



Alzheimer's disease: Prevention Strategy

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ABSTRACT: Alzheimer's disease (AD) is one of the age-related infections which can develop to Dementia and nowadays both pervasiveness and rate of dementia rise considerably with propelling age $A\beta$ plaques are commonly found in Alzheimer's patients. neurofibrillary tangles are irregular growth of protein in the brain. Paul Block and George Mannesco believe that $A\beta$ plaques exist, after they discovered circular buildup. AD is eventually caused by neuronal malfunction and death. $A\beta$ cellulose bodies are considered to be less poisonous than $A\beta$ oligomers. A union of blood pressure in adulthood will increase their risk of dementia and Alzheimer's disease. In the research they found out that old people with 75+ years and the following period are having more risk of dementia and AD. BMI has a bifacial association with dementia and AD has several studies. Due to the uncertain pathophysiological mechanism of Alzheimer's disease, it is crucial for selecting a precise target population, need for a large sample size, and high cost of the prevention research, it has been a main issue to conduct primary prevention trials. Commonly, healthy seniors are a primary target demographic. Non-pharmacological treatments are helping the patient by enhancing a protective lifestyle like doing physical exercise and a healthy diet. Biomarkers have a priority role to design which group will get in preventative trials, a higher risk of progression of dementia will cut down the studies, however it will decrease the general public's ability to find the entire community. Primary prevention will evade illness and accomplice pathologies before they arise. Additionally, secondary prevention contains screening to detect disease in its early stages. Tertiary prevention is treating an illness to avoid complex injuries and disability. In a research study, the use of drugs, vitamins, or lifestyle treatments can prevent Alzheimer's disease, according to the natural definition term the outcome can be a lot of different paths. The possibility of clinical research of AD prevention is full of obstacles.

KEYWORDS: Alzheimer's disease, Environmental risk factors Prevention, Risk-Reduction, Vascular risk factors.

INTRODUCTION

The maturing of the population is an overall spectacle, and concentrating on age-related infections has turned into a significant issue from both a logical and a general wellbeing aspect [1]. Dementia is a condition described by loss of intellect capacities in numerous spaces that outcomes in impedance in typical exercises of day-to-day living and loss of freedom [2]. Both pervasiveness and rate of dementia rise dramatically with propelling age, and 70% of all dementia cases happen in individuals matured 75 year-old and older [3]. The overall expansion in the quantity of more seasoned grown-ups, more articulated in the 80 years old of age bunch, makes sense of the plague extent expected by dementia [1]. Alzheimer's disease (AD) is viewed as the most widely recognized reason for dementia, representing 60-70% of all dementia cases [4]. The signs of AD neuropathology in the cerebrum are the presence of extracellular plaques made out of amyloid- β ($A\beta$) and intracellular neurofibrillary tangles (NFTs) made out of hyperphosphorylated totals of the microtubule-related tau protein [5, 6]. Prevention is customarily partitioned into three levels: essential, auxiliary, and tertiary counteraction [7]. Essential avoidance expects to lessen the frequency of the infection by dispensing with or treating explicit gamble factors, which might diminish or postpone the advancement of dementia [8]. Auxiliary counteraction plans to early discovery of the sickness, before any side effect has arisen, when therapy could stop its movement [9]. Tertiary avoidance intends to diminish the effect of complexities and handicap of long haul infections [10]. This review aims to aggregate prevention and solution of AD which cause by non-modifiable risk factors and genetic factors.

A. Pathophysiology of Alzheimer's disease

Extensive research is devoted to understanding the pathophysiology of AD and developing effective treatments [11]. AD is a progressive and very complicated neurodegenerative disease [12]. It is one of the most common causes of dementia worldwide [13]. Extracellular aggregates of $A\beta$ plaques and intracellular aggregates of neurofibrillary tangles (NFTs) constituted hyperphosphorylated microtubule-associated- τ [14, 15]. $A\beta$ plaques are reported as histological features of AD [11]. Plaques grow initially in the basal, temporal, and orbitofrontal neocortex areas of the brain and then spread to the hippocampus, amygdala,



diencephalon, and basal ganglia in later stages [16]. In crucial situations, A β is also present in the mesencephalon, the lower brain stem, and the cerebellar cortex [17]. This A level induces the production of τ -tangles in the locus coeruleus, transentorhinal, and entorhinal regions of the brain [15]. The disease progresses to the hippocampus and neocortex during the crucial phase [18].

In 1892, Paul Block and George Mannesco hypothesised the existence of A β plaques after discovering circular buildup in the brains of aged patients [1]. Glenner extracted beta-amyloid from the meningeal arteries of Alzheimer's patients and partially discovered the peptide sequence after almost a century of investigation [10]. A is a transmembrane protein generated via the amyloidogenic pathway by hydrolysis of the A β precursor protein (APP) [17]. Three studies have demonstrated that APP generates C-terminal fragments upon hydrolysis by α -, β -, γ -secretases [15]. Under normal conditions, the first non-amyloidogenic pathogenic route provides neurotrophic and neuroprotective products for nerve cells, such as the C-terminal fragment (CTF)- α , the soluble ectodomain of APP- α (sAPP α), and other smaller fragments, via the participation of β - and γ -secretases [19]. The second process is the amyloidogenic pathological pathway, in which APP is cleaved to CTF- β by β -secretase and subsequently to various lengths of A β peptides by γ -secretase, including A β 42, which is more prone to aggregation, plaque formation, and neurotoxicity than A β 40 [20]. The third pathway is the alternate processing method utilised by η -secretase under physiological settings [21].

A β in SPs is believed to be the beginning agent of AD pathogenesis [22]. In the form of neurotoxic amyloid plaques, A β is deposited in the hippocampus, and the basal region attracts additional A β to form insoluble aggregates and produces mitochondrial damage, unstable homeostasis, and synaptic dysfunction [14]. Microglia and astrocytes are stimulated to cause inflammatory and oxidative responses [23]. AD is eventually caused by neuronal malfunction and death [24]. Tau protein kinase 1 can be triggered by A β , resulting in aberrant tau protein phosphorylation and accelerating the development of tau disease by boosting the production of paired helical filaments (PHFs) and neurofibrillary tangles (NFT) [25, 26]. Soluble A β oligomers are believed to be more poisonous than A β cellulose bodies [27]. Ferreira publicly established the "A β oligomer pathogenic theory" in 2011, proposing that soluble A β oligomers are the beginning components that lead to a sequence of pathological alterations in AD [14]. Multiple investigations have documented an increase of A β oligomers in the cerebrospinal fluid (CSF) of AD patients [28]. A β oligomers begin to accumulate *in vivo* 10 years or even decades before clinical symptoms and contribute to long-term potentiation (LTP) inhibition and enhanced long-term depression (LTD) by acting on multiple receptors, including NMDA-type glutamate and 7-nicotinic acetylcholine (7-nACh) receptors, resulting in synaptic dysfunction and impaired learning and memory [12]. A β 42 oligomers also cause oxidative damage to synaptic membranes and stimulate tau protein hyperphosphorylation [14]. Currently, treatment efforts based on the A β hypothesis aim to decrease A β production and aggregation and promote A β clearance. Controlling BACE1 and γ -secretase activity is the most direct method for reducing A β production [29]. However, γ -secretase inhibitors harm several organs and lack substrate specificity for APP [30]. The medicine avagacestat, which was the first to undertake clinical trials, had severe adverse effects, including tumours, gastrointestinal issues, and rashes, and failed to provide the expected results; as a result, related experiments have been discontinued [31]. The usage of Encore's tarenflurbil, which has high security, has also been discontinued since cognitive impairment has not improved noticeably [32]. In rare circumstances, other medications have performed worse than placebos, and unpleasant effects have increased (e.g., semagacestat) [31]. In contrast, BACE1 inhibitors have more substrate selectivity and are one of the primary areas of research and development for anti-AD drugs [20]. However, other Phase III trials have failed to demonstrate substantial therapeutic advantages and have shown unforeseen undesirable side effects, such as the inhibitor verubecestat's ability to lower A in CSF by up to 90% [33]. Early in 2018, it was reported that linked clinical trials will be terminated [32]. A Phase II/III trial of the BACE1 inhibitor umibecestat was also halted in July 2019 due to participants' cognitive decline [20, 21].

B. Risk factors

Vascular risk factors and disorders

An association of elevated blood pressure in midlife with an increased risk of dementia and AD later in life has been reported in several population-based studies, while follow-up studies of late-life blood pressure and risk of dementia yield mixed results, largely depending on the length of follow-up [34]. The short-term follow-up studies (e.g., less than 3 years) often found no association or even an inverse association between blood pressure and risk of dementia and AD [35]. However, studies of 75 years and older with a longer follow-up period (more than 6 years) also revealed an increased risk of dementia associated with low blood pressure, suggesting that among very old people low blood pressure may also contribute to the development of dementia, possibly



by influencing cerebral blood perfusion [24]. For BMI, the bidirectional association with dementia and AD has been shown in several studies, and longitudinal studies of elderly people have associated accelerated decline in BMI with subsequent development of dementia [34]. This implies that low BMI and weight loss in advanced age can be interpreted as markers for preclinical dementia [36]. Regarding serum total cholesterol, the importance of the pattern of change in cholesterol levels after midlife has been shown by two studies with a long follow-up, reporting that a decline in plasma total cholesterol after midlife may be associated with the risk of cognitive decline, dementia and AD in late life [15]. These findings suggest that high total serum cholesterol in midlife seems to be a risk factor for dementia and AD in advanced age, while decreasing serum cholesterol after midlife may reflect ongoing disease processes and represent a marker of early stages in the development of dementia and AD [32]. The use of statins (cholesterol-lowering drugs) in relation to dementia has been investigated in several community studies, with mixed findings [37, 38]. Some observational studies suggest a protective effect, while others did not, and clinical trials using statins for prevention of cognitive decline or dementia mainly reported no effects [39]. Diabetes mellitus has been associated with increased risk of dementia and AD over adult life, but the risk is stronger when diabetes occurs in mid-life than in late-life [40]. Also pre-diabetes, impaired glucose regulation, and impaired insulin secretion have been associated with and increased risk of dementia and AD [25, 32, 41].

Cerebrovascular lesions and cardiovascular diseases have been shown to be risk factors for dementia and AD [18, 42]. Several population-based studies reveal an approximately two- to four-fold increased risk of incident dementia associated with clinical stroke (post-stroke dementia) [1, 14]. It is probable that an association of clinical stroke with AD is rarely reported due to the fact that a history of stroke is part of the current criteria for excluding the diagnosis of AD [43]. However, asymptomatic cerebrovascular lesions such as silent brain infarcts and white matter lesions have been associated with an increased risk of dementia and AD, although the association with AD is likely to be due to the inclusion of mixed dementia cases [38]. The Cardiovascular Health Study found that cardiovascular disease was associated with an increased incidence of dementia, with the highest risk seen among people with peripheral arterial disease, suggesting that extensive peripheral atherosclerosis is a risk factor for dementia [2, 36]. Atrial fibrillation, heart failure, and severe atherosclerosis measured with ankle-to-brachial index are also associated with the increased risk of dementia and AD [44].

Environmental and other factors

Current smoking is another major risk factor for dementia and AD, and based on the worldwide prevalence of smoking, about 14% of all AD cases are potentially attributable to this risk factor [45]. Although it is not entirely clear whether depression is a risk factor for or a preclinical symptom of dementia, studies with long-term follow-up support the risk-factor hypothesis [44]. Other conditions have been proposed as risk factors for dementia and AD, but the evidence is still sparse [2]. These include occupational exposure, traumatic brain injury and infections [2]. Occupational exposure to heavy metals such as aluminum and mercury has been suggested to be a risk factor for AD; even high consumption of aluminum from drinking water has been associated with an elevated risk of AD and dementia [46]. In addition, occupational exposure to extremely-low-frequency electromagnetic fields (ELF-EMFs) has been related to an increased risk of dementia and AD.

Traumatic brain injury has been extensively investigated as a possible risk factor for AD [47]. The meta-analysis of case-control studies supported an association between a history of head injury and the increased risk of AD [44]. In contrast, some longitudinal studies found that AD was not associated with head trauma or only associated with severe traumatic head injury [33, 48]. The role of viral and bacterial organisms in the development of chronic neurodegeneration is long established [49]. Thus, *Treponema pallidum* and HIV, in particular, have been associated with the development of dementia [32]. Other infections in the central nervous system (CNS), particularly *Herpes Simplex virus type 1*, *Chlamydomphila pneumoniae* and several types of Spirochetes, have been suggested as possible aetiological agents in the development of sporadic AD, but with little consistent evidence [1, 23]. It has also been suggested that peripheral infections may have a role in accelerating neurodegeneration in AD by activating already primed microglial cells within the CNS [10, 14, 50].

C. Prevention of AD

Due to the unclear pathophysiological mechanism of Alzheimer's disease, the difficulty in accurately selecting the target population, the need for an extensive sample size, the long duration of follow-up, the high cost of the prevention study, adverse events of the prevention drugs being studied, and the related ethical issues, it has been challenging to conduct primary prevention trials in AD [51]. Typically, the target demographics of primary prevention are healthy seniors [52]. The subject enrichment tactics



include investigating subjects with increased risk factors for AD, such as older individuals, those with a positive family history of AD, and Apo E4-positive individuals [3]. Each of these approaches is intended to enhance the likelihood of developing AD, thereby reducing the sample size or time of follow-up [53]. People with memory problems but no objective cognitive impairment (subjective cognitive impairment or "pre-MCI"), who have a higher chance of developing dementia, are also interested [16, 54].

D. Non-pharmacological treatments

Non-pharmacological therapies are possible: modifying risk factors (primarily vascular) and enhancing protective variables through lifestyle changes are of significant interest (predominantly physical exercise, cognitive stimulation, and a healthy diet) [55, 56]. Current research, like the Multidomain Alzheimer Prevention Trial (MAPT) in Toulouse, France, combines omega-3 supplementation with multidomain therapies [36, 57].

E. Pharmacological interventions

Various risk and protective variables have been linked to AD, particularly in middle age, and they are susceptible to prevention [47]. Some prospective randomised trials focusing on vascular risk factors, such as systolic hypertension, have shown a decrease in the prevalence of dementia, whereas others have not [48]. These contradictory findings may be partially explained by the varying effects of antihypertensive medications on AD-related pathways [58]. However, they have resulted in a US task force not endorsing the treatment of systolic hypertension or any other lifestyle modification as a preventative measure against AD [48]. Despite this, most research suggests that preventing strokes is an effective method for preventing dementia, either via the control of vascular risk factors or through excellent post-stroke treatment [48].

Another option would be to attack the preclinical pathophysiology of AD directly [59]. Several potential pathophysiological targets for primary prevention of Alzheimer's disease include amyloid plaques, soluble amyloid, neurofibrillary tangles, loss of neurotransmitters, synapse loss, inflammation, and oxidative stress [32]. Positivity of biomarkers can play an essential role in determining which group to participate in a preventative trial: a higher risk of progression to dementia will shorten the study but reduce the generalizability of the findings to the entire community [16, 37]. Diagnostic biomarkers play a crucial role in population enrichment by refining selection criteria, stratifying populations, and boosting the statistical power of trials [33]. As with outcome measurements, endpoint biomarkers can be used to assess the rate of illness development and detect medication treatment effects [32]. The adverse effects of medications are not negligible, especially in asymptomatic individuals. These risk-benefit considerations are crucial for research ethics boards and regulators: "Safety must be the primary consideration because an agent that will be administered to thousands of healthy normal individuals, the majority of whom will never develop a disease, must be remarkably free of side effects" [60].

F. Contrasted with Risk-Reduction

Prevention, which is often described as "the act of preventing something from occurring or developing," has been referenced in scholarly works dating back to the eighteenth century [43, 53]. Nature has recently defined "disease prevention" as "a process through which individuals, especially those with risk factors for a disease, are treated to prevent a disease from happening" [3]. Treatment usually begins before or shortly after the onset of illness symptoms. Patient education, lifestyle changes, and medication may be used in treatment. According to the American College of Preventative Medicine, prevention's purpose is "to preserve, promote, and maintain health and well-being and to avoid disease, disability, and death" [59]. According to Nature's definition, illness prevention is a multi-step procedure including "treatment" at various phases of a disease's evolution [59]. The World Health Organization (WHO) classifies preventive treatments as either primary, secondary, or tertiary. Primary prevention tries avoiding illness and its associated pathologies before they arise, whereas secondary prevention involves screening to detect disease in its early stages, before symptoms appear, to halt or stop its course [42, 59]. Tertiary prevention is treating an illness to avoid complications and reduce disability [42]. According to Nature and the WHO, illness prevention is achievable even after the beginning of symptoms [42]. Reducing the likelihood of unfavourable outcomes, such as the loss of patient autonomy, the development of concomitant disorders, and mortality due to disease, is therefore not necessarily synonymous with "preventing" disease in the conventional sense [42].



G. Implementing prevention research findings in clinical practice

Critics of the word "prevention" as it pertains to AD may dispute the viability of preventative techniques in clinical practice, especially given the absence of an authorised pharmaceutical prescription and lifestyle strategy, as is customary for most chronic diseases (e.g., hypertension, hyperlipidemia, diabetes) [49]. It is essential to note, however, that clinical research methodology and clinical practice for Alzheimer's risk reduction are separate. In a research study, the use of drugs, vitamins, or lifestyle treatments may "prevent" AD according to Nature's definition of the term, but practically, the outcomes may vary due to numerous variables [26]. For instance, patient compliance contributes to the efficacy of preventative programmes. In clinical practice, nonadherence can develop for various reasons, including stigmas, societal pressures, the expensive expense of pharmaceuticals, and an inability to recognise change before and after therapeutic intervention. Heterogeneity of treatment effect refers to the notion that different patients respond differently to the same treatment for the same ailment [11]. Therefore, it is challenging to duplicate clinical studies in practice, suggesting that even if "prevention" is achievable under rigorous parameters, it may not be easily provable in a clinical context [24]. In addition to diagnosing and treating illness states, it will be essential from a clinical research standpoint to investigate strategies to enhance individuals' health [42].

H. Limitations and Future Plans

Several clinical studies, including many of those described in the preceding section, aim to find solutions through therapies designed to reduce the risk of AD [28, 58]. However, the feasibility of clinical research into AD prevention is hampered by several apparent hurdles. An obstacle is evaluating ethical factors [41]. For instance, the requirement of a randomised, placebo-controlled study for interventions such as exercise, diet, proper sleep hygiene, disease treatment, and other risk factor intervention variables would necessitate the exclusion of low-risk, evidence-based risk factor modification techniques from one study group [31]. In addition, most interventional studies are multimodal, making it difficult to separate the influence of certain modifiable risk variables [26]. While population attributable risk (PAR) offers the proportion of cases that can be "attributed" to a specific risk factor, more research is required to disentangle the effect of individual risk factors for AD [35, 43]. Most previous research was epidemiological, emphasising connections rather than causes [24]. In light of the high correlation between heart disease and Alzheimer's disease, more studies must investigate how cardiac risk factors impact the emergence of dementia-related diseases such as Alzheimer's disease [59]. Similar fundamental science and clinical research investigations are required to demonstrate AD prevention's feasibility and efficacy [7, 46].

I. Conclusion

Even while the evidence for some risk and protective variables in dementia and AD is still limited, and their significance has to be elucidated further, observational studies suggest various modifiable factors that may be controlled to prevent or postpone the onset of dementia. In addition, epidemiological studies suggest that the life-course approach model and the complex character of dementia and AD should be considered when developing any preventative strategy. In therapeutic contexts, the usage of the phrases "prevention" or "risk reduction" is ultimately determined by the particular practitioner or clinician-researcher. The treatments' overall short-term and long-term goals may also play a role in the decision.

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Cite this Article: Bongkod Kitisripanya (2022). Alzheimer's disease: Prevention Strategy. International Journal of Current Science Research and Review, 5(7), 2745-2752