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Association of Modern Lifestyle with Risk of Alzheimer's Disease and Related Dementias

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ABSTRACT

Alzheimer's disease (AD) is the most common incurable neurodegenerative disease caused by amyloid-β plaques and tau hyperphosphorylation as neurofibrillary tangles (NFTs) in the brain, which leads to neuronal death, cognitive impairment, and memory loss. There are few therapeutic choices for this disease as a result it has become a major public health problem and the financial impact on sufferers and the social health care system is enormous. This review focuses on lifestyle interventions involved in delaying or preventing Alzheimer's disease. Lifestyle factors include unhealthy diet, smoking, alcohol consumption, sleep disturbance, stress, cardiovascular diseases, obesity, diabetes, education, and social engagement, which are considered important risk factors for the development of Alzheimer's disease. We conclude that healthy diets, exercise, and a better lifestyle can lower the risk of AD and reduce the progression of dementia in individuals.

INTRODUCTION:

Due to the advancements in healthcare technology, early disease detection, and an enhanced pharmacovigilance system, human life expectancy is increasing globally. Age-related disorders will likewise increase exponentially over time [1]. In normal bodily homeostasis, aging is a process regulated by numerous genetic and molecular pathways. Dementia is one of the most serious worldwide health concerns facing the world's aging population in the twenty-first century. Alzheimer's disease (AD) is the most frequent type of dementia (60-70 percent of cases, according to WHO 2021) and the most common progressive neurodegenerative disease. Alzheimer's disease is characterized by memory loss and changes in behavior and character. The disease starts in the hippocampus's entorhinal cortex. The pathophysiology of Alzheimer's disease (AD) is chacterized by the accumulation of beta-amyloid plaques (Aβ) outside the neuron and the formation of neurofibrillary tangles (NFTs) and tau protein inside the neuron, which leads to cognitive and memory loss, neuron death, and brain tissue destruction [3]. Age, family history, stress, socioeconomic level, education, neuroinflammation, and lifestyle are all risk factors for AD pathogenesis. Despite numerous studies, digitalization of the drug development process, and clinical trials, no effective therapy for Alzheimer's disease has been developed. As a result, leading a healthy lifestyle reduces the chance of Alzheimer's disease. We summarised lifestyle factors and their roles in the progression and prevention of Alzheimer's disease in this review.

EPIDEMIOLOGY AND INDIA'S SCENARIO:

The World Health Organization (WHO) considers dementia as a public health issue. Now it become 7th leading cause of death worldwide of them 65% are women. According to WHO 2022, more than 55 million people have dementia, with 10 million new cases diagnosed each year. This number could rise to 139 million by 2050. WHO launched several programs to reduce disease risk and increase awareness, diagnosis, treatment, research, and information on dementia, such as the 'Global Action Plan on the Public Health Response to Dementia 2017-2025,' 'Global Dementia Observatory (GDO) Knowledge Exchange Platform', 'mDementia Handbook,' and 'iSupport'[2].

In terms of genetic factors, lifestyle, culture, and socioeconomic considerations, India is a diverse country. The Indian population has a high prevalence of diseases such as hypertension and diabetes, which are risk factors for dementia. According to the Global Burden of Disease Study (2016), approximately 2.93 million individuals in India have

dementia [12]. For early diagnosis of dementia and reduce the burden Indian Council of Medical Research (ICMR) developed 'Multilingual Dementia Research and Assessment Toolbox (MUDRA Toolbox)' which includes various cognitive tests in five languages [13].

PATHOPHYSIOLOGY ASSOCIATED WITH ALZHEIMER'S DISEASE:

I. Accumulation of β-amyloid plaques and Hyperphosphorylation of tau protein:

Amyloid-β and tau proteins are the two main proteins involved in the pathogenesis of Alzheimer's disease. Amyloid-β (Aβ) protein of 39-43 amino acid residues that are generated intracellularly in the brain. The enzymes β-secretase and γ-secretase break the amyloid precursor protein (APP) and produce Aβ protein. Differences in Aβ protein accumulation and clearance result in the formation of β-amyloid plaques or senile plaques. Aβ protein is essential for neuronal function and neurotoxicity. Accumulation of β-amyloid plaque in the cerebral cortex, hippocampus, and amygdala promotes synaptic loss, axonal and dendritic damage, and microglial activation [4,5].

Tau proteins are responsible for microtubule assembly and stabilization, and are located in chromosome 17q21. Hyperphosphorylated tau proteins forms neurofibrillary tangles (NFT). NFTs twisted each other and form paired helical filament (PHF) which accumulates in the axon and dendrites and results neuronal loss in the learning and memory center of the brain [4,5].

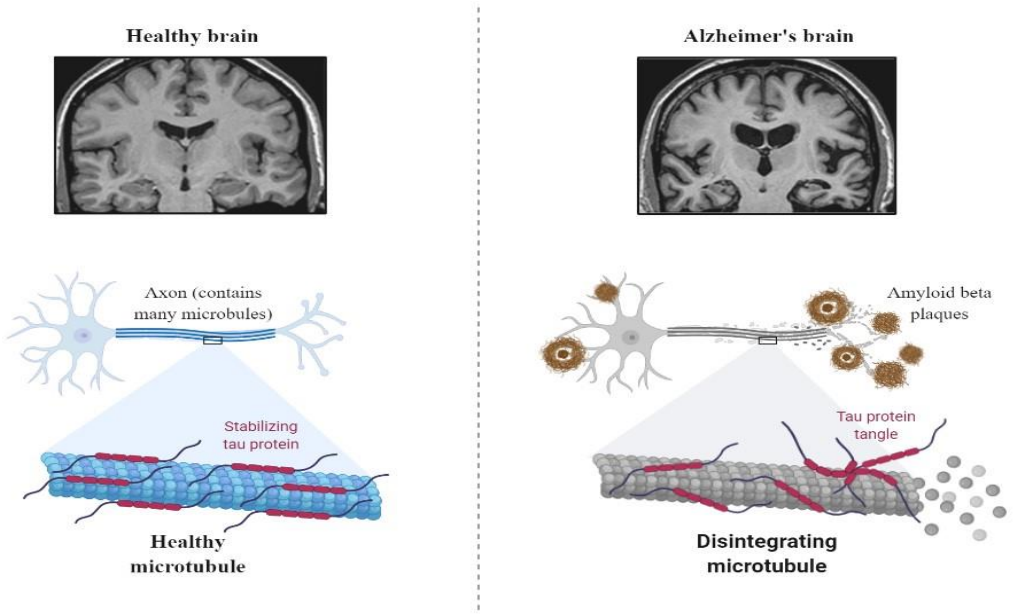

Fig 1: Physiological structure of Healthy brain and Alzheimer's brain

II. Mitochondrial dysfunction:

Mitochondria are the cell's powerhouse. Mitochondrial dysfunction is defined as a change in the process of mitochondrial dynamics and biogenesis. In the case of mitochondrial biogenesis, the number and size of mitochondria increase, which is regulated by PPARs, hormones (thyroid, glucocorticoid, oestrogen), transcription factors, nuclear respiratory factors NRF1&2, and proteins [6]. In mitochondrial dynamics, mitochondria maintain their function, structure, and shape. Reddy et al. discovered that mitochondrial dysfunction is associated with aging and aging-related metabolic and neurodegenerative disorders [7]. Defective mitochondria accumulate as mitochondrial functioning, oxidative balance, and apoptosis are impaired with age. Overproduction of reactive oxygen species (ROS) induced by mitochondrial dysfunction, resulting in oxidative damage [8]. Because the mTOR signaling system is associated with cell growth, mitochondrial function, and autophagy, it may be a promising target for Alzheimer's disease treatment [9]. In disease conditions autophagy causes the accumulation of Aβ protein. The human brain has a lower oxidant capacity than other organs. Aging causes an increase in free radical generation and a decrease in antioxidant capacity, both of which have an impact on the brain [10].

III.Inflammation in the neurone:

Not only misfolded amyloid or tau protein causes neuroinflammation, some immunological mechanism is also involved in the brain. Excess free radicals, such as NO, have been linked to neuroinflammation and neuronal death in recent studies [11].

LIFESTYLE LINKED TO ALZHEIMER'S DISEASE

The majority of Alzheimer's disease cases develop beyond the age of 65. Researchers believe that chronic diseases like Alzheimer's are caused by a combination of circumstances rather than a single cause. Various animal study data and human observational study data have shown modern lifestyle factors, the environmental factor may progress the pathogenesis of the disease and a cautious lifestyle may prevent the disease.

I. Unhealthy Nutrition & Diet:

In recent years, there is a growing interest in the role of nutrition in the prevention of AD and evidence supporting the role of nutrition in AD [14]. Vitamins, fatty acids, carbohydrates, metals, and antioxidants are associated with Alzheimer's disease. Vitamins A, C, and β-

carotene have been linked to inhibition of Aβ formation. Vitamins E, C, and B6 have been shown to reduce oxidative stress. Polyphenols, a natural antioxidant, prevent the synthesis of Aβ protein and inactivate free radicals. Resveratrol, a dietary polyphenol found in peanuts, soybeans, and pomegranates protects against β-amyloid plaque formation [15]. In the mouse model, dietary metal supplementation such as zinc reduces both the tau protein and Aβ pathogenesis [16]. As a result, a lack of essential nutrients results in a decrease in cognitive function [17]. Fresh fruits and green leafy vegetables are high in antioxidants and vitamins, which may reduce the risk of Alzheimer's disease [18]. Epidemiological studies have revealed that eating fish can lower the incidence of dementia [19]. Drinking tea and coffee reduces the risk of Alzheimer's disease. Tea polyphenols modulate oxidative stress and inhibit cognitive impairment and caffeine has been shown to prevent Alzheimer's disease [20]. Milk with vitamin D, magnesium, and phosphorus has been shown to reduce cognitive impairment and structural changes in the brain. Reduced consumption of milk products increases the risk of Alzheimer's disease [21]. Higher saturated fatty acid levels indicate poor cognitive performance, whereas higher unsaturated fatty acid levels indicate improved cognitive function [22]. Animal studies have demonstrated that omega-3 fatty acids can reduce Aβ protein synthesis. Saturated fatty acids impair cognitive function and increase the risk of Alzheimer's disease. The consumption of red and processed meat impacts oxidative stress and Aβ deposition [23]. As a result, more research is needed to understand the causative risk associated with nutrition and AD.

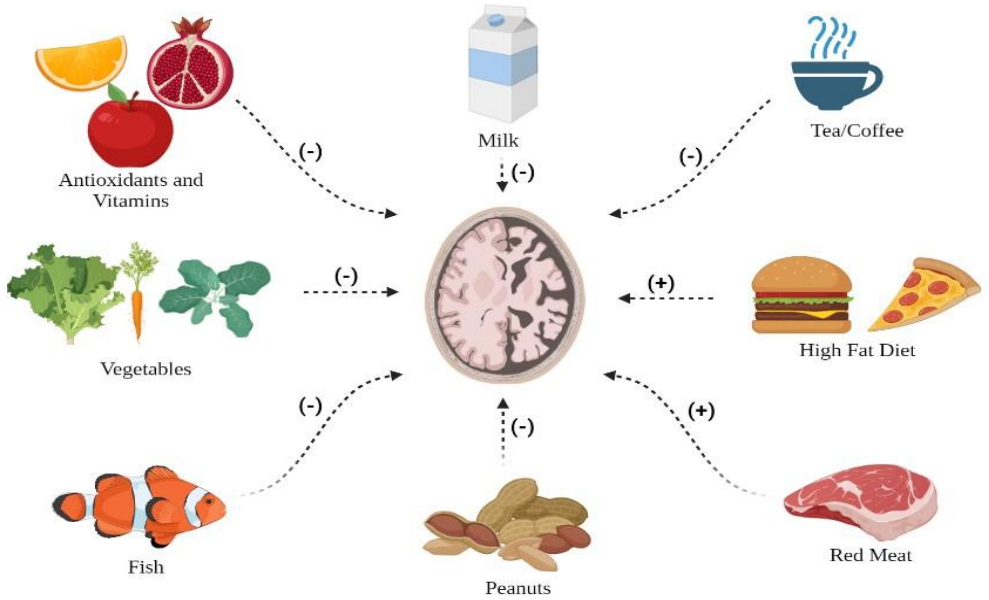

Fig 2: Diet and Nutrition linked to Alzheimer's Disease

II.Smoking:

For many years, smoking was considered to be a risk factor for the development of Alzheimer's disease. Not only do smokers have a higher risk of Alzheimer's disease, but passive smoke exposure may also increase the risk [24]. Anbarasi et al. reported that regular cigarette smoke exposure promotes mitochondrial damage and increased oxidative stress in a rat model [25]. In vitro study data from microglia (BV-2) cells suggest that cigarette smoke can induce the release of pro-inflammatory cytokines (IL-1β) and TNF-α [26]. Exposure to nicotine appeared to boost the production of nuclear transcription factor kappa B (NF-κB) and trigger the production of reactive oxygen species (ROS) in mesencephalic cells [28]. In Sprague-Dawley rats, cigarette smoking causes brain aging and pre-AD pathology [27].

Smokers have lower grey matter density as compared to non-smokers. Smoking reduces antioxidant levels (vitamin C, glutathione, and superoxide dismutase) and induce oxidative stress, resulting in tau protein and beta-amyloid plaque formation in humans [29]. Because smoking is a modifiable risk factor, all smokers should be encouraged to quit due to the increased chance of developing dementia and Alzheimer's disease.

III.Alcohol Consumption:

According to epidemiological studies, mild to moderate alcohol intake can reduce the risk of AD, while alcoholism is related to cognitive impairment and dementia. Limited drinking in early age may play a protective role in risk of dementia at old age [30]. Alcohol consumption reduces insulin resistance and platelet aggregation. Ethanol regulates the metabolism of fatty acids (long-chain omega-3 fatty acids) [31]. Moderate beer consumption play a protective role for preventing of AD. Red wine, which contains resveratrol and other polyphenols, protects against the formation of β-amyloid plaques and oxidative stress [32]. As a result, excessive alcohol consumption should be avoided for a variety of other medical and social reasons.

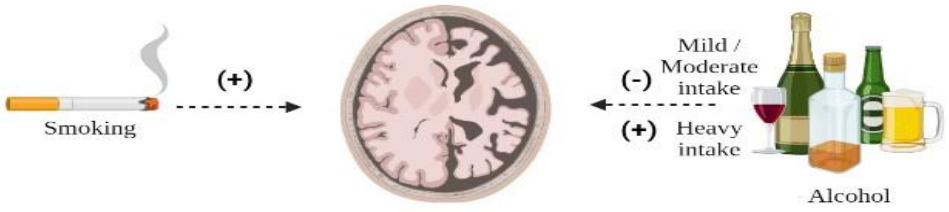

Fig 3: Smoking and Alcohol consumption linked to Alzheimer's Disease

IV.Sleep Disturbance:

The Centers for Disease Control and Prevention (CDC) considers insufficient sleep to be a "public health epidemic". Sleep disruption and circadian dysfunction may promote the development of Alzheimer's disease [33]. Sleep is a natural biological activity that helps in the proper functioning of body organs and the brain, and its disturbance can be considered as a marker of neurodegeneration [34]. Extracellular Aβ is present in CSF in a soluble form, which reduces during sleep and increases during wakefulness [35]. According to Xie L et al., natural sleep increases 60% of interstitial space in the brain, which increases the clearance of metabolites in interstitial fluid, such as Aβ [36]. It was also found that disrupting sleep for one night in healthy people can cause Aβ -plaque accumulation in the brain [37]. Therefore, sleep disturbance could be a modifiable risk factor and a novel target for disease-modifying therapy in the prevention of Alzheimer's disease.

V.Stress and Depression:

History of depression and stress increase the risk of dementia. According to animal studies, persistent stress can be a risk factor in the progression of AD, and trauma or shock at an early stage can increase the risk of AD in old life [38]. Sotiropoulos et al. reported that glucocorticoid treatment causes hyperphosphorylation of tau protein, which leads to the formation of neurofibrillary tangles in wild mice [39]. Cortisol levels in humans rise during stressful situations, increasing the risk of cognitive impairment. It is assumed that stress may cause hippocampal damage or may affect the hormonal balance and immune functioning which are suspected in progression of AD [40]. Researchers found that SSRIs, the medicines of choice for depression and anxiety, can reduce Aβ-plaque accumulation, hence reducing AD pathogenesis [41]. This mechanism and results combined to indicate the need for further research in developing the role of stress in progression of AD.

VI.Medical Factors:

Cardiovascular illness, obesity, diabetes, and other chronic conditions are linked to an increased risk of Alzheimer's disease.

A. **Cardiovascular Disease:** Cardiovascular problems have been linked to the progression of Alzheimer's disease. In the event of a disease condition, the cerebral perfusion rate decreases, resulting in a decrease in brain metabolism and brain lesions associated with AD [42]. Cerebral infractions are frequently detected in Alzheimer's disease brain. AD patients who

have suffered from stroke experience reduced cognitive impairment [43]. Hypertension and high blood pressure have been identified as risk factors in the progression of Alzheimer's disease in three longitudinal studies involving Finnish individuals aged 21 years on average [44], Japanese-American men aged 25 years [45], and Swedish adults aged 9-15 years [46]. Hypertension is associated with blood vessel thickening and lumen narrowing, resulting in decreased cerebral blood flow, creating cerebral oedema and becoming a risk factor for Alzheimer's disease [47]. As a result, cardiovascular disease may be a modifiable risk factor for preventing and delaying AD.

B. **Obesity:** Obesity is a condition where excess fat accumulates in the body, which represents a risk to health. Increase in body fat results in a decrease in blood supply to the brain which causes vascular dementia, memory loss, and brain ischemia. It also may affect impaired glucose tolerance which affects the peripheral tissues and blood vessels. Thus, obesity is a renowned risk factor for type 2 diabetes and CVDs which are identified as risk factors in the progression of AD [48].

C. **Diabetes:** Data from epidemiological research reveal that the majority of persons with Alzheimer's disease have diabetes. Impaired glucose tolerance and hyperinsulinemia have been linked to the development of Alzheimer's disease and cognitive impairment [49]. Adults who carried the APOE4 allele were shown to develop AD and vascular dementia in association with diabetes, according to the Honolulu Asia Aging Study [50].

VII.Education:

There are very few studies that show an association between low education on cognitive decline and dementia. Some studies in developing countries found that there is no relationship between education and AD. Recent observational data from cohort studies show that more highly educated members of the cohort are a lesser chance to develop cognitive impairment [51]. The relationship between education and AD is complex, there are various possibilities. Higher education is related to a better economic situation, healthier food, and a healthier lifestyle, all of which reduce the prevalence of the disease [52]. As a result, the relationship between poor education, poverty, and demographic health variables shows a clear grasp of the role of education in AD.

VIII. Social Engagement:

Social involvement is vital in lowering the risk of AD. In old age, low participation in social engagement may increase the progression of dementia. Living alone, feeling lonely, and having fewer social connections raise the risk of cognitive decline [53]. A longitudinal study found that persons who reported loneliness had double the chance of progression of disease. Virtual interaction appears to be protective. According to one study, older people who use the internet regularly have better cognitive health [54].

IX.Environmental Factors:

Environmental factors such as pollution and metal exposure have been shown to boost attentiveness. People who reside in places with high levels of air pollution have greater levels of inflammatory markers and Aβ. Prolonged exposure to ozone and particulate matter raises the risk of AD. Increased copper exposure decreases memory function. [55]. Copper interacts with Aβ, and high amounts of copper and iron in the soil increase the disease's severity [56].

CONCLUSION

Age-related diseases are becoming more of a concern as the world's population grows. The increasing prevalence of dementia adds to the social and economic burdens. In the clinical experiment, many pharmacological treatments targeting Aβ and tau proteins failed to produce sufficient outcomes. Nutrition, alcohol, smoking, sleep, stress, education, and environment may be viable non-pharmacological interventions for the prevention of Alzheimer's disease. These changes in lifestyle if carefully applied may be very helpful in reducing the growth in the incidence of Alzheimer’s disease and reducing the economic burden on affected individuals and society.

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CONFLICT OF INTEREST

No conflict of interest.

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