ISSN (0): Applied, ISSN (P): Applied Volume 1, Issue 1, 2025. Page: 16-26.

International Journal of Research in Medicine and Ayurveda

www.ijrma.com

Review Article

RISK FOR ALZHEIMER`S DISEASE IN WOMEN- A REVIEW

Amit Mia*

BCDA College of Pharmacy and Technology Affiliated to Maulana Abul Kalam Azad University of Technology (Formerly Known as West Bengal University of Technology), 78, Jessore Road (south), Hridaypur, Barasat, Kolkata -700127, India.

ABSTRACT

Dementia is most commonly caused by Alzheimer's disease, a degenerative brain illness. Dementia's typical symptoms include challenges with language, remembering, and solving problems additional cognitive abilities that impact an individual's capacity to execute regular activities. Female sex, together with advanced age and the apolipoprotein E (APOE)-4 genotype, is a significant risk factor for late-onset Alzheimer's disease. Given that AD pathology begins decades before clinical symptoms appear, women's increased risk cannot be attributed solely to their longer life expectancy. Recent research into the sex-specific pathophysiological mechanisms behind AD risk has identified the menopause transition (MT). Many symptoms of MT, which typically ends in reproductive senescence, are neurological in nature, including disturbance of estrogen-regulated systems such as thermoregulation, sleep, and circadian rhythms, depression and impairment in multiple cognitive domains. Preclinical investigations have indicated that during MT, the estrogen network separates from the brain bioenergetic system. The ensuing hypometabolic state may act as a basis for neurological impairment. Indeed, translational brain imaging studies show that 40-60-year-old perimenopausal and postmenopausal women have an AD-endophenotype defined by lower metabolic activity and higher brain amyloid-beta deposition as compared to premenopausal women and age-matched males. This review highlights the MT as a window of opportunity for therapeutic approaches to correct for brain bioenergetic crisis and reduce the consequent elevated risk of Alzheimer's disease in women. Drugs have entered the clinical trials, like AN-1792, solanezumab, bapineuzumab, semagacestat, avagacestat and tarenflurbil for the treatment of Alzheimer`s disease. More research is needed to find cure for Alzheimer's disease.

KEYWORDS: Dementia, Alzheimer’s disease, Apolipoprotein, Hypometabolic, Pregnancy complication.

Article Info

Article Received: 19 May 2025,
Article Revised: 10 June 2025,
Published on: 01 July 2025.

***Corresponding author:**
Amit Mia*
BCDA College of Pharmacy and Technology Affiliated to Maulana Abul Kalam Azad University of Technology (Formerly Known as West Bengal University of Technology), 78, Jessore Road (south), Hridaypur, Barasat, Kolkata -700127, India.
amitmia2021@gmail.com

INTRODUCTION

Dementia is most commonly caused by Alzheimer's disease, a degenerative brain illness. A condition, or collection of symptoms, known as dementia has several causes. Dementia's typical symptoms include challenges with language, remembering, and solving problems additional cognitive abilities that impact an individual's capacity to execute regular activities.[1] These challenges arise due to nerve neurons in the areas of the brain related to cognitive function has been harmed. In cases of Alzheimer's illness, neurons in different brain regions will ultimately destroy, including those that facilitate to be able to perform fundamental body functions like walking as well as swallowing. Individuals with the disease's last stages are bedridden and in need of 24-hour care. Dementia in the end, illness is deadly.[2,3] Alzheimer`s disease (AD) was initially identically identified in a female patient in 1901.Amyloid-b (Ab) plaques and fibrillar tau tangles are the illness`s histological hallmarks.[4] More than 5.5 million Americans suffer from Alzheimer's disease (AD), the most frequent cause of dementia. Women make up two thirds of those affected. Age is a recognized risk factor for AD development; after age 60, the risk doubles every ten years. Women are known to live longer than men, which accounts for the variation in the disease's prevalence. There is conflicting evidence from incidence studies about sex differences in AD. Most studies show no sex differences in AD incidence. According to a meta-analysis of seven population-based studies on the incidence of AD, the rate of rise in incidence decreases after the age of 85.[5] The variations in AD by sex and gender could be explained by a variety of different

biological pathways. These include variations in the risk arising from genetics, aging response, hormonal impacts, co-morbidities related to mental health and pregnancy, and lifestyle/psychosocial factors influencing cognitive reserve.[6]

EPIDEMIOLOGY

Globally, dementia prevalence appears to be influenced by cultural and socioeconomic variations across national boundaries. It's interesting to note that industrialized countries seem to have greater rates of dementia overall and AD in particular nations. As an evaluation concerning the prevalence of dementia worldwide, the increased was ascribed to wealthy nations to variations in the degree of exposure to cerebrovascular risk factors include diabetes, smoking, obesity, and high blood pressure.[7] This percentage is predicted to increase to 71.2% by 2040 from 60.1% of all dementia patients in developing nations in 2001. Particularly in China, India, and Latin America, where dementia is quickly emerging as the main public health issue, the aging population shift is happening quickly.[8] According to the Delphi Consensus Study, dementia prevalence was lowest in less developed parts of the world, such the Middle East and Africa, and highest in the Americas. By 2040, the dementia prevalence in Latin America will be comparable to that in North America. Japan is the developed nation with the lowest prevalence of dementia overall and Alzheimer's disease specifically. Furthermore, dementia prevalence was comparatively consistent throughout Eastern European nations.[9]

Table 1: Summary of some studies that evaluate the prevalence of dementia in respective countries or regions.

Country	Study	Year	Women AD Above 60 Years	Men AD Above 60 Years	Prevalence Of Dementia	Reference
Europe	Collaborative Study	1990	4.4%>65 years	2.3%>65 years	6.4%>65 years	[10,15]
Italy	ILSA study	1993	6.55%>65 years	4.4%>65 years	12.47%>65 years	[11,15]
USA	ADAMS	2007	2.4%>65 years	2.1%>65 years	14%>71 years	[12,15]
Latin America	Delphi consensus study	2005	4.5%>65 years	3.1%>65 years	7.3%>75 years	[9,15]
Africa	Systematic Analysis	2012	15.1%>50 years	5.2%>65 years	2.4%>50 years	[13,15]
China	People's republic of China study	2010	1.9%>60 years	0.8%>65 years	3.0%>60 years	[14,15]
India	Aging study in India	2018	7.50%>60 years	4.40%>60 years	8.01%>60 years	[62]

Women are more likely than men to get Alzheimer's disease and other dementias. Women make up over two thirds of those in the United States suffering from Alzheimer's.[16] In the US, there are 5.3 million adults 65 and older who have Alzheimer's disease; 3.3 million of these are women and 2.0 million are men. Estimates from ADAMS show that among those 71 years of age and older, 11% of men and 16% of women have Alzheimer's or other dementias.[17] The Framingham Heart Study data, which was used in a recent study, suggests that men who live past 65 may have a healthier cardiovascular risk profile and, consequently, an apparent lower risk of dementia than women of the same age because men have a higher rate of death from cardiovascular disease than women.[18]

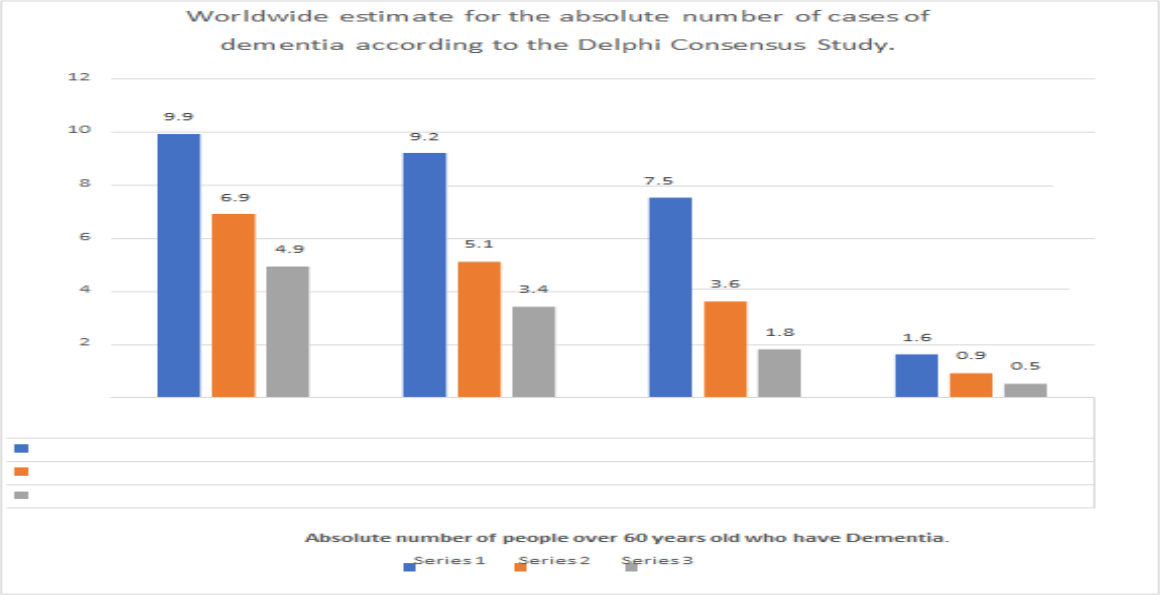

Figure 1: Worldwide estimate for the absolute number of cases of dementia according to The Delphi Consensus Study.[9]

PATHOPHYSIOLOGY

Alzheimer's disease is pathologically defined by the deposition of aberrant neuritic plaques and neurofibrillary tangles in the brain. These degenerative alterations are followed by neuronal loss, particularly of cholinergic neurons in the basal forebrain and neocortex.

Based on the pathological data, two major pathophysiological explanations have been proposed

a. The Cholinergic Hypothesis suggests that the development of AD may be significantly influenced by the brain's decreased acetylcholine (Ach) levels, which are caused by neuronal death in the Nucleus Basalis of Meynert. The early degeneration of cholinergic neurons in AD emphasizes the significance of ach in cognitive functions, leading to this theory. Cholinergic synaptic loss and reduced ach released are thought to be two ways that beta- amyloid impairs cholinergic function. Clinical studies on older women with anticholinergics have shown deleterious effects on memory.[19]

b. The Amyloid Hypothesis is presently the pathophysiological cause for AD that is most well accepted, particularly in cases of hereditary AD. According to the amyloid hypothesis, β- and γ-secretase enzymes are responsible for the production of amyloid beta (Aβ) peptide from amyloid precursor protein (APP). Alpha and beta secretases typically cleave APP, forming minuscule fragments that are not neurotoxic; however, gamma secretase and beta secretase consecutive cleavage produces 42 amino acid peptides (Aβ42). Aβ42 levels that are elevated induce amyloid to aggregate and subsequently cause neuronal damage. Aggregated fibrillary amyloid protein is preferred over normal APP breakdown by Aβ42.[20]

Based on the histopathology data, three major histopathological explanations have been proposed

a. Neuritic Plaques: Neuritic plaques are minute spherical lesions with a core of extracellular amyloid beta-peptide (Aβ) and expanded axonal terminals. In Alzheimer's disease, Aβ depositions occur around meningeal and cerebral arteries, as well as in the cortical Gray- matter. Gray matter deposits are multifocal and merge to form miliary structures known as plaques. However, in certain cases, brain scans have indicated the presence of amyloid plaques in women without dementia. Other women with dementia who had several brain scans, on the other hand, showed no indication of plaques.[21]

b. Neurofibrillary Tangles: Neurofibrillary tangles are fibrillary intracytoplasmic formations made up of a protein known as tau. Tau protein's major function is to maintain axonal microtubule stability. Microtubules, which run along neuronal axons, are necessary for intracellular trafficking. Tau promotes microtubule stability and assembly along neuronal axons. Extracellular beta-amyloid aggregation causes tau hyperphosphorylation in Alzheimer's disease. Because of this aberrant phosphorylation, tau becomes misfolded and clumps within neurons. Neurofibrillary tangles are twisted paired helical filaments made up of tau clumps. Neurofibrillary tangles first form in the hippocampus and then extend throughout the cerebral cortex. Tau-aggregates accumulate within the neurons.[21]

c. Cortical Neuronal Degeneration: One of the most common degenerative changes is granulovacuolar degeneration of hippocampal pyramidal neurons. Alzheimer's disease cognitive decline is connected to fewer presynaptic boutons from pyramidal neurons in specific cerebral cortex layers. In particular, laminae III and IV. The decrease in their density may have a greater impact on cognitive performance than the simple increase in the number of plaques characteristic of Alzheimer's disease.[22]

SIGNS & SYMPTOMS

Alzheimer's symptoms can from ordinary cognitive impairments that occur with women more than man age. Individuals' Alzheimer's symptoms vary, just as much as women do lifestyle. The most common early sign is a progressive decline in the capacity to recall new information. As neurons in other sections of the brain are damaged and killed, women experience a variety of problems, including neuro-behavioural symptoms including agitation, insomnia, and delusions. Each woman experiences symptoms differently, with some advancing from mild to moderate and severe. Cognitive and functional abilities deteriorate as the disease worsens. In the later stages, women become bedridden and dependent on 24-hour care, lose their ability to speak, and require assistance with basic everyday tasks like eating, dressing, washing, and using the restroom. Women who experience mobility challenges are more susceptible to infections, such as pneumonia, which is an infection of the lung women more than man. Women who have Alzheimer's disease frequently die as a result of pneumonia associated to the disease. An individual is susceptible to dying from malnutrition and dehydration associated with Alzheimer's disease when the disease damages brain cells in the regions that regulate swallowing.[25]

Memory Loss That Disrupts Daily Life: Memory loss is one of the most typical symptoms of Alzheimer's, particularly forgetting things you've recently learned. Other ones include repeatedly asking for the same information, forgetting significant dates or events, and becoming more and more dependent on memory aides. (Example: Sometimes forgetting names or appointments, but remembering them later).

Challenges In Planning & Solving Problems: Some women feel that their capacity to create and adhere to plans or deal with numbers changes. They can find it difficult to follow a recipe they are familiar with. They can find it difficult to focus and find that tasks take much longer than they used to.

Confusion With Time & Place: Alzheimer's patients who are women are more likely to forget dates, seasons, and the passing of time than males. If something is not happening right away, they could find it difficult to understand. They occasionally lose track of their location and method of travel.[26]

Trouble Understanding Visual Images & Spatial Relationships: In several cases, visual impairments are indicative of Alzheimer's disease. They might have trouble reading, estimating distance, and distinguishing between colours or contrasts, which could make driving challenging for them. (Examples: Vision changes related to cataracts, glaucoma or age-related macular degeneration).

Changes In Mood & Personality: People with Alzheimer's disease may experience changes in their personalities and moods. People may start to feel afraid, nervous, confused, distrustful, or melancholy. While they are with friends, at work, at home, or in other situations that are outside of their comfort zones, they could become quickly disturbed.[27]

DIAGNOSIS

An Alzheimer's test does not exist. Rather, in order to assist in making a diagnosis, doctors employ a range of methods and instruments, frequently with the assistance of experts like neurologists and geriatricians.

They consist of the following

I. Getting information from the person about their health and family history, especially any psychiatric conditions and any changes in their cognition or behaviour.
II. Getting feedback from a family member about cognitive and behavioural changes.
III. Doing physical and neurological assessments as well as cognitive testing.
IV. Blood tests and brain imaging should be performed on the patient to rule out further possible causes of dementia symptoms, such as tumours or specific vitamin deficiencies.

Alzheimer's must be diagnosed by a thorough and meticulous medical examination. While diagnosing dementia is almost always possible for doctors, pinpointing the precise cause can be challenging. The patient may need to finish the necessary examinations and tests over the course of several days or weeks, and the doctor may need time to review the findings and formulate a diagnosis.[28]

FACTOR AFFECTING OF ALZHEIMER `S DISEASE FOR WOMEN

There are Some major Factor which have affected of Alzheimer `s disease for women including:

a. Apolipoprotein E4 genetic risk.
b. Telomere shortening and aging.
c. Pregnancy complication.
d. Hormonal effect.
e. Psychiatric co-morbidities-depression and insomnia.
f. Brain structure.
g. Metabolic conditions.

a. Apolipoprotein E4 Genetic Risk

The most powerful genetic risk factor for late-onset sporadic AD is the apolipoprotein E4 (APOE4) allele. Patients with the E4/E4 genotype have a higher chance of developing AD compared to those with the E4/E3 genotype, and the APOE4 allele creates a dose-dependent risk of developing AD. The human body contains large amounts of the protein known as apolipoprotein E (APOE).[29] Primary producers of APOE in the brain are astrocytes.[30] Amyloid-beta protein transcription, synthesis, aggregation, and clearance are all significantly impacted by the APOE protein in AD.[31] For both sexes, the APOE4 allele confers an equivalent risk of AD development. Though moderate cognitive impairment (MCI) is more common in males than women with the APOE4 allele. Women with the APOE3/3 or APOE3/4 genotypes are also more likely than men to develop AD among MCI patients.[32] Women with one copy of the APOE4 allele had a fourfold higher chance of developing AD at a younger age, 65–75 years old, according to a meta-analysis of 27 trials including 58,000 participants.[33] In addition, the cerebrospinal fluid of female carriers showed higher levels of total tau, a hallmark of neuronal degeneration in AD. But the lack of an educational level control in many studies may make them more complicated.[34] According to a study examining the longitudinal rates of change from baseline in 398 MCI patients, women with MCI experienced higher rates of progression in their cognitive and functional abilities than did males. In carriers of APOE4, the effect was stronger. In this study, men's educational attainment was statistically higher, however the difference was not very substantial.[35] The evidence that is currently available indicates that APOE4 may modify AD risk in a sex specific way.

b. Telomere Shortening And Aging

Telomeres are the DNA structures at the ends of chromosomes. They play an essential role in preventing chromosomal breakdown. Telomere shortening has been linked to reduced stem cell activity, regeneration, and organ maintenance as people age. The enzyme telomerase counteracts this reaction by introducing repetitive telomeres into the terminal DNA. Reduced telomere length is connected with Alzheimer's disease, particularly in females.[36] Evidence suggests that APOE4 carriers have shorter leukocyte telomere lengths than noncarriers.[37] This lends weight to the hypothesis that APOE4 carriers age prematurely. Telomere length varies greatly across genders. Women have considerably longer telomere length than men of the same age, and this impact appears to be influenced by estrogen. Estrogen reduces oxidative damage and increases telomerase activity.[38] In a two-year research, healthy postmenopausal women who had APOE4 showed considerable leucocyte telomere shortening

compared to noncarriers.[39] Furthermore, APOE4 carriers who continued to receive hormonal replacement therapy showed no telomere erosion, which was not observed in noncarriers. As a result, hormone therapy may reduce the risk of Alzheimer's disease for people who are vulnerable. Another explanation for this discrepancy could be sex differences in educational attainment, which appear to have a protective impact against telomere shortening.[40]

c. Pregnancy Complication

Retrospective studies indicate that women who have preeclampsia have an increased risk of stroke even decades later. Pregnancy related difficulties expose women who are at risk for cerebrovascular consequences. These women's higher risk of stroke put them at risk for vascular dementia as well as cognitive loss. Another study found that women with pregnancy hypertension issues were more likely to develop cognitive difficulties, particularly lower working memory and language learning, 15 years later.[41] Vascular dementia may result from a stroke or small vessel disease. Patients with vascular dementia typically have reduced processing speed, difficulties in executive function, and visual memory, although verbal learning is unaffected. The study on hypertensive disease of pregnancy found reduced working memory and language learning, which contradicts the current findings. Problems that are more common among persons with Alzheimer's disease. Pregnancy problems may affect cognition by contributing to mixed dementia. Mixed dementia caused by both Alzheimer's disease and vascular reasons is widespread, with various forms of small artery disease supporting both etiology.[42]

d. Hormonal Effect

Early research in Cache County, Utah suggests a potential "window of opportunity" for hormone therapy to improve cognition. In population-based research of over 2,000 nondemented women over 65 (controlling for variables like lesser education, depression, and APOE ϵ4 status), lifetime hormonal replacement therapy (HRT) use was associated with better baseline mini-mental status exam scores and a slower rate of cognitive decline.[43] A prospective study of 1,889 women from Cache County, Utah found that those who used HRT had a lower risk of Alzheimer's disease compared to those who did not (adjusted HR, 0.59; 95% CI, 0.36-0.96). The risk changed with the length of HRT usage, with the sex-specific increase for women disappearing after more than 10 years.[44] These findings suggest that the positive effect of HRT is timing dependent. Both investigations were conducted in a single county, making their generalizability uncertain. Educational and socioeconomic characteristics may have influenced who could participate. A 2003 randomized controlled trial, The Women's Health Initiative Memory Study (WHIMS), found that postmenopausal women aged 65-79 without a hysterectomy who received estrogen and progesterone had twice the risk of dementia compared to controls. The increased risk of dementia in women receiving hormone therapy would result in 23 additional cases of dementia per 10,000 women each year.[45] This well-designed experiment convincingly revealed that postmenopausal hormone replacement has a deleterious impact on cognition. Studies on the therapeutic window for HRT have yielded varied results. Prospective cohort research found that women who utilized any sort of hormone replacement therapy within 5 years of menopause had a 30% lower incidence of Alzheimer's disease. This benefit was also observed in women who received HRT for more than ten years following menopause. A 20-year prospective cohort study from Finland of women aged 47 to 56 found no clear evidence that postmenopausal hormone replacement treatment reduces Alzheimer's disease. However, a protective relationship between long-term (>10 years) self-reported HT consumption and AD was found. This finding suggests that starting HT in the early postmenopausal period may be more effective.[46] A retrospective population-based analysis found that women with 5 or more pregnancies had a 1.7-fold higher risk of Alzheimer's disease compared to those with 1-4 completed pregnancies. Furthermore, women who had incomplete pregnancies were half as likely to develop Alzheimer's disease as those who had never had an incomplete pregnancy.[47] It's unclear whether these findings are related to hormonal changes, differences in medical comorbidities, or education/socioeconomic position.

e. Psychiatric co-morbidities-depression and insomnia

Depression has been linked to an increased risk of Alzheimer's disease, with women having twice the risk as males.[48] There is evidence that early-life depression can be a risk factor for later-life dementia, and that depression later in life can be a precursor to dementia.[49] A meta-analysis of relevant research revealed a positive relationship between the length of time after a depression diagnosis and the probability of acquiring Alzheimer's disease, implying that depression is a risk factor.[50] According to the WHIMS study, women with depression were approximately twice as likely to develop MCI and AD.[51] The degree and timing of depression appear to be associated with the chance of acquiring Alzheimer's disease. A study found that patients with MCI and active depression within the last two years had a 41.7% conversion rate to AD, compared to 31.6% for patients with a more remote history of depression.[52] Insomnia may increase the risk of cognitive deterioration and Alzheimer's disease. Sleep is essential for cognitive function, particularly memory consolidation. Several longitudinal investigations indicated that patients with insomnia were twice as likely to experience cognitive impairment or be diagnosed with Alzheimer's disease.[53] Women have a higher incidence of sleeplessness. It is unclear if sleeplessness is an independent risk factor for Alzheimer's disease or is linked to it through its interactions with stress and sadness.[54]

f. Brain Structure

Research suggests that gender disparities in Alzheimer's risk may be due to differences in brain anatomy caused by risk factors. Men tend to have a bigger brain capacity, making them less susceptible to pathological agents and experiencing slower structural loss than women. Brain imaging studies indicate that male MCI and AD patients experience slower yearly shrinkage rates. Men with MCI showed less brain atrophy and slower decrease in cognitive 12 tasks compared to women. They also showed less atrophy in several regions after being diagnosed with AD. Women, on the other hand, have more cortical thickness than men throughout their lives, which could be protective. Quantitative proteomics studies show changes in white matter and mitochondrial proteomes, redox proteins, ATP synthase, and cytochrome oxidase in women. These pathophysiological increases in women show that once neurodegeneration begins, women experience it faster than men. Furthermore, women may be more sensitive to the AD pathologic biomarkers than men. A recent study found that women have greater CSF total tau and Aβ42 levels, faster cognitive impairment, and hippocampus shrinkage, indicating worse pathogenic alterations than men.[55] Adverse life events can cause changes in brain structure and function, increasing the likelihood of post-traumatic stress disorder, depression, and other neuropsychiatric diseases. It's crucial to examine sex differences in resilience. Stress during prenatal and early postnatal life may increase the risk of socialization diseases in male offspring, while stress during puberty may increase the risk of depression, anxiety, and post-traumatic stress disorder in female offspring. While there is evidence of sex variations in structural integrity responses to pathologic insults in AD, the underlying molecular mechanism remains unknown.

g. Metabolic Conditions

Metabolic differences between sexes may impact brain health in older age. Obesity has been linked to an increased incidence of MCI in women but not in men.[56] A higher body mass index, which accounts for waist circumference (as a measure of lean body mass), has been shown to be protective of cognitive decline in women but not men over four years.[57] Type-2 diabetes, which is frequently associated with obesity, has been linked to a higher risk of dementia in women but not males, though not consistently.[58] Diabetic women with higher waist circumference have a higher risk of cardiovascular disease and dementia compared to diabetic men.[59] This could be due to sex-specific body composition and fat distribution, which could be influenced by sex hormones. The intricacy of metabolic parameters between sexes at various ages may help explain the inconsistent findings. Genetic abnormalities in enzymes converting androgens to estogens, as well as lack of activity in estrogen receptors, can cause metabolic diseases in both sexes.[60] Early menopause (before 45 years old) and premature ovarian insufficiency (before 40 years old) have been linked to a higher incidence of type 2 diabetes compared to women of normal menopausal age (after 45).[61] Possible explanations for these relationships include estrogen's 13 modulation of insulin production and secretion, as well as the interplay of other sex hormones such as testosterone, which have also been linked to type 2 diabetes.[62]

Treatment

Pharmacologic Treatments

Currently, there are around 24 million cases of Alzheimer's disease globally, and the overall number of persons with dementia is expected to increase fourfold by 2050. Currently, only two types of medications are approved to treat Alzheimer's disease: a. cholinesterase inhibitors (naturally occurring, synthetic, and hybrid analogues) and b. NMDA antagonists. Several physiological processes in AD damage Ach-producing cells, reducing cholinergic transmission throughout the brain. Acetyl cholinesterase inhibitors (AChEIs), which are classed as reversible, irreversible, and pseudo-reversible, work by Preventing cholinesterase enzymes (AChE and butryl cholinesterase (BChE)) from degrading ACh, resulting in increased ACh levels in the synaptic cleft. Overactivation of NMDAR increases inflexed Ca2+ levels, promoting cell death and synaptic dysfunction. NMDAR antagonist reduces NMDAR glutamate receptor over activation and, as a result, Ca2+ influx while restoring normal activity. Although these two classes have therapeutic effects, they only treat symptoms of AD and do not cure or prevent the illness. Only a few clinical trials on Alzheimer's disease have been conducted in the recent decade, with poor results. To create effective treatments for Alzheimer's disease, various processes have been hypothesized. These include aberrant tau protein metabolism, amyloid, inflammatory response, and cholinergic and free radical damage. According to studies, physical activity can promote brain health and lessen Alzheimer's disease by activating brain vascularization, plasticity, neurogenesis, and reducing inflammation by decreasing a production, all of which result in improved cognitive function in older adults. Furthermore, the Mediterranean diet, intellectual engagement, and higher education may all slow the progression of Alzheimer's disease and memory loss while increasing brain capacity and cognitive capabilities. Research suggests that a multi-domain strategy, including lifestyle (diet, exercise, and cognitive training), depression of AD symptoms, and reducing cardiovascular risk factors, can improve cognitive performance and prevent new instances of AD in older adults.[63]

Table 2: Characteristics of current treatment of alzheimer's disease.

Agent	Formulation	Dose	Regimen	Indication
Cholinesterase inhibitors				
Donepezil	Tablet	5mg	Begin with 5mg daily and advance to 10mg daily after 4-6 weeks	Mild to moderate Alzheimer's disease
Rivastigmine	Capsule	1.5mg,1mg	Begin with lowest dose twice daily and increase at 2weeks interval to highest dose	Mild to moderate Alzheimer's disease
Nmda receptor antagonist				
Memantine	Tablet	5mg	Advance daily to twice daily	Mild to severe Alzheimer's disease

Currently, only two types of medications are approved to treat Alzheimer's disease[63]

a. Cholinesterase Inhibitors: The cholinergic hypothesis proposes that Alzheimer's disease is caused by a decrease in acetylcholine (ACh) biosynthesis. Increasing cholinergic levels by reducing acetyl cholinesterase (AChE) is one of the treatment techniques for improving cognitive and neural cell function. AChEIs are used to block acetylcholine breakdown in synapses, resulting in continuous cholinergic receptor activation. Tacrine (tetrahydroaminoacridine) was the first FDA (Food and Drug Administration)-approved cholinesterase inhibitor drug for the treatment of Alzheimer's disease, acting by increasing ACh in muscarinic neurons, but it was withdrawn from the market shortly after its introduction due to a high incidence of side effects such as hepatotoxicity and a lack of benefits, as seen in several trials. AChEIs, including donepezil, rivastigmine, and galantamine, are being used to treat AD symptoms. Another technique for treating Alzheimer's disease is to increase choline reuptake, which increases acetylcholine production at presynaptic terminals. This can be accomplished by focusing on the choline transporter (CHT1), which is important for delivering choline for ACh production. Developing 15 medications that can increase CHT1 at the plasma membrane may be the future of Alzheimer's disease treatment.[64]

Donepezil

Donepezil, a second-generation AChEI derived from indanone benzyl piperidine, is widely recognized as the most effective Alzheimer's disease medication. Donepezil binds to acetyl cholinesterase in a reversible manner, inhibiting acetylcholine hydrolysis and resulting in a greater concentration of ACh at synapses. The medication is well tolerated, with moderate and temporary cholinergic side effects affecting the gastrointestinal and neurological systems. Donepezil is a treatment for Alzheimer's disease that improves cognition and behavior without affecting the illness's progression.[65]

b.N-methyl d-aspartate (NMDA) Antagonists: NMDAR is thought to play a significant role in the pathogenesis of AD. NMDAR stimulation increases signal transduction and gene transcription, resulting in long-term potentiation (LTP), which is crucial for synaptic neurotransmission, learning, and memory. Over activation of NMDARs generates aberrant Ca2+ signalling and overstimulation of glutamate, the major excitatory amino acid in the CNS, resulting in excitotoxicity, synaptic dysfunction, neuronal cell death, and a loss in cognitive performance. Several NMDAR uncompetitive antagonists have been created and tested in clinical trials; however, the majority of them were unsuccessful due to limited efficacy and side effects.[66]

Memantine: Memantine, a low-affinity uncompetitive antagonist of the NMDAR glutamate receptor, prevents over-activation of the glutaminergic pathway, which can cause neurotoxicity in Alzheimer's patients. Memantine is using for treatment moderate to severe Alzheimer's disease alone or in combination with AChEIs. Memantine is a safe and well-tolerated medication that blocks excitatory receptors without disrupting normal synaptic transmission. Its low affinity causes it to be quickly displaced from NMDAR by high glutamate concentrations, preventing persistent blockage. The latter is connected with significant adverse effects, particularly in terms of learning and memory.[67]

Promising future therapies

Disease-Modifying Therapeutics (DMT): DMT aims to slow the progression of Alzheimer's disease by targeting many pathophysiological processes. This is in contrast to symptomatic therapy, which focuses on restoring cognitive function and reducing symptoms such as 16 sadness or delusions without affecting or changing the condition. DMTs, orally administered immunotherapies or small compounds, are being developed to prevent or slow the course of Alzheimer's disease. Several DMTs have been developed and tested in clinical trials, including AN-1792, a synthetic A-beta peptide with the immune adjuvant QS-21. This was the first active immunotherapy for Alzheimer's disease, but was discontinued due to a meningoencephalitis side effect in 6% of patients. Several medicines, such as anti-A beta antibodies (solanezumab and bapineuzumab), secretase inhibitors (semagacestat 6, avagacestat 7, and tarenflurbil 8), and BACE inhibitors (Lanabecestat 9, verubecestat 10, and atabecestat 11), failed in clinical studies. DMT failures can be caused by starting therapy too late, treating the wrong target, using

improper drug doses, and not understanding AD etiology. several immunotherapies developed over decades, including: CAD106 is an active immunotherapy that generates A antibodies in animal models. It consists of numerous copies of A-beta 1-6 peptide attached to Q coat protein, a virus-like. Clinical trials are ongoing for particle and CNP520 (umibecestat, 12), a tiny drug that inhibits beta-scretase-1 (BACE-1) and thereby suppresses A formation. CNP520 has been shown to lower A plaque formation and levels in the brain and CSF in rats, dogs, and healthy adults over 60 years old. Clinical investigations are now ongoing. Additionally, aducanumab, gantenerumab, and crenezumab are human A monoclonal antibodies that strongly bind to aggregated A. These antibodies are currently being studied in clinical trials with other DMTs listed in.[68]

Table 3: Disease-Modifying Therapeutics Agents (Dmt).

Disease modifying agents	Mechanism of action
Phase 3 clinical trial	
ADUCANUMAB	Monoclonal antibody-target beta amyloid and remove it.
GANTENERUMAB	Monoclonal antibody – binds and removes beta amyloid.
CAD106B	Amyloid vaccine- stimulate production of antibodies against beta amyloid.
TRx0237 (LMTX)	Tau protein aggregation inhibitors.
PHASE 2 CLINICAL TRIAL	
CRENEZUMAB	Monoclonal antibody- targets soluble oligomers and removes beta amyloid.
ABBV- 8E12	Monoclonal antibody – prevents tau Propagation.
ABvac40	Active immunotherapy- target beta amyloid and removes it.

Disease modifying agents for the treatment of Alzheimer's disease in clinical trials.[68]

Non-Pharmacologic Therapy

Non-pharmacologic therapies are ones that do not require medication. Non-pharmacologic therapy is frequently used to preserve or improve cognitive function, ability to do everyday tasks, and general quality of life. They can also be used to treat behavioural symptoms such depression, apathy, wandering, sleep difficulties, agitation, and violence. Examples include digital memory training, listening to favoured music to stimulate recall, and using specific lighting to reduce sleep issues. Non-pharmacologic therapy, like existing pharmacologic medicines, have not been found to affect the progression of Alzheimer's disease.[69] Reviews and meta-analyses of non-pharmacologic therapies tested in randomized controlled trials show that some are beneficial for individuals with Alzheimer's dementia. These include cognitive stimulation and exercise. Specifically, a 332 Alzheimer's Association / Alzheimer'& Dementia meta-analysis discovered that aerobic exercise, as well as a combination of aerobic and non-aerobic exercise, can improve cognitive performance.[70] Research indicates that exercise improves cognitive function and slows cognitive decline in individuals with Alzheimer's dementia. More randomized controlled trials with larger sample numbers are needed to assess the impact of exercise on cognitive decline. A second systematic review discovered that cognitive stimulation improved cognitive function and well-being.[71]

CONCLUSION

Alzheimer's disease is a significant threat to society due to the aging population and lack of adequate medical therapy. Women appear to be more affected than men due to their longer lifespan and maybe the influence of estrogen deprivation. Understanding clinical distinctions between men and women will help improve disease understanding and patient care. One intriguing theory is that estrogen may benefit memory and other deficiencies in Alzheimer's disease, both as a preventive strategy and after the disease has progressed. Further research in this key area is necessary and will most likely be conducted. However, unless the cause of Alzheimer's disease is discovered, an effective intervention to arrest or cure it does not appear to be imminent. Women outnumber men in clinical trials of potential treatment medicines for Alzheimer's disease, suggesting that overall health consciousness may be future risk. The risk of Alzheimer's disease from environmental exposures in women's overall life experiences remains unknown. Advances in women's general standing in society may help shield them from the ravages of Alzheimer's disease to the extent that education and work encourage the growth of brain areas such as the association cortex, which are preferentially harmed in AD, generating a neuronal reserve. The genetic variations related to gender and sex, the aging process, hormonal fluctuations, psychiatric disorders, and psychosocial factors all contribute to the variation in the risks for this ailment. More research is needed to find a cure for Alzheimer's disease.

ACKNOWLEDGEMENT

I take this opportunity to express my profound gratitude to My guide Mr. Milon Kumar Maity (Associated Professor) B.C.D.A. College of Pharmacy & Technology, for his exemplary guidance, monitoring and constant encouragement throughout this project. I am obliged to my Principal Prof. (Dr.) Diptendu Goswami, for the valuable information provided by him. Furthermore, I am grateful for his cooperation during my project. Lastly, I am thankful for the almighty, My Parents who deserves a special mention for their inseparable support and love, also My Brothers, Sisters and all of My Friends for their constant encouragement and contribution, without which this project wouldn't be possible.

REFERENCES

1. Alzheimer's Association. 2017 Alzheimer's disease facts and figures. Alzheimer's & Dementia, 2017; 13(4): 325-373.
2. Wilson, R. S., Segawa, E., Boyle, P. A., Anagnos, S. E., Hi zel, L. P., & Bennett, D. A. The natural history of cognitive decline in Alzheimer's disease. Psychology and aging, 2012; 27(4): 1008.
3. Barker, W. W., Luis, C. A., Kashuba, A., Luis, M., Harwood, D. G., Loewenstein, D., ... & Duara, R. Relative frequencies of Alzheimer disease, Lewy body, vascular and frontotemporal dementia, and hippocampal sclerosis in the State of Florida Brain Bank. Alzheimer Disease & Associated Disorders, 2002; 16(4): 203-212.
4. Lopez-Lee, C., Torres, E. R. S., Carling, G., & Gan, L. Mechanisms of sex differences in Alzheimer's disease. Neuron, 2024.
5. Gao, S., Hendrie, H. C., Hall, K. S., & Hui, S. The relationships between age, sex, and the incidence of dementia and Alzheimer disease: a meta-analysis. Archives of general psychiatry, 1998; 55(9): 809-815.
6. Chêne, G., Beiser, A., Au, R., Preis, S. R., Wolf, P. A., Dufouil, C., & Seshadri, S. Gender and incidence of dementia in the Framingham Heart Study from mid-adult life. Alzheimer's & Dementia, 2015; 11(3): 310-320.
7. Rizzi, L., Rosset, I., & Roriz-Cruz, M. Global epidemiology of dementia: Alzheimer's and vascular types. BioMed research international, 2014; 2014(1): 908915.
8. Kalaria, R. N., Maestre, G. E., Arizaga, R., Friedland, R. P., Galasko, D., Hall, K., ... & Antuono, P. Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. The Lancet Neurology, 2008; 7(9): 812-826.
9. Ferri, C. P., Prince, M., Brayne, C., Brodaty, H., Fratiglioni, L., Ganguli, M., ... & Scazufca, M. Global prevalence of dementia: a Delphi consensus study. The lancet, 2005; 366(9503): 2112-2117.
10. Lobo, A., Launer, L. J., Fratiglioni, L., Andersen, K., Di Carlo, A., Breteler, M. M. B., ... & Hofman, A. Prevalence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. Neurology, 2000; 54(5): S4.
11. Di Carlo, A., Baldereschi, M., Amaducci, L., Lepore, V., Bracco, L., Maggi, S., ... & ILSA Working Group. Incidence of dementia, Alzheimer's disease, and vascular dementia in Italy. The ILSA Study. Journal of the American Geriatrics Society, 2002; 50(1): 41 48.
12. Thies, W. 2011 Alzheimer's disease facts and figures. Alzheimer's & Dementia, 2011; 7(2): 208-244.
13. George-Carey, R., Adeloye, D., Chan, K. Y., Paul, A., Kolčić, I., Campbell, H., & Rudan, I. An estimate of the prevalence of dementia in Africa: a systematic analysis. Journal of global health, 2012; 2(2).
14. Chiu, H. F. K., & Zhang, M. Dementia research in China. International journal of geriatric psychiatry, 2000; 15(10): 947-953.
15. Gustavsson, A., Norton, N., Fast, T., Frölich, L., Georges, J., Holzapfel, D., ... & van der Flier, W. M. Global estimates on the number of persons across the Alzheimer's disease continuum. Alzheimer's & Dementia, 2023; 19(2): 658-670.
16. Hebert, L. E., Weuve, J., Scherr, P. A., & Evans, D. A. Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. Neurology, 2013; 80(19): 1778 1783.
17. Green, R. C., Cupples, L. A., Go, R., Benke, K. S., Edeki, T., Griffith, P. A., ... & MIRAGE Study Group. Risk of dementia among white and African American relatives of patients with Alzheimer disease. Jama, 2002; 287(3): 329-336.
18. Chêne, G., Beiser, A., Au, R., Preis, S. R., Wolf, P. A., Dufouil, C., & Seshadri, S. Gender and incidence of dementia in the Framingham Heart Study from mid-adult life. Alzheimer's & Dementia, 2015; 11(3): 310-320.
19. Hampel, H., Mesulam, M. M., Cuello, A. C., Farlow, M. R., Giacobini, E., Grossberg, G. T., ... & Khachaturian, Z. S. The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. Brain, 2018; 141(7): 1917-1933.
20. Paroni, G., Bisceglia, P., & Seripa, D. Understanding the amyloid hypothesis in Alzheimer's disease. Journal of Alzheimer's Disease, 2019; 68(2): 493-510.
21. Serrano-Pozo, A., Frosch, M. P., Masliah, E., & Hyman, B. T. Neuropathological alterations in Alzheimer disease. Cold Spring Harbor perspectives in medicine, 2011; 1(1): a006189.
22. Thakur, A. K., Kamboj, P., Goswami, K., & Ahuja, K. J. J. A. P. R. Pathophysiology and management of Alzheimer's disease: An overview. J anal pharm Res., 2018; 9(2): 226-35.
23. Hassin, G. B. Peripheral Nerves: Anatomic and Pathologic Considerations. Archives of Neurology & Psychiatry, 1932; 27(1): 58-78.
24. Braak, H., & Braak, E. Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiology of aging, 1997; 18(4): 351-357.
25. Katzman, R. The prevalence and malignancy of Alzheimer disease: a major killer. Archives of neurology, 1976; 33(4): 217-21.
26. Fernando, M. S., & Ince, P. G. Vascular pathologies and

cognition in a population-based cohort of elderly people. Journal of the neurological sciences, 2004; 226(1-2): 13-17.
27. Bateman, R. J., Xiong, C., Benzinger, T. L., Fagan, A. M., Goate, A., Fox, N. C., ... & Morris, J. C. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. New England Journal of Medicine, 2012; 367(9): 795-804.
28. Roberts, R., & Knopman, D. S. Classification and epidemiology of MCI. Clinics in geriatric medicine, 2013; 29(4): 753-772.
29. Verghese, P. B., Castellano, J. M., & Holtzman, D. M. Apolipoprotein E in Alzheimer's disease and other neurological disorders. The Lancet Neurology, 2011; 10(3): 241 252.
30. Huang, Y., Weisgraber, K. H., Mucke, L., & Mahley, R. W. Apolipoprotein E: diversity of cellular origins, structural and biophysical properties, and effects in Alzheimer's disease. Journal of Molecular Neuroscience, 2004; 23: 189-204.
31. Theendakara, V., Peters-Libeu, C. A., Bredesen, D. E., & Rao, R. V. Transcriptional effects of ApoE4: relevance to Alzheimer's disease. Molecular neurobiology, 2018; 55: 5243-5254.
32. Altmann, A., Tian, L., Henderson, V. W., Greicius, M. D., & Alzheimer's Disease Neuroimaging Initiative Investigators. Sex modifies the APOE-related risk of developing Alzheimer disease. Annals of neurology, 2014; 75(4): 563-573.
33. Corder, E. H., Ghebremedhin, E., Taylor, M. G., Thal, D. R., Ohm, T. G., & Braak, H. The biphasic relationship between regional brain senile plaque and neurofibrillary tangle distributions: modification by age, sex, and APOE polymorphism. Annals of the new-York Academy of Sciences, 2004; 1019(1): 24-28.
34. Neu, S. C., Pa, J., Kukull, W., Beekly, D., Kuzma, A., Gangadharan, P., ... & Toga, A. W. Apolipoprotein E genotype and sex risk factors for Alzheimer disease: a meta-analysis. JAMA neurology, 2017; 74(10): 1178-1189.
35. Tsiknia, A. A., Edland, S. D., Sundermann, E. E., Reas, E. T., Brewer, J. B., Galasko, D., ... & Alzheimer's Disease Neuroimaging Initiative. Sex differences in plasma p tau181 associations with Alzheimer's disease biomarkers, cognitive decline, and clinical progression. Molecular psychiatry, 2022; 27(10): 4314-4322.
36. Liu, M., Huo, Y. R., Wang, J., Liu, S., Liu, S., Wang, J., & Ji, Y. Telomere shortening in Alzheimer's disease patients. Annals of Clinical & Laboratory Science, 2016; 46(3): 260-265.
37. Jacobs, E. G., Kroenke, C., Lin, J., Epel, E. S., Kenna, H. A., Blackburn, E. H., & Rasgon, N. L. Accelerated cell aging in female APOE-ε4 carriers: implications for hormone therapy use. PloS one, 2013; 8(2): e54713.
38. Adler, N., Pantell, M. S., O'Donovan, A., Blackburn, E., Cawthon, R., Koster, A., ... & Epel, E. Educational attainment and late life telomere length in the Health, Aging and Body Composition Study. Brain, behavior, and immunity, 2013; 27: 15-21.
39. Conte, A., Defazio, G., Ferrazzano, G., Hallett, M., Macerollo, A., Fabbrini, G., & Berardelli, A. Is increased blinking a form of Blepharospasm. Neurology, 2013; 80(24): 2236-2241.
40. Honig, L. S., Schupf, N., Lee, J. H., Tang, M. X., & Mayeux, R. Shorter telomeres are associated with mortality in those with APOE ϵ4 and dementia. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society, 2006; 60(2): 181-187.
41. Bayne, S., Jones, M. E., Li, H. E., & LIU, J. P. Potential roles for estrogen regulation of telomerase activity in aging. Annals of the New York Academy of Sciences, 2007; 1114(1): 48-55.
42. Inoue, Y., Shue, F., Bu, G., & Kanekiyo, T. Pathophysiology and probable etiology of cerebral small vessel disease in vascular dementia and Alzheimer's disease. Molecular neurodegeneration, 2023; 18(1): 46.
43. Carlson, M. C., Zandi, P. P., Plassman, B. L., Tschanz, J. T., Welsh-Bohmer, K. A., Steffens, D. C., ... & Breitner, J. C. Hormone replacement therapy and reduced cognitive decline in older women: the Cache County Study. Neurology, 2001; 57(12): 2210 2216.
44. Zandi, P. P., Carlson, M. C., Plassman, B. L., Welsh-Bohmer, K. A., Mayer, L. S., Steffens, D. C., ... & Cache County Memory Study Investigators. Hormone replacement therapy and incidence of Alzheimer disease in older women: the Cache County Study. Jama, 2002; 288(17): 2123-2129.
45. Shumaker, S. A., Legault, C., Rapp, S. R., Thal, L., Wallace, R. B., Ockene, J. K., ... & WHIMS Investigators. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. Jama, 2003; 289(20): 2651-2662.
46. Imtiaz, B., Tuppurainen, M., Rikkonen, T., Kivipelto, M., Soininen, H., Kröger, H., & Tolppanen, A. M. Postmenopausal hormone therapy and Alzheimer disease: a prospective cohort study. Neurology, 2017; 88(11): 1062-1068.
47. Jang, H., Bae, J. B., Dardiotis, E., Scarmeas, N., Sachdev, P. S., Lipnicki, D. M., … & Kim, K. W. Differential effects of completed and incomplete pregnancies on the risk of Alzheimer disease. Neurology, 2018; 91(7): e643-e651
48. Ownby, R. L., Crocco, E., Acevedo, A., John, V., & Loewenstein, D. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. Archives of general psychiatry, 2006; 63(5): 530-538.
49. Kessing, L. V. Depression and the risk for dementia. Current opinion in psychiatry, 2012; 25(6): 457-461.
50. Goveas, J. S., Espeland, M. A., Woods, N. F., Wassertheil-Smoller, S., & Kotchen, J. M. Depressive symptoms and incidence of mild cognitive impairment and probable dementia in elderly women: the

Women's Health Initiative Memory Study. Journal of the American Geriatrics Society, 2011; 59(1): 57-66.
51. Gallagher, D., Kiss, A., Lanctot, K., & Herrmann, N. Depression and risk of Alzheimer dementia: a longitudinal analysis to determine predictors of increased risk among older adults with depression. The American Journal of Geriatric Psychiatry, 2018; 26(8): 819-827.
52. Lobo, A., LóPez-Antón, R., De-La-CÁmara, C., Quintanilla, M. Á., Campayo, A., Saz, P., & Zarademp Workgroup. Non-cognitive psychopathological symptoms associated with incident mild cognitive impairment and dementia, Alzheimer's type. Neurotoxicity research, 2008; 4: 263-272.
53. Cricco, M., Simonsick, E. M., & Foley, D. J. The impact of insomnia on cognitive functioning in older adults. Journal of the American Geriatrics Society, 2001; 49(9): 1185-1189.
54. Ryan, C. L., & Siebens, J. Educational Attainment in the United States: 2009. Population Characteristics. Current Population Reports, 2012; P20-566. US Census Bureau.
55. Artero, S., Ancelin, M. L., Portet, F., Dupuy, A., Berr, C., Dartigues, J. F., ... & Ritchie, K. Risk profiles for mild cognitive impairment and progression to dementia are gender specific. Journal of Neurology, Neurosurgery & Psychiatry, 2008; 79(9): 979-984.
56. Rodriguez-Fernandez, J. M., Danies, E., Martinez-Ortega, J., & Chen, W. C. Cognitive decline, body mass index, and waist circumference in community-dwelling elderly participants: results from a nationally representative sample. Journal of geriatric psychiatry and neurology, 2017; 30(2): 67-76.
57. Kim, Y. H., Kim, N. H., Jung, M. H., & Kim, H. J. Sex differences in metabolic risk indicator of dementia in an elderly urban Korean population: A community-based cross-sectional study. Geriatrics & gerontology international, 2017; 17(11): 2136-2142.
58. Dementia, including death as a competing risk, in individuals with diabetes: Results from the ADVANCE trial. Diabetes, Obesity and Metabolism, 23(8): 1775-1785.
59. Kautzky-Willer, A., Harreiter, J., & Pacini, G. Sex and gender differences in risk, pathophysiology and complications of type 2 diabetes mellitus. Endocrine reviews, 2016; 37(3): 278-316.
60. Anagnostis, P., Christou, K., Artzouchaltzi, A. M., Gkekas, N. K., Kosmidou, N., Siolos, P., ... & Goulis, D. G. Early menopause and premature ovarian insufficiency are associated with increased risk of type 2 diabetes: a systematic review and meta-analysis. European journal of endocrinology, 2019; 180(1): 41-50.
61. Sharma, K. Cholinesterase inhibitors as Alzheimer's therapeutics. Molecular medicine reports, 2019; 20(2): 1479-1487.
62. Breijyeh, Z., & Karaman, R. Comprehensive review on Alzheimer's disease: causes and treatment. Molecules, 2020; 25(24): 5789.
63. Liu, J., Chang, L., Song, Y., Li, H., & Wu, Y. The role of NMDA receptors in Alzheimer's disease. Frontiers in neuroscience, 2019; 13: 43.
64. Prvulovic, D., Hampel, H., & Pantel, J. Galantamine for Alzheimer's disease. Expert opinion on drug metabolism & toxicology, 2010; 6(3): 345-354.
65. Tolar, M., Abushakra, S., Hey, J. A., Porsteinsson, A., & Sabbagh, M. Aducanumab, gantenerumab, BAN2401, and ALZ-801—the first wave of amyloid targeting drugs for Alzheimer's disease with potential for near term approval. Alzheimer's research & therapy, 2020; 12(1): 95.
66. Groot, C., Hooghiemstra, A. M., Raijmakers, P. G., van Berckel, B. N., Scheltens, P., Scherder, E. J., ... & Ossenkoppele, R. The effect of physical activity on cognitive function in patients with dementia: a meta-analysis of randomized control trials. Ageing research reviews, 2016; 25: 13-23.
67. Farina, N., Rusted, J., & Tabet, N. The effect of exercise interventions on cognitive outcome in Alzheimer's disease: a systematic review. International Psychogeriatrics, 2014; 26(1): 9-18.
68. Lee, J., Meijer, E., Langa, K. M., Ganguli, M., Varghese, M., Banerjee, J., ... & Dey, A. B. Prevalence of dementia in India: National and state estimates from a nationwide study. Alzheimer's & Dementia, 2023; 19(7): 2898-2912. 25
69. Cummings, J. L., Morstorf, T., & Zhong, K. Alzheimer's disease drug development pipeline: few candidates, frequent failures. Alzheimer's research & therapy, 2014; 6: 1-7.
70. Alzheimer's Association. 2016 Alzheimer's disease facts and figures. Alzheimer's & Dementia, 2016; 12(4): 459-509.
71. Shigihara, Y., Hoshi, H., Shinada, K., Okada, T., & Kamada, H. Non pharmacological treatment changes brain activity in patients with dementia. Scientific reports, 2020; 10(1): 6744.