**Bulletin of Environment, Pharmacology and Life Sciences**
Bull. Env. Pharmacol. Life Sci., Vol 11 [8] July 2022 : 107-113

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

**REVIEW ARTICLE** **OPEN ACCESS**

# Knowledge of Alzheimer's Disease: A systematic review

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**ABSTRACT**

*Alzheimer's disease is a cause of dementia that affects the part of brain that controls memory, language, thought and movement. AD affects almost a million of people worldwide and is expected to increase 3 times by the year 2050. It primarily occurs due to accumulation of Plaques and neurofibrillary tangles in the brain. The plagues are a product of Amyloid Precursor protein (APP), when degraded by the β-secretase and then by Y-secretase, they get deposited extracellularly on the neuron. This β-amyloid deposition extracellularly alters the tau protein by hyperphosphorylation inside the axon, which results in the formation of tau aggregates inside the neurons. The tau aggregates are then converted into neurofibrillary tangles (NFTs). These NFTs first occur at hippocampus and then move to cerebral cortex of the brain, but the cause for the formation of plaques is still unknown. Some factors that are found to be of risk for Alzheimer's disease are Hypertension, Diabetes, cerebrovascular disease, smoking and alcohol consumption, obesity. Factors like proper diet planning, education, cognitive reserve, and sufficient mental and physical health that help to reduce or increase the onset of dementia and Alzheimer's disease. No cure has been developed for Alzheimer's disease so far and dementia rather there are treatments for Mild Cognitive Impairment (MCI) and mild Alzheimer's disease. Food and Drug Administration (FDA) approves three categories of drugs and those are "Disease- modifying (Aducanumab)", "N- Methyl-D-Aspartate receptor antagonist (Memantine)" and "Acetylcholinesterase receptor inhibitor (Rivastigmine)".*

***Keywords:*** *Alzheimer's disease, Dementia, β-amyloid, neurofibrillary tangles, Acetylcholinesterase inhibitor*

Received 16.06.2022 Revised 30.06.2022 Accepted 30.07. 2022

## INTRODUCTION

Dementia may be described as a scientific syndrome characterised through a cluster of signs and symptoms that are manifested through problems in memory, disturbances in language and different cognitive functions, modifications in behaviours, and impairments in activity of everyday living. Alzheimer disease (AD) is the most common cause of dementia and sixth common death cause in United States (US) [1], leading to functional deficits, slow but progressive cognitive changes in the behaviours. AD effects the brain parts that manages the language, thought, judgement, attention and memory that begins with a moderate memory loss, possibly resulting in loss of capability to hold a conversation and react to the surroundings. Alzheimer's disease (AD) causing dementia seen worldwide, with US affected approximately 5.5 million people and estimated global prevalence of about 24 million [2]. Alzheimer's disease (AD) is predicted to be double in number every 5 years and alone in United States, the number might reach nearly 14 million by 2050 [1]. Worldwide the prevalence of Alzheimer's disease (AD) growing rapidly on the part of population i.e., People with age 65 years and older, as this age sector is growing rapidly in the global population compare with other age sector group [3]. It is seen that the first appearance of symptoms of Alzheimer's disease after age 60-65. Alzheimer's disease is less commonly seen younger population [4]. The main cause of Alzheimer's disease is still unknown, but it is known that there is not only a single cause of this disease, there are plenty of factors that might causes AD. Currently there is an absence of cure for Alzheimer's disease, though treatment is there for the improvement of the symptoms. Alzheimer's disease caused be death of the neural cells leading to neurodegenerative disease. There is a role of genetics in the early and late stage of AD (Alzheimer's disease) [5].

## PATHOPHYSIOLOGY

Alzheimer's disease is slow and progressive disorder whose pathophysiology is known but the main cause for the pathophysiology is still unknown. But there are many risk factors that are associated to the pathology of this disease that we will discuss later in this paper.

Generally, Alzheimer's disease is due to accumulation of plaques and neurofibrillary tangles but genes also play an important role in its development.

Plaques are microscopical lesions that are spherical in structure that contain β-amyloid peptide as the centre that is covered by axon ending of neurons. Amyloid precursor protein (APP) is the precursor protein from which the β-amyloid peptide is derived due to the action of α-, β-, ϒ- secretase enzyme. α- or β-secretase enzyme breaks the amyloid precursor protein (APP) in small fragments that is not harmful (non-toxic) to the neurons. But, consecutive breakdown of amyloid precursor protein by β-secretase then by the ϒ-secretase lead to formation of 42 amino-acid proteins called as β-amyloid 42 [5]. Increase in the concentration of β-amyloid peptide results in the aggregation of β-amyloid protein in the extracellular of neuron which causes the neuronal toxicity. The aggregation of the β-amyloid occurs near Meningeal, Grey matter and Cerebral vessels of the brain. This deposition around the grey matter is called as senile plaques [5]. The β-amyloid 42 is seen that, its hydrophilic part forms a bond with metal ions like copper (II), this leads to the abnormal but stable β-amyloid aggregates results in neurotoxicity [6].

Neurofibrillary tangles (NFTs) are fibrous structure that are found in the cytoplasm of neuron. These Neurofibrillary tangles are formed intracellularly a protein called Tau protein. Inside the axon, microtubules are found that help in the intracellular transportation. In normal human, tau protein main function is to stabilize the microtubules that are present inside the axon and help in the microtubule's assembly. In Alzheimer's disease (AD), deposition of the β-amyloid extracellularly on neurons. This β-amyloid deposition leads to the hyperphosphorylation of tau protein inside the axon. The hyperphosphorylation of Tau protein results in the formation of tau aggregates inside the neurons. These tau aggregates transform into a pair of twisted helical filament known as neurofibrillary tangles (NFTs). These neurofibrillary tangles are occurring first in Hippocampus (found deep inside temporal lobe of brain), then this gradually moves into the cerebral cortex of the brain [5].

Alzheimer's disease is also caused due to genes, where the mutated genes are passed (inherited) from parents to offspring as an autosomal dominant disease. This happens due to mutation of 3 specific genes: 1. APP gene on chromosome-21, where mutation of this leads in the formation and aggregation of extracellular β-amyloid proteins. 2. PSEN-1 (Presenilin-1) on chromosome-14 and 3. PSEN-2 (Presenilin-2) on chromosome-1, where mutation of both these genes interfere the functionof ϒ-secretase enzyme that ultimately leads in the aggregation of β-amyloid peptide.

Plaques are not much correlated to Alzheimer's disease as that of Neurofibrillary tangles (NFTs). These are the possible and known pathophysiologies of Alzheimer's disease (AD) till date, but still there is a lack of information about the main reason for these causes.

## FACTORS THAT INCREASE THE RISK OF AD:

### Hypertension

In an observational studies, increase in the blood pressure in a mid-age, was seen to be linked to late-life Alzheimer's disease (AD) [7, 8]. In late-life, both low and high blood pressure was somewhat associated to Alzheimer's disease [9-13]. In Alzheimer's disease and dementia, use of anti-hypertensive medications showed a protective effect in some longitudinal studies [14-16]. These protective effects of antihypertensive medications may be due to delaying the process of atherosclerosis, improving the perfusion in cerebral region [16].

### Diabetes

Diabetes is a metabolic syndrome, which is a clump of many risk factors that is classified by abnormality in blood glucose level, metabolism of lipoproteins, insulin, and obesity. In a population study on Finnish population, it was found that diabetes related risk factors to be associated with an increase number of Alzheimer's disease in the elderly ones [16]. In several longitudinal studies it has been reported that, person with diabetes have increased risk of bothneurodegenerative type of dementia but also vascular type of dementia [17-19]. This risk factor was confirmed in a systematic review by G. Biessels, S. Staekenborg, E. Brunner *et al.* [20]. It has been proposed that diabetes has a direct role in the accumulation of β-amyloid peptides in the brain due to hyperinsulinemia that disrupts the β-amyloid clearance in the brain as it competes for the enzyme that degrade the insulin (Insulin-degrading enzyme) [21]. There is around double increased risk of Alzheimer's disease in people with type-II diabetes [22-23].

### Smoking and alcohol consumption

Previous cross-sectional and case-control studies reported that there is low rate of Alzheimer's disease among the person who do not smoke as compare to the smokers [24] but some prospective studies shows that there is an increase risk or no relation of Alzheimer's disease in the smokers [25]. It was found in numerous follow-up studies that person with cigarette smoking, especially the noncarrier of gene Apolipoprotein-E (APOE) ε4 allele has increased risk of Alzheimer's disease (AD) [16-29]. In the brain, smoking increase the risk of Alzheimer's disease and dementia by up-regulating (cholinergic metabolism) cholinergic nicotinic receptor of the brain [30]. Decrease in cholinergic, result in decrease in the levels of choline acetyl transferase, acetylcholine and nicotinic acetyl choline receptors are always found in the brain

of Alzheimer's disease patients [31].

Alcohol abuse is known to be cause "alcoholic dementia". Little-to-moderate consumption of alcohol shows that there is decrease incidence of dementia and Alzheimer's disease [32]. In the middle age of the heavy drinkers increase risk of dementia and Alzheimer's disease threefold times in the late-life, especially person that carry the gene Apolipoprotein-E (APOE) ε4 allele [33].

**Cerebrovascular disease**

There is evidence that, cerebrovascular disease and Alzheimer's disease exists correspondingly, of dementia and Alzheimer's disease (AD) sign is available [34]. In a MRI (Magnetic Resonance Imaging) scan it was noted that white-matter hyperintensity, silent brain infarction and stoke increases the risk of Alzheimer's disease and dementia [35, 36]. Person with dementia, by MRI scan, white matter hyperintensity is observed frequently, but the contribution of white matter towards the cause of dementia and Alzheimer's disease is still notclear [37]. Stroke can result in dementia and Alzheimer's disease by atrophy (Destruction) of parenchyma of the brain [38, 39].

**Obesity and Body Mass index (BMI)**

In many prospective studies it is reported that high or low body weight, weight gain and also weight loss can result in risk for dementia and Alzheimer's disease [40-43]. There is a high risk of Alzheimer's disease (AD) due to low Body Mass Index (BMI) in late life over a 5-6 yr. period [42, 44]. After the age of 65 yr., it was measured that Body mass Index is inversely linked tothe risk of Alzheimer's disease, whereas obesity at an age around 50 (Mid-age), measured to be having high risk of development of dementia and Alzheimer's disease in late-life [45]. Many case-control and cross-sectional studies show that the a clear evident that malnutrition, low BMI or underweight are risk factors for dementia, Alzheimer's disease and atrophy (age related brain change) [46]. A systematic review by *Gustafson D.* study showed that decrease in the Body Mass Index in late-age results in disorders related to dementia, whereas rise in BMI during mid-age shows high risk factors for dementia and Alzheimer's disease [47].

**FACTORS THAT DECREASE THE RISK OF AD.**

**Dietary factor**

Diet plays a very important role in several disorders to vascular system, so maintaining a good diet is very important for every age group. It is found in many studies that increase in diet and supplement intake like vitamins-C and vitamin-E or any antioxidants have decline risk of Alzheimer's disease [48]. Many studies reported that diet containing fish and unsaturated fatty acids might show protective effects against Alzheimer's disease and dementia [49], but cholesterol and saturated fatty acids diet can increase the risk of Alzheimer's disease [50]. The risk of Alzheimer's disease can be due to high fat diet which leads to elevation of cholesterol level in the body and blood vessels (Vascular risk) in the brain [51]. It has been reported in many studies that intake of diet including the omega-3-fatty acids or fish, which is a main componentfor brain development in early stage, decreases the risk of dementia and Alzheimer's disease [52, 53]. Intake of diet with high content of fruits, fish and vegetables called as "Mediterranean diet" reported to be decrease the risk of Alzheimer's disease and dementia [54]. One studyreported that intake of diet including high folate didn't show any significant decrease in risk of Alzheimer's disease and dementia [55], whereas another shows significant intake of high folate diet decrease the risk of Alzheimer's disease [56] .

**Physical and mental activities**

Physical and Mental activities are the main factors if done regularly results in significant reduction of Alzheimer's disease. A review of RCTs (Random Controlled Trials) reported that 8out of 11 RCTs shows improvement in cognitive function with aerobic exercise in old age people who didn't know about the cognitive impairment [57]. Physical exercises help in cognitivefunction by affecting gene transcription and some neurotrophic factor. This also helps in the improving the vascular health and promoting the plasticity of brain [58]. Regular physical activity, in person with Apolipoprotein-E (APOE) ε4 allele gene, in the mid-life shows protective effect against Alzheimer's disease and dementia in late-life [59]. In some studies, they failed to show the relation between Alzheimer's disease and physical activities [60, 61]. Mental activities such as dancing, gardening, playing board games, reading, watching television shows protective effects against risk of dementia and Alzheimer's disease examined [62]. In a study done by The Canadian Study of Health and Aging, reported that more complex work is associated with decrease risk of Alzheimer's disease and dementia (vascular dementia) [63].

**Cognitive reserve**

Cognitive reserve and neural reserve is improved by education that lead to pathological change inside the brain and result in delaying the dementia and Alzheimer's disease [64]. Person with high education and attainment of high occupation shows delay in the onset of dementia. In some longitudinal studies and

cross-sectional studies, it has been suspected that less education leads to increase risk of Dementia and Alzheimer's disease [64, 65]. In some studies it has been viewed that there is no relation between the education level of a person and the risk of dementia and Alzheimer's disease [66, 67].

## TREATMENT

Till date there is no cure for dementia and Alzheimer's disease. There is only treatment for the symptoms that arise by Alzheimer's disease.

FDA approved 3 types of categories of medication for the treatment of dementia and Alzheimer's disease: 1. Acetylcholinesterase inhibitor 2. NMDA receptor antagonist 3. Disease- modifying drugs.

### Acetylcholinesterase inhibitor (AChEIs)

This class of drugs helps to block the breakdown of acetylcholine (a chemical found in the human body helps in neuronal communication), result in increase in the level of acetylcholine. Acetylcholine chemical is very important as it helps in cognitive function, learning and memory.

Food and Drug Administration (FDA) approved 3 medications for the treatment of Alzheimer's disease (AD) and dementia, those are Rivastigmine, Donepezil, Galantamine.

**Rivastigmine:** This is used to treat Mild Cognitive Impairment (MCI) and in Dementia stage. This drug is taken oral and transdermal formulation. It works by blocking the breakdown of butyrylcholine (Similar to acetylcholine) and acetylcholine inside the brain by acting reversible inhibitor to butyrylcholinesterase and acetylcholinesterase. Some common side effects are gastrointestinal problems like diarrhoea, indigestion, nausea, vomiting [68].

**Galantamine:** used to treat mild and moderate stages of Alzheimer's disease and MCI. It is a rapid acting drug an inhibitor of acetylcholinesterase receptor. Act by increase in more releaseof acetylcholine by activating the nicotinic receptor in the brain and preventing the disintegration of acetylcholine. This drug dosing is done twice-daily. Some common side effects are loss of appetite, nausea, vomiting, diarrhoea.

**Donepezil:** This drug is used to treat all stage of Alzheimer's disease. A rapid acting drug that is reversible acetylcholinesterase inhibitor. It works by preventing the disintegration of acetylcholine inhibitor in the brain. Dosing of this drug is taken once-daily. Some common sideeffects of donepezil are muscle cramps, weight loss, nausea, vomiting. Sleep disturbance is the side-effect of only Donepezil [69].

All these 3 drugs show benefit measure in double-blind, placebo-controlled trial [3].

### N-Methyl-D-Aspartate (NMDA) antagonist

This class of drug is approved by the FDA for the treatment of moderate to severe Alzheimer's disease (AD). Memantine is a NMDA receptor antagonist that blocks the excess glutamate toxiceffects and accumulation of calcium is slowed down intracellularly and regulates glutamate activation. Memantine is usually taken with cholinesterase inhibitors. Some common sideeffects are headache, dizziness, constipation, confusion [5].

### Disease-modifying medication

Aducanumab is the only disease-modifying drug that is approved by FDA to treat Alzheimer's disease and dementia. Aducanumab is the immunotherapy is to treat mild Alzheimer's disease and MCI (Mild Cognitive Impairment). This dose is taken intravenously one hour every 4 weeks. This class of drug work by cleaning the excess β-amyloid inside the brain to decrease the plaque concentration. Some side effects are bleeding or fluid production inside the brain due to Amyloid-related imaging abnormality (ARIA), confusion, headache, dizziness [68].

## DISCUSSION

Alzheimer's disease (AD) basically qualifies as a progressive neurodegenerative disorder broadly symbolised by behaviour and cognitive impairment that eventually pose as a problem with day-to- day functional living activities. The disorder so far, has no possible known cure, and its rate of progression and advancement is always variable and subjective. Further, this disease in terms of treatment in the early phase is quite difficult, and there are no specific laboratory or imaging tests to confirm the diagnosis or betterment as such. The drugs that are available to treat the condition only show results for the mild version of the disease but also have many other side effects that are not well tolerated. Alzheimer's disease is a systemic disorder and creates tension in family lives as a whole. These individuals often wander directionlessly, fall, and have uncountable behavior.

Problems and loss of memory to name a few. Most patients end up in a medical institution because they become unmanageable at home. Many guidelines and recommendations have been constructed on how to approach, monitor and treat Alzheimer patients. Singular measures cannot alone prevent or arrest the disease. Having said that, health care workers have a very important role in ensuring thatthe patient with remains safe and can lead a decent quality of life at the least.

As discussed in the body of this paper we can firmly say that it is diseases that has forever been a subject

of discussion for researchers and that is precisely there have been innumerable sorts of research studies that have been conducted and a still in conduct to get to the core of this chronic medical condition.

## CONCLUSION

Alzheimer's disease is usually initially associated with typical symptoms such as impaired memory, but with the due course of time, the individual has a chance possibility of developing severe cognitive and behavioural symptoms like depression, anxiety, anger, irritability, insomnia, andparanoia and many more, most of which are associated with old age and decreasing nervous consciousnesses in the body. With the progression of the disease most of them will require assistance with daily life activities. Eventually, even normal activities like walking becomes difficult and many may not be able to eat or develop swallowing difficulties that lead to aspiration pneumonia.

The time from diagnosis to death is changes from person to person; some individuals may die within five years, and others may sustain for almost ten years, but overall, the quality of life is invariably very poor. While an interprofessional approach to the management of Alzheimer patients is usually recommended, an analysis of several studies also reveals that this approach hardly has an impact on the care of patients. However, because of the heterogeneity in the previous studies, more robust studies will be required to determine what type of approach works best for managing these patients.

## REFERENCES


1. Alzheimer 's disease Fact Sheet | National Institute on Aging. Accessed May 19, 2022. https://www.nia.nih.gov/health/alzheimers-disease-fact-sheet
2. Mayeux R, Stern Y. (2012). Epidemiology of Alzheimer Disease. *Cold Spring Harb Perspect Med*.2(8). doi:10.1101/CSHPERSPECT.A006239
3. Apostolova LG. Alzheimer Disease. *Continuum (Minneap Minn)*. 2016;22(2 Dementia):419- 434. doi:10.1212/CON.0000000000000307
4. What is Alzheimer's Disease? | CDC. Accessed May 18, 2022. https://www.cdc.gov /aging/aging info/alzheimers. htm
5. Kumar A, Sidhu J, Goyal A, Tsao JW. (2020). Alzheimer Disease - PubMed. In: Accessed May 18, 2022. https://pubmed.ncbi.nlm.nih.gov/29763097/
6. Rana M, Sharma AK. (2019). Cu and Zn interactions with Aβ peptides: consequence of coordination on aggregation and formation of neurotoxic soluble Aβ oligomers. *Metallomics*. 11(1):64-84. doi:10. 1039/C8MT00203G
7. Kivipelto M, Helkala EL, Laakso MP, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ Br Med J*. 2001;322(7300):1447. doi:10.1136/BMJ.322.7300.1447
8. Launer LJ, Ross GW, Petrovitch H, et al. (2000). Midlife blood pressure and dementia: the Honolulu– Asia aging study. *Neurobiol Aging*. 21(1):49-55. doi:10.1016/S0197- 4580(00)00096-8
9. Waldstein SR, Giggey PP, Thayer JF, Zonderman AB. (2005). Nonlinear relations of blood pressure tocognitive function: The Baltimore longitudinal study of aging. *Hypertension*. 2005; 45(3):374-379. doi:10.1161/01. HYP.0000156744.44218.74
10. Borenstein AR, Wu Y, Mortimer JA, et al. (2005). Developmental and vascular risk factors for Alzheimer's disease. *Neurobiol Aging*. 26(3):325-334.doi:10.1016/J. NEUROBIOLAGING. 2004.04.010
11. Skoog I, Lernfelt B, Landahl S, et al. (1996). 15-year longitudinal study of blood pressure and dementia. *Lancet*. ;347:1141-1145. doi:10.1016/S0140-6736(96)90608-X
12. Morris MC, Scherr PA, Hebert LE, Glynn RJ, Bennett DA, Evans DA. Association of Incident Alzheimer Disease and Blood Pressure Measured From 13 Years Before to 2 Years After Diagnosis in a Large Community Study. *Arch Neurol*. 2001;58(10):1640-1646. doi:10.1001/ARCHNEUR.58.10.1640
13. Ruitenberg A, Skoog I, Ott A, et al. (2001). Blood Pressure and Risk of Dementia: Results from the Rotterdam Study and the Gothenburg H-70 Study. *Dement Geriatr Cogn Disord*. 12(1):33-39. doi:10.1159/000051233
14. Khachaturian AS, Zandi PP, Lyketsos CG, et al. (2006). Antihypertensive Medication Use and Incident Alzheimer Disease: The Cache County Study. *Arch Neurol*. 63(5):686-692. doi:10.1001/ ARCHNEUR. 63.5.NOC60013
15. Yasar S, Corrada M, Brookmeyer R, Kawas C. (2005). Calcium channel blockers and risk of AD: the Baltimore Longitudinal Study of Aging. *Neurobiol Aging*. 26(2):157-163.doi:10.1016/J.NEUROBIOLAGING. 2004.03.009
16. Qiu C, Winblad B, Fratiglioni L. (2005). The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol*. 4(8):487-499. doi:10.1016/S1474- 4422(05)70141-1.
17. Irie F, Fitzpatrick AL, Lopez OL, et al. (2008). Enhanced Risk for Alzheimer Disease in Persons With Type 2 Diabetes and APOE ε4: The Cardiovascular Health Study Cognition Study. *Arch Neurol*. 65(1):89-93. doi:10.1001/ARCHNEUROL.2007.29
18. Akomolafe A, Beiser A, Meigs JB, et al. (2006). Diabetes Mellitus and Risk of Developing Alzheimer Disease: Results From the Framingham Study. *Arch Neurol*. 63(11):1551-1555. doi:10.1001/ARCHNEUR.63.11.1551
19. Arvanitakis Z, Wilson RS, Bienias JL, Evans DA, Bennett DA. (2004). Diabetes Mellitus and Risk of Alzheimer Disease and Decline in Cognitive Function. *Arch Neurol*.4;61(5):661-666. doi:10.1001/ARCHNEUR.61.5.661
20. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. (2006). Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol*. 5(1):64-74. doi:10.1016/S1474- 4422(05)70284-2
21. Farris W, Mansourian S, Chang Y, et al. (2003). Insulin-degrading enzyme regulates the levels of insulin, amyloid

β-protein, and the β-amyloid precursor protein intracellular domain in vivo. *Proc Natl Acad Sci U S A*. 100(7):4162. doi:10.1073/PNAS.0230450100
22. Luchsinger JA, Tang MX, Shea S, Mayeux R. (2004). Hyperinsulinemia and risk of Alzheimer disease. *Neurology*. 63(7):1187-1192. doi:10.1212/01.WNL.0000140292.04932.87
23. Luchsinger JA, Tang MX, Stern Y, Shea S, Mayeux R. (2001). Diabetes Mellitus and Risk of Alzheimer's Disease and Dementia with Stroke in a Multiethnic Cohort. *Am J Epidemiol*. 154(7):635-641. doi:10.1093 /AJE /154.7.635
24. Fratiglioni L, Wang HX. (2000). Smoking and Parkinson's and Alzheimer's disease: review of the epidemiological studies. *Behav Brain Res*. 113(1-2):117-120. doi:10.1016/S0166- 4328(00)00206-0
25. Doll R, Peto R, Boreham J, Sutherland I.(2000). Smoking and dementia in male British doctors: prospective study. *BMJ Br Med J*. 320(7242):1097. doi:10.1136/BMJ.320.7242.1097
26. Merchant C, Tang MX, Albert S, Manly J, Stern Y, Mayeux R. (1999). The influence of smoking on the risk of Alzheimer's disease. *Neurology*. 52(7):1408-1408. doi:10.1212/WNL.52.7.1408
27. Liu CC, Kanekiyo T, Xu H, Bu G. (2013). Apolipoprotein E and Alzheimer disease: risk, mechanisms, and therapy. *Nat Rev Neurol*. 9(2):106. doi:10.1038/NRNEUROL.2012.263
28. Alzheimer's Disease Genetics Fact Sheet (2022). National Institute on Aging. Accessed May 21, 2022. https://www.nia.nih.gov/health/alzheimers-disease-genetics-fact-sheet
29. Aggarwal NT, Bienias JL, Bennett DA, et al. (2006). The Relation of Cigarette Smoking to Incident Alzheimer's Disease in a Biracial Urban Community Population. *Neuroepidemiology*. 26(3):140-146. doi:10.1159/000091654
30. Whitehouse PJ, Martino AM, Wagster M V., et al. (1988). Reductions in [3H]nicotinic acetylcholine binding in Alzheimer's disease and Parkinson's disease. *Neurology*. 38(5):720-720. doi:10.1212/WNL.38.5.720
31. Shi Q, Gibson GE. (2007). Oxidative stress and transcriptional regulation in Alzheimer disease. *Alzheimer Dis Assoc Disord*. 21(4):276-291. doi:10.1097/WAD.0B013E31815721C3
32. Huang W, Qiu C, Winblad B, Fratiglioni L. (2002). Alcohol consumption and incidence of dementia in a community sample aged 75 years and older. *J Clin Epidemiol*. 55(10):959-964. doi:10.1016/S0895-4356 (02)00462-6
33. Anttila T, Helkala EL, Viitanen M, et al. (2004). Alcohol drinking in middle age and subsequent risk of mild cognitive impairment and dementia in old age: a prospective population based study. *BMJ*. ;329(7465):539. doi:10.1136/BMJ.38181.418958.BE
34. Schneider JA, Bennett DA. (2010). Where Vascular meets Neurodegenerative Disease. *Stroke*. 41(10 Suppl):S144. doi:10.1161/STROKEAHA.110.598326
35. Honig LS, Tang MX, Albert S, et al. (2003). Stroke and the Risk of Alzheimer Disease. *Arch Neurol*. 60(12):1707-1712. doi:10.1001/ARCHNEUR.60.12.1707
36. Vermeer SE, Prins ND, den Heijer T, et al. (2009). Silent Brain Infarcts and the Risk of Dementia and Cognitive Decline. *http://dx.doi.org/101056/NEJMoa022066*. 348(13):1215-1222.doi:10.1056/NEJMOA022066
37. Wright CB, Festa JR, Paik MC, et al. (2008). White Matter Hyperintensities and Subclinical Infarction:Associations with Psychomotor Speed and Cognitive Flexibility. *Stroke*. 39(3):800. doi:10. 1161/STROKEAHA.107.484147
38. Jellinger KA. (2002). The pathology of ischemic-vascular dementia: An update. *J Neurol Sci*. 203:153-157. doi:10.1016/S0022-510X(02)00282-4
39. Fein G, Di Sclafani V, Tanabe J, et al. (2000). Hippocampal and cortical atrophy predict dementia in subcortical ischemic vascular disease. *Neurology*. 55(11):1626. doi:10.1212/WNL.55.11.1626
40. Waldstein SR, Katzel LI. (2005). Interactive relations of central versus total obesity and blood pressure to cognitive function. *Int J Obes 2006 301*. 30(1):201-207. doi:10.1038/sj.ijo.0803114
41. Razay G, Vreugdenhil A. (2005). Obesity in middle age and future risk of dementia: Midlife obesity increases risk of future dementia. *BMJ Br Med J*. 331(7514):455.doi:10.1136/BMJ.331.7514.455
42. Nourhashémi F, Deschamps V, Larrieu S, Letenneur L, Dartigues JF, Barberger-Gateau P. (2003). Body mass index and incidence of dementia. *Neurology*. 60(1):117-119. doi:10.1212/01.WNL.0000038910.46217.AA
43. Buchman AS, Wilson RS, Bienias JL, Shah RC, Evans DA, Bennett DA. (2005). Change in body mass index and risk of incident Alzheimer disease. *Neurology*. 65(6):892-897. doi:10.1212/01.WNL.0000176061.33817.90
44. Atti AR, Palmer K, Volpato S, Winblad B, De Ronchi D, Fratiglioni L. (2008). Late-Life Body Mass Index and Dementia Incidence: Nine-Year Follow-Up Data from the Kungsholmen Project. *J Am Geriatr Soc*. ;56(1):111-116. doi:10.1111/J.1532-5415.2007.01458.X
45. Fitzpatrick AL, Kuller LH, Lopez OL, et al. (2009). Mid- and Late-Life Obesity: Risk of Dementia in theCardiovascular Health Cognition Study. *Arch Neurol*. 66(3):336. doi:10.1001/ARCHNEUROL.2008.582
46. Faxén-Irving G, Basun H, Cederholm T. (2005). Nutritional and cognitive relationships and long- term mortality in patients with various dementia disorders. *Age Ageing*. 34(2):136- 141. doi:10.1093/AGEING/AFI023
47. Gustafson D. (2006). Adiposity indices and dementia. *Lancet Neurol*. 5(8):713-720. doi:10.1016/S1474-4422(06)70526-9
48. Barberger-Gateau P, Raffaitin C, Letenneur L, et al. (2007). Dietary patterns and risk of dementia. *Neurology*. 69(20):1921-1930. doi:10.1212/01.WNL.0000278116.37320.52
49. Huang TL, Zandi PP, Tucker KL, et al. (2005). Benefits of fatty fish on dementia risk are stronger for those without APOE ε4. *Neurology*. ;65(9):1409-1414.doi:10.1212/ 01.WNL. 0000183148.34197.2E
50. Laitinen MH, Ngandu T, Rovio S, et al. (2006). Fat Intake at Midlife and Risk of Dementia and Alzheimer's Disease: A Population-Based Study. *Dement Geriatr Cogn Disord*. 22(1):99-107. doi:10.1159/000093478
51. Sparks DL, Kuo YM, Roher A, Martin T, Lukas RJ. (2000). Alterations of Alzheimer's Disease in the Cholesterol-fed Rabbit, Including Vascular Inflammation: Preliminary Observations. *Ann N Y Acad Sci*. 903(1):335-344. doi:10.1111/J.1749-6632.2000.TB06384.X

52. Van Gelder BM, Tijhuis M, Kalmijn S, Kromhout D. (2007). Fish consumption, n−3 fatty acids, and subsequent 5-y cognitive decline in elderly men: the Zutphen Elderly Study. *Am J Clin Nutr*. 85(4):1142-1147. doi:10.1093/AJCN/85.4.1142
53. Schaefer EJ, Bongard V, Beiser AS, et al. (2006). Plasma Phosphatidylcholine Docosahexaenoic Acid Content and Risk of Dementia and Alzheimer Disease: The Framingham Heart Study. *Arch Neurol*. 63(11):1545-1550. doi:10.1001/ARCHNEUR.63.11.1545
54. Scarmeas N, Stern Y, Tang MX, Mayeux R, Luchsinger JA. (2006). Mediterranean Diet and Risk for Alzheimer's Disease. *Ann Neurol*. 59(6):912. doi:10.1002/ANA.20854
55. Morris MC, Evans DA, Schneider JA, Tangney CC, Bienias JL, Aggarwal NT. (2006). Dietary folate and vitamins B-12 and B-6 not associated with incident Alzheimer's disease. *J Alzheimers Dis*. 9(4):435. doi:10.3233/JAD-2006-9410
56. Luchsinger JA, Tang MX, Miller J, Green R, Mayeux R.(2007). Relation of Higher Folate Intake to Lower Risk of Alzheimer Disease in the Elderly. *Arch Neurol*. 64(1):86-92. doi:10.1001/ARCHNEUR.64.1.86
57. Angevaren M, Aufdemkampe G, Verhaar H, Aleman A, Vanhees L. (2008). Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. *Cochrane Database Syst Rev*. 2008;(3).doi:10.1002/14651858.CD005381.PUB3/INFORMATION/EN
58. Qiu C, Kivipelto M, Von Strauss E. (2009). Epidemiology of Alzheimer's disease: Occurrence, determinants, and strategies toward intervention. *Dialogues Clin Neurosci*. 11(2):111- 128. doi:10.31887/dcns.2009.11.2/cqiu
59. Rovio S, Kåreholt I, Helkala EL, et al. Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. *Lancet Neurol*. 2005;4(11):705-711. doi:10.1016/S1474-4422(05)70198-8
60. Wilson RS, Bennett DA, Bienias JL, et al. Cognitive activity and incident AD in a population- based sample of older persons. *Neurology*. 2002;59(12):1910-1914. doi:10.1212/01.WNL.0000036905.59156.A1
61. Verghese J, Lipton RB, Katz MJ, et al. (2009). Leisure Activities and the Risk of Dementia in the Elderly. *http://dx.doi.org/101056/NEJMoa022252*. 12:54-58.doi:10.1056/NEJMOA022252
62. Crowe M, Andel R, Pedersen NL, Johansson B, Gatz M. (2003). Does Participation in Leisure Activities Lead to Reduced Risk of Alzheimer's Disease? A Prospective Study of Swedish Twins. *Journals Gerontol Ser B*. ;58(5):P249-P255. doi:10.1093/GERONB/58.5.P249
63. Kröger E, Andel R, Lindsay J, Benounissa Z, Verreault R, Laurin D. (2008). Is Complexity of Work Associated with Risk of Dementia?The Canadian Study of Health and Aging. *Am J Epidemiol*. 167(7):820-830. doi:10.1093/AJE/KWM382
64. Qiu C, Bäckman L, Winblad B, Aguero-Torres H, Fratiglioni L. (2001). The Influence of Education on Clinically Diagnosed Dementia Incidence and Mortality Data From the Kungsholmen Project.*Arch Neurol*. 58(12):2034-2039. doi:10.1001/ARCHNEUR.58.12.2034
65. Ngandu T, Von Strauss E, Helkala EL, et al. (2007). Education and dementia. *Neurology*. 69(14):1442-1450. doi:10.1212/01.WNL.0000277456.29440.16
66. Chandra V, Pandav R, Dodge HH, et al. (2001). Incidence of Alzheimer's disease in a rural community in India. *Neurology*. 57(6):985-989. doi:10.1212/WNL.57.6.985
67. Hall KS, Gao S, Unverzagt FW, Hendrie HC. (2000). Low education and childhood rural residence. *Neurology*. 54(1):95-95. doi:10.1212/WNL.54.1.95
68. How Is Alzheimer's Disease Treated? (2022). National Institute on Aging. https://www.nia.nih .gov/health/how-Alzheimer's-disease-treated
69. Hussein W, Sağlik BN, Levent S, et al. (2018). Synthesis and Biological Evaluation of New Cholinesterase Inhibitors for Alzheimer's Disease. *Mol A J Synth Chem Nat Prod Chem*. 23(8). doi:10.3390/ MOLECULES23082033



**CITATION OF THIS ARTICLE**

R Panghal, R Chanan, A Rauthan. Knowledge of Alzheimer's Disease: A systematic review. Bull. Env.Pharmacol. Life Sci., Vol 11 [8] July 2022 : 107-113