), 257–262.

5- Metaxas, A., & Kempf, S. J. (2016). Neurofibrillary tangles in Alzheimer's disease: Elucidation of the molecular mechanism by immunohistochemistry and tau protein phospho-proteomics. Neural Regeneration Research, 11(10), 1579–1581.

6- Dulewicz, M., Kulczyńska-przybik, A., & Mroczko, B. (2020). Neurogranin and VILIP-1 as molecular indicators of neurodegeneration

7-

8- in Alzheimer's disease: A systematic review and meta-analysis. International Journal of Molecular Sciences, 21(21), 1–19.

9- Huang, S. Y., Yang, Y. X., Kuo, K., Li, H. Q., Shen, X. N., Chen, S. D., Cui, M., Tan, L., Dong, Q., & Yu, J. T. (2021). Herpesvirus infections and Alzheimer's disease: a Mendelian randomization study. Alzheimer's Research and Therapy, 13(1), 1–8.

10- Van Cauwenberghe, C., Van Broeckhoven, C., & Sleegers, K. (2016). The genetic landscape of Alzheimer's disease: Clinical implications and perspectives. Genetics in Medicine, 18(5), 421–430.

11- Sun, X., Chen, W. D., & Wang, Y. D. (2015). β-Amyloid: The key peptide in the pathogenesis of Alzheimer's disease. Frontiers in Pharmacology, 6(SEP), 1–9.

12- Castro, P., Zaman, S., & Holland, A. (2017). Alzheimer's disease in people with Down's syndrome: the prospects for and the challenges of developing preventative treatments. Journal of Neurology, 264(4), 804–813.

13- Perea, J. R., Bolós, M., & Avila, J. (2020). Microglia in Alzheimer's disease in the context of tau pathology. Biomolecules, 10(10), 1– 26.
14- Hou, Y., Dan, X., Babbar, M., Wei, Y., Hasselbalch, S. G., Croteau, D. L., & Bohr, V. A. (2019). Aging as a risk factor for neurodegenerative disease. Nature Reviews Neurology, 15(10), 565–581.
15- Anwal, L. (2021). A Comprehensive Review on Alzheimer's Disease. World Journal of Pharmacy and Pharmaceutical Sciences, 10(7), 1170.
16- Wainaina, M. N., Chen, Z., & Zhong, C. (2014). Environmental factors in the development and progression of late-onset Alzheimer's disease. Neuroscience Bulletin, 30(2), 253–270.
17- Hu, N., Yu, J. T., Tan, L., Wang, Y. L., Sun, L., & Tan, L. (2013). Nutrition and the risk of Alzheimer's disease. BioMed Research International, 2013.
18- Abate, G., Marziano, M., Rungratanawanich, W., Memo, M., & Uberti, D. (2017). Nutrition and AGE-ing: Focusing on Alzheimer's Disease. Oxidative Medicine and Cellular Longevity, 2017.
19- Koyama, A., Hashimoto, M., Tanaka, H., Fujise, N., Matsushita, M., Miyagawa, Y., Hatada, Y., Fukuhara, R., Hasegawa, N., Todani, S., Matsukuma, K., Kawano, M., & Ikeda, M. (2016). Malnutrition in Alzheimer's disease, dementia with Lewy bodies, and frontotemporal lobar degeneration: Comparison using serum albumin, total protein, and hemoglobin level. PLoS ONE, 11(6), 1–7.
20- Du, K., Liu, M., Pan, Y., Zhong, X., & Wei, M. (2017). Association of serum manganese levels with Alzheimer's disease and mild cognitive impairment: A systematic review and meta-analysis. Nutrients, 9(3).
21- Fülöp, T., Itzhaki, R. F., Balin, B. J., Miklossy, J., & Barron, A. E. (2018). Role of microbes in the development of Alzheimer's disease: State of the Art - An International Symposium Presented at the 2017 IAGG Congress in San Francisco. Frontiers in Genetics, 9(SEP), 1–16.
22- Santiago, J. A., & Potashkin, J. A. (2021). The Impact of Disease Comorbidities in Alzheimer's Disease. Frontiers in Aging Neuroscience, 13(February), 1–13.
23- Lee, H. J., Seo, H. I., Cha, H. Y., Yang, Y. J., Kwon, S. H., & Yang, S. J. (2018). Diabetes and Alzheimer's Disease: Mechanisms and Nutritional Aspects. Clinical Nutrition Research, 7(4), 229.
24- Ownby, R. L., Crocco, E., Acevedo, A., John, V., & Loewenstein, D. (2006). Depression and risk for Alzheimer disease: Systematic review, meta-analysis, and metaregression analysis. Archives of General Psychiatry, 63(5), 530–538.
25- Leng, Y., Diem, S. J., Stone, K. L., & Yaffe, K. (2018). Antidepressant Use and Cognitive Outcomes in Very Old Women. Journals of Gerontology - Series A Biological Sciences and Medical Sciences, 73(10), 1390–1395.
26- Bhushan, I., Access, O., Kour, M., Kour, G., Gupta, S., Sharma, S., & Yadav, A. (2018). Alzheimer's disease: Causes & treatment-A review 1 MedDocs Publishers Annals of Biotechnology. 1(1).
27- Bethune, K. (2010). Thesis: Diagnosis and Treatment of Alzheimer's Disease: Current Challenges. Outstanding Honors Theses, 1–32.
28- Wang, S., Liu, H. Y., Cheng, Y. C., & Su, C. H. (2021). Exercise dosage in reducing the risk of dementia development: Mode, duration, and intensity—A narrative review. International Journal of Environmental Research and Public Health, 18(24).
29- Marioni, R. E., Proust-Lima, C., Amieva, H., Brayne, C., Matthews, F. E., Dartigues, J. F., & Jacqmin-Gadda, H. (2015). Social activity, cognitive decline, and dementia risk: A 20-year prospective cohort study Chronic Disease epidemiology. BMC Public Health, 15(1), 1– 8.
30- Santos, C. Y., Snyder, P. J., Wu, W. C., Zhang, M., Echeverria, A., & Alber, J. (2017). Pathophysiologic relationship between Alzheimer's disease, cerebrovascular disease, and cardiovascular risk: A review and synthesis. Alzheimer's and Dementia: Diagnosis, Assessment and Disease Monitoring, 7, 69–87.
31- Yen, F.-S., Wang, S.-I., Lin, S.-Y., Chao, Y.-H., & Wei, J. C.-C. (2022). The impact of heavy alcohol consumption on cognitive impairment in young old and middle old persons. Journal of Translational Medicine, 20(1), 1–13.
32- Piano, M. R. (2017). Alcohol's Effects on the Cardiovascular System. Alcohol Research : Current Reviews, 38(2), 219–241.
33- McAllister, T. W. (2011). Neurobiological consequences of traumatic brain injury. Dialogues in Clinical Neuroscience, 13(3), 287– 300.
34- Kamer, A. R., Janal, M. N., & de Leon, M. (2015). Letter to the editor regarding Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. Alzheimer's and Dementia: Diagnosis, Assessment and Disease Monitoring, 1(4), 385–386.
35- Kamal, M. A., & Bahbah, E. I. (2021). Alzheimer Disease and Sleep Disorders: Insights into the Possible Disease Connections and the Potential Therapeutic Targets (Part II). CNS & Neurological Disorders - Drug Targets, 20(8), 674–676.
36- Snyder, B., Shell, B., Cunningham, J. T., & Cunningham, R. L. (2017). Chronic intermittent hypoxia induces oxidative stress and inflammation in brain regions associated with early-stage neurodegeneration. Physiological Reports, 5(9), 1–13.
37- Loughrey, D. G., Kelly, M. E., Kelley, G. A., Brennan, S., & Lawlor, B. A. (2018). Association of age-related hearing loss with cognitive function, cognitive impairment, and dementia a systematic review and meta-analysis. JAMA Otolaryngology - Head and Neck Surgery, 144(2), 115–126.

38- Chen, G. F., Xu, T. H., Yan, Y., Zhou, Y. R., Jiang, Y., Melcher, K., & Xu, H. E. (2017). Amyloid beta: Structure, biology, and structure-based therapeutic development. Acta Pharmacologica Sinica, 38(9), 1205–1235.
39- Kivipelto, M., & Mangialasche, F. (2021). Dementia research in 2020: moving forward despite the COVID-19 pandemic. The Lancet Neurology, 20(1), 3–5.
40- McKhann, G., Drachman, D., Folstein, M., & Katzman, R. (1984). Views & reviews Clinical diagnosis of Alzheimer's disease : Neurology, 34(7), 939.
41- Butz, A. M., & Christopher S. von Bartheld, J. B. and S. H.-H. (2017). 乳鼠心肌提取 HHS Public Access. Physiology & Behavior, 176(12), 139–148.
42- Dubois, B., Hampel, H., Feldman, H. H., Scheltens, P., Andrieu, S., Bakardjian, H., Benali, H., Bertram, L., Broich, K., Cavedo, E., Crutch, S., Duyckaerts, C., Frisoni, G. B., Gauthier, S., Gouw, A. A., Habert, M., Holtzman, D. M., Kivipelto, M., Lista, S., … Devices,
43- M. (2019). HHS Public Access (Vol. 12, Issue 3).
44- Knopman, D. S., Jack, C. R., Wiste, H. J., Weigand, S. D., Vemuri, P., Lowe, V., Kantarci, K., Gunter, J. L., Senjem, M. L., Ivnik, R. J., Roberts, R. O., Boeve, B. F., & Petersen, R. C. (2012). Short-term clinical outcomes for stages of NIA-AA preclinical Alzheimer's disease. Neurology, 78(20), 1576–1582.
45- Vega, J. N., & Newhouse, P. A. (2014). Mild Cognitive Impairment: Diagnosis, Longitudinal Course, and Emerging Treatments.
46- Current Psychiatry Reports, 16(10), 1–18.
47- Cedarbaum, J. M., Jaros, M., Hernandez, C., Coley, N., Andrieu, S., Grundman, M., & Vellas, B. (2013). The rationale for use of the Clinical Dementia Rating Sum of Boxes as a primary outcome measure for Alzheimer's disease clinical trials. Alzheimer's and Dementia, 9(1 SUPPL.), S45–S55.
48- Tahami Monfared, A. A., Byrnes, M. J., White, L. A., & Zhang, Q. (2022). Alzheimer's Disease: Epidemiology and Clinical Progression. Neurology and Therapy, 11(2), 553–569.
49- Jack, C. R., Knopman, D. S., Jagust, W. J., Shaw, L. M., Aisen, P. S., Weiner, M. W., Petersen, R. C., & Trojanowski, J. Q. (2010). Hypothetical Pathological Cascade in Alzheimer's Disease. Lancet Neurology, 9(1), 1–20.
50- Fisher, G., & Roget, N. (2014). Diagnostic and Statistical Manual of Mental Disorders. In Encyclopedia of Substance Abuse Prevention, Treatment, & Recovery. https://doi.org/10.4135/9781412964500.n104
51- Weller, J., & Budson, A. (2018). Current understanding of Alzheimer's disease diagnosis and treatment. F1000Research, 7(0), 1–9. https://doi.org/10.12688/f1000research.14506.1
52- Harrison, J. E., Weber, S., Jakob, R., & Chute, C. G. (2021). ICD-11: an international classification of diseases for the twenty-first century. BMC Medical Informatics and Decision Making, 21, 1–10.